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An Updated Review on Skin Conditions and Its Treatments, with Insights on Cellular and Molecular Mechanisms of Drugs

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ABSTRACT

Background: Skin problems can affect patient lives by resulting in psychosocial effects. The most exposed organ is the skin of the body. Skin diseases occur worldwide and a matter of serious concern. This appreciation for the age, sex, and location of lesions. Some common infections which affect the skin such as Bacterial infections, Viral infections, Fungal infections, Parasitic infections, Rashes, Acne, Warts, Atopic dermatitis, Psoriasis, and also including Some medications used in the treatment of skin diseases such as anti-fungal, anti-viral, anti-inflammatory, retinoid, corticosteroids and oral isotretinoin. **Objective:** This review showcases the molecular mechanisms involved in skin conditions and their treatments. **Method:** The data were done by selected a combination of review and research papers from various databases such as EMBASE, Europe PMC, FSTA- Food Science and Technology, Nutrition, Google Scholar, PubMed, Merck Index, MedlinePlus, Indian citation index, Science Open, PubMed, Scopus, Semantic Scholar, World Wide Science, Shodhganga, Science Direct and keyword used: mechanism of "antifungal", "antiviral", "anti-inflammatory", "retinoid", "corticosteroids" "skin diseases treatment" from the year 1970-2020. **Conclusion:** This review paper on allopathic medication can cure different types of skin diseases. Describe the mechanism of action some drugs such as Retinoids influence a various variety of cellular processes Griseofulvin effective against Dermatophytes. Amphotericin B exerts its action on the major 5 levels of cells. Anti-inflammatory drug for acne treatment is the inflammatory disease of the skin is treated by oral isotretinoin. Antiviral drugs used for skin problem treatment mainly used herpes related. Corticosteroid medications are used in skin conditions in vasculitis and inflammatory diseases. These are effective in skin problems and it's proven by their molecular mechanisms.

INTRODUCTION

Skin diseases are a very common and major health problem. Which is affected by a high proportion of the population mostly adults in the whole world [1]. Skin is the outer covering and the largest body part of the human body. The skin contains many structures and specialized cells [2]. Some most common skin problem was diagnoses such as viral warts, sebaceous gland diseases, benign tumors, eczemas, and fungal infections [3]. Skin divided into 3 main layers such are epidermis, hypodermis, and dermis, these layers have distinct role providers in almost all functions of the skin [4]. Generally about one of the three patient practitioners suffers from skin disorder [5]. In nature, most dermatologic diseases are chronic [6]. On patients skin diseases can heavy place in psychological burden and emotional which far worse than physical impact [7]. Skin problems are effects in youth especially by increased consciousness and their beauty of body and most of that aggravates by anxiety [8]. However, the skin can be pale, sensitive, dry, sagging, or tired. People lacking in their essential nutrients such as B complex vitamins, beta-carotene, and vitamins C and E so they suffer from skin drying problems [9].. Damaged skin severely will try to heal by forming scar tissue. This occurs depigmented and discolored [10]. Treatments of dermatological are divided into 5 external applications of drugs such as physical therapies, systemic therapies (oral administration of drugs, and injections), laser therapies, and surgical therapies. These treatments are most important in dermatology. In physical therapy including warming/cooling and irradiation on the affected site are frequently applied [11]. The skin protects the whole body from noxious stimuli like ultraviolet (UV) irradiation, microorganisms, irritants, and allergens. And a major role of its makeup and structure, epidermis are particularly the most superficial part. Keratinocytes are the main cellular component of the epidermis, but also there are melanocytes, gamma delta T-lymphocytes, Merkel cells, and Langerhans cells. Keratinocytes preserve their ability in the basal layer of the epidermis to proliferate and also upward to form the granular layer and spinous layer [12].

Some common infections and categories of skin diseases

Bacterial infections: some skin infections are caused by various bacteria. The most common bacteria are streptococci and staphylococci. Bacteria are mostly infected on the topmost layer of skin, deeper layers of skin, the follicles. If these infections are not treated right then they spread throughout the whole body. For example Lyme disease, impel folliculitis, cellulitis.

Generally, these bacterial infections are treated for the best result with antibiotics medicines [13].

Viral infections: These infections occur due to penetrating the virus in the stratum and also infected in the inner layer of skin. For example shingles (herpes zoster), herpes simplex warts. Some common viral infections are measles, chickenpox. Viral infection cannot be treated with antibiotics medications.

Fungal infections: Fungal infection occurs due to harmless fungi which always present on the surface of the skin. This infection due to when fungal organisms enter the body. These are usually superficial, hair, nails, affecting the skin, athlete's foot, ringworm, lock, and itch. For people who take a longtime antibiotic with a suppressed immune system, fungi may spread into the body and caused serious disease.

Parasitic infections: These infections are also known as epidermal parasitic skin diseases (EPSD). EPSD occur worldwide and known since the earliest times. EPSD consists of some parasite exposure like scabies and lice. Particular six EPSD is most important such as scabies, tungiasis (sand flea disease), and hookworm-related cutaneous larva migrans (HrCLM), and pediculosis this including body lice, head lice, and pubic lice infestation. The EPSD host-parasite restricted for interaction to the stratum corneum, and the upper layer of the epidermis, the complete ectoparasites life-cycle. In parasitic infection consider the leishmaniasis, onchocerciasis, and loiasis and also affected the dermis layer of the skin [14].

Rashes: The red inflamed area of skin is a symptom of rashes. These are seen in individual spots and or in also group spots. Due to cause by allergy, infection, irritation, and underlying disease. These occur by structural defects like malfunctioning oil glands and pores blocked.

Acne: It is also called pimples. It is a very common condition of the skin and is characterized by so many spots which are called papules, nodules cysts, pustules, and comedones like blackheads and whiteheads. Acne coincides with development when puberty of androgen hormones, these hormones occur by the sebaceous gland which produces the sebum (oil), which blockage and associated the typical spots with acne on the skin surface [15, 16, 17].

Warts: Warts are common skin diseases caused by Human Papilloma Virus. There are 2 types such as plantar warts (verruca plantaris) and common warts (Verruca Vulgaris). Warts are flesh-colored lesions by occurring most frequently on the fingers, hands, and knees.

Atopic dermatitis (eczema): It is a common inflammatory skin condition that manifests as a red and scaly rash that is very itchy. It inherited condition which runs in families along with hayfever and asthma. It affects the face in infants on their behind the knee and elbow with increased depending on age and environmental exposure irritants [18].

Tumors and cancers: When skin cells begin faster multiply than normal skin cells these growths arise and formation of tumors and cancer. Even not every skin growth was cancerous. Only a few tumors are harmless and cannot be spread. Skin cancer was the most common of all the cancer types and mostly this affecting in 800,000 Americans every year. It is generally caused by sun exposure and there have 90% of cases. The three categories of skin cancers are basal cell cancer it is the most curable, squamous cell cancer which may spread, and malignant melanoma is the most deadly form. It prevents by protecting the skin against the damaging by ultraviolet rays effects. Improve the chances by early detection to cure and Regular self-examinations [19].

Psoriasis: Psoriasis is a common inflammatory skin disease. This is characterized by a scaly rash, red, and can be itchy. A typical lesion is a distinctly raised plaque by silvery scale. It classically occurs on the knees, elbows, and the scalp, but it can affect any part of the body on occasion, also in the flexures. It can affect the nails to become pitted, fragile, and discolored [20].

Some medications used in the treatment of skin diseases by dermatological condition

Describe the dermatological conditions studied by identified the drugs used as self-medication in every skin disease is shown in table no.1 [21-26].

Table No. 1: Enlists the dermatological condition and some medications used [21-26]

S.No.	Dermatological conditions	Medications
01.	Psoriasis	Not specify the therapeutic strategies used.
02.	Scabies	Topical used: Antifungal drugs, Soaps, herbs, and creams with corticosteroids, antibiotic creams, and also used antihistamines, anti-scabies lotion
03.	Several dermatological conditions	Topical: Anti-acne medications, moisturizing products combinations, antifungal, corticosteroids, and barrier creams, bought from street vendors, Systemic: Anti-histamines, analgesics, antibiotics and Corticosteroids.

The vehicle used in the treatment of skin diseases

The main function of vehicles helps to permeate the skin. These act on agents who have some actions like cooling, lubrication, drying, and including hydration, purification, protection, softening, and itch relief. Vehicles should be colorless, non-stimulating, stable (non-denaturing), and scentless, moderately viscous, and moderately absorbable further describe in table no. 2 [27].

Table No. 2: Below are some vehicle used in the treatment of various skin diseases [27]

S.No	Vehicles	Characteristics	Skin lesions target
01.	Lotion	No greasy feeling, easily apply on the scalp.	On the scalp eczematous lesions
02.	Ointment	Oleaginous-Least irritating, superior in skin protection emulsified- oleaginous ointment, Less greasy than readily penetrates the skin	Any skin lesion
03.	Cream	Readily penetrates the skin.	Chronic hypertrophic lesions.
04.	Tape	Strong protective effect and drug Penetration	lichenified lesions

Allopathic medication and their mechanism of actions for the treatment of skin disorder:

Retinoid: Retinoid are those medications which are Retin-A and Tazorac. In gels formulation or creams formulation and derived from vitamin A for used to treat skin conditions like acne. A family comprises of retinoid are vitamin A (retinol) and its various natural derivatives are: retinoic acid, retinaldehyde, esters, and retinyl and also having a large group of family for synthetic derivatives [28]. Retinol having a 20-carbon molecule that consists of a side chain with four double bonds alcohol end groups, cyclohexyl ring. Hence, *all-trans-retinol* is their name. Vitamin A does not be synthesized from the body where it needed to be supplied to the body. Naturally, they are present in the form of ester and beta-carotene [29]. In keratinocytes, retinoids are found in basically two types: retinyl esters – probably in the storage form and retinol. This esterification is completed by two enzymes such as lecithin: retinol acyltransferase and acyl CoA: retinol acyltransferase. Metabolism of retinyl esters in retinol is done by retinyl ester hydrolase [30]. Retinoids are involved in commonly some skin disorders such as embryogenesis, differentiation, vision, growth, proliferation, inflammation, and apoptosis. Retinal is an essential part of vision and rhodopsin pigment [31]. Classification of retinoid-based on reflecting a time of introduction and structural features and into four generations the first generation involved: retinol, retinaldehyde, tretinoin, isotretinoin, alitretinoin, and second-generation are: etretinate and acitretin the third generation are: adapalene, tazarotene the fourth generation are: seletinoid G [32].

Mechanism of action of retinoid

Retinoids are well known to influence a various variety of cellular processes such are differentiation, cellular growth, cell surface alterations, and immune modulation. So many tissue effects are mediated by their interaction by their nucleic acid receptors and specific cellular.

The cytoplasm receptors include the Cellular Retinoic acid-binding protein which was a type I and type II [33]. In 1987 the nucleic acid receptors were discovered to reveal the mechanism of action for tretinoin and their analogs bring about their biological effects. These nuclear receptors (tretinoin) are related to nuclear DNA transcription factors. They comprise two groups and each is encoded by 3 genes. The nuclear retinoic acid receptor called RARs and consists of three forms RAR- α RAR-β, RAR-γ they are activated by RAR all-trans-

retinoic acid (tretinoin). RAR distinct to the DNA and retinoid-binding domains, in the skin of human RARs comprises of retinoid X receptors (RXRs) in the form of heterodynes [34]. RARs and RXRs are present in the normal skin to provide the necessary machinery for the retinoid repair process in the photodamaged skin. The heterodimer complex binds in the DNA which is known as retinoic. Heterodimer bind only RAR specific retinoid (tretinoin) to RARE and initiate transcriptional activity, retinoid (9-cis retinoic acid) does not consist confer additional trans-activation induced by the RAR retinoid which showed in fig 1. Associate the RXR protein with the presence of RAR protein. This way is probably topical retinoid for improving photoaging [35, 36].

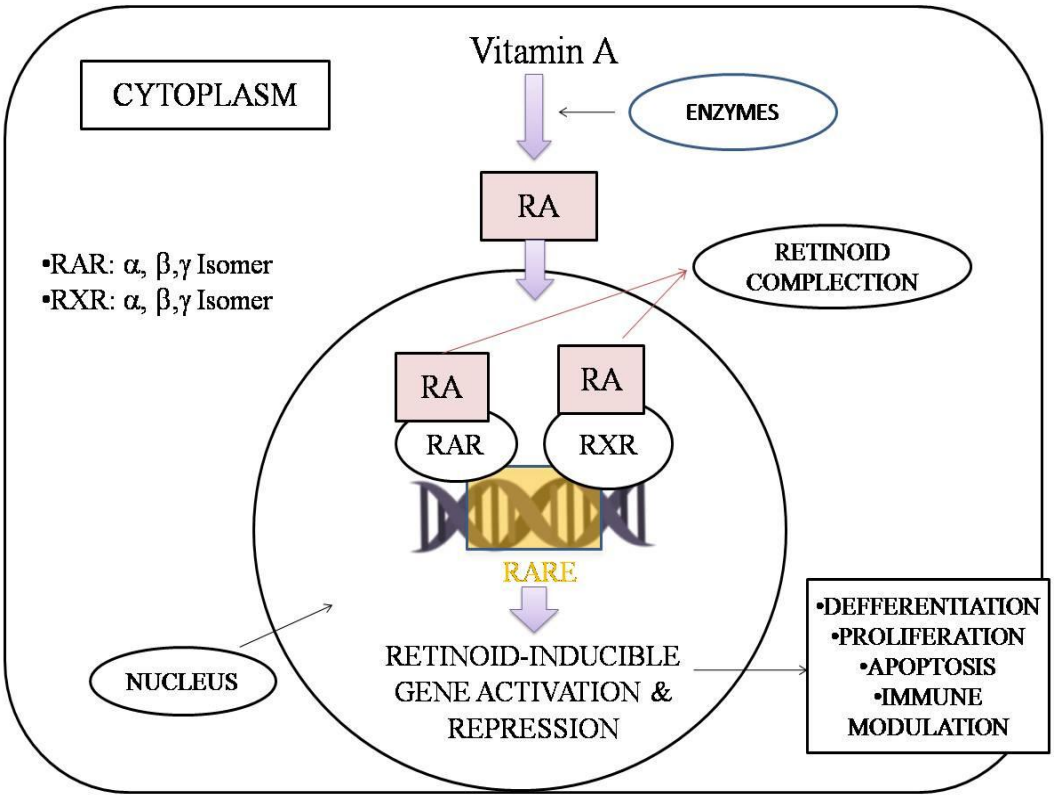

Figure No. 1: Mechanism of action of retinoids showing the role of Cellular Retinoic acid-binding protein [37].

Anti-fungal drugs

Superficial fungal infection is a very common disease of the skin. Diagnoses of fungal infection of the skin by physical examinations such as skin scrapings for microscopic examination, Wood's lamp, and fungal cultures [38]. These infections include tinea pedis, Tinea versicolor, tinea corporis, Malassezia furfur, and candidal infections, tinea capitis, tinea

cruristinea manuum, and tinea barbae. In fungal infection diseases used oral and topical agents for treatment modalities. Oral therapies include ketoconazole, griseofulvin, and itraconazole, and topical treatments, including nystatin, haloprogin, miconazole, selenium sulfide, tolnaftate, clotrimazole, and sodium thiosulfate. Dermatophytes are fungi and it causes a superficial infection on the skin. This infection transmission spread from person to person by animal or soil contact [39]. On the scalp, the fungal infection is referred to as tinea pedis, which is SFI of foot and groin infection referred to as tinea cruris and other SFI due to tinea corporis [40]. Candida skin infection is very common which occurs in any area of the body. This is found in intertriginous regions. This infection is affected where the two skin areas rub together includes the groin, skin folds, between fingers, and toe. The fungus thrives in moist, sweaty, and warm conditions [41]. Candida infections tend to be more prevalent in such infants, diabetes people, inflammatory disorders patients, weakened immune system, working in wet conditions, overweight. Symptoms on body location are rashes, cracks in the skin, red or purple patches, soreness, white, flaky substance, scaling, and erythema, and maceration, red and white lesions in the mouth.

Mechanism of action of antifungal drugs

Griseofulvin

Griseofulvin is obtained from streptomyces griseus and it is effective against Dermatophytes. Griseofulvin react by disrupting spindle and binds to tubulin and cytoplasmic microtubule production inhibiting the mitotic spindle formation which results in the inhibition separation of small nuclei and fungal mitosis [42, 43].

Amphotericin B

Amphotericin B is a polyene antifungal drug and developed in the 1950s and is used intravenously to treat candidiasis, cryptococcal meningitis, invasive aspergillosis, and mucormycosis. In vitro resistance to amphotericin B is common such as A. terreus, Fusarium species, Aspergillus tanneri, and Scedosporium prolificans these show a polyene resistance [44, 45]. AmB was affected on the fungal cell based on two methods: ergosterol binding at the membrane then inducing pore formation and induction of oxidative damage by ergosterol sequestration. Amphotericin B exerts its action on major 5 levels on cells such are: at membrane AmB bind on ergosterol (1) pore formation, induction of ergosterol sequestration (2) consisting of a membrane stability disruption. Amphotericin B induces oxidation burst.

The remaining mechanism of this was unknown, but several possibilities by Amphotericin B act as prooxidant directly (3) and reactive oxygen species (ROS) induce as accumulation. So, the intracellular effect may require binding on ergosterol previously (4) ROS is a product of respiratory chain so it cannot be discarded that's way Amphotericin B influences the activity of mitochondrial (5) in this way contribute the oxidation burst. The effect of multiple deleterious free radicals on essential compounds of cells such as protein, DNA, membrane, mitochondria were resulting in cell death shown in fig no.2 [46- 48].

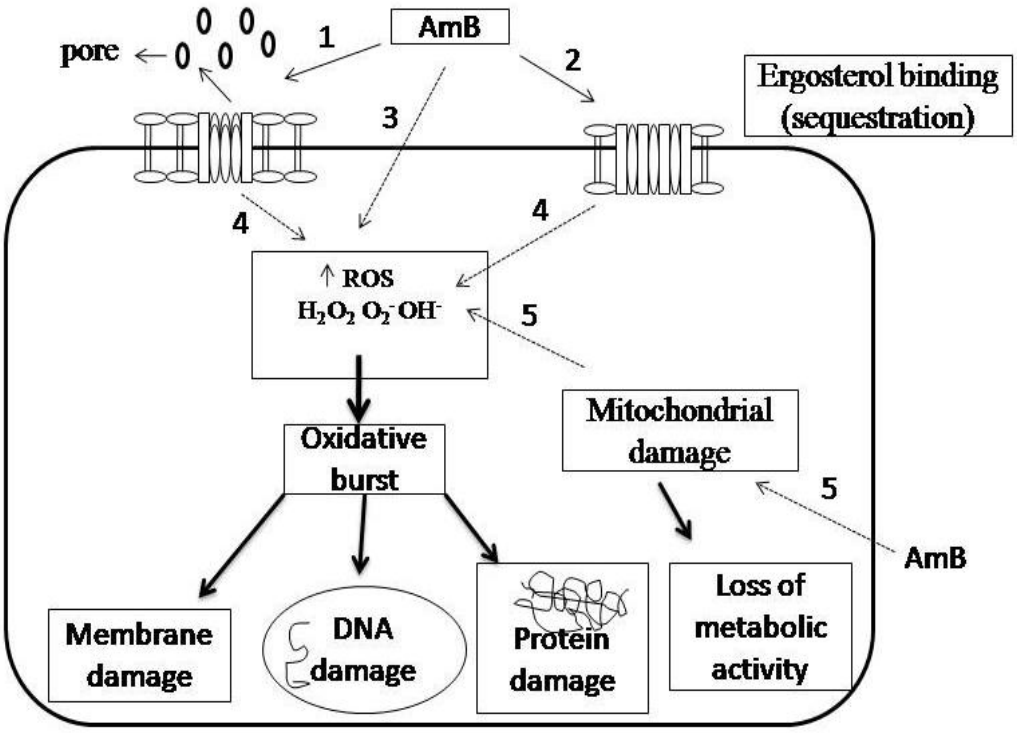

Figure No. 2: Mechanism of action of Amphotericin B and its binding sites for causing DNA damage, membrane damage, etc. [49].

Anti-inflammatory drug for acne treatment

The most common inflammatory disease on the skin is Acne vulgaris. It affects Up to 80% of adolescents of whole countries [50]. The main four major factors involved in acne pathogenesis are hyperpolarization, increased sebum production, comedo formation, perifollicular inflammation [51].

Oral isotretinoin:

Oral isotretinoin molecular name 13-cis retinoic acid, an isomer of All-trans retinoic acid (ATRA). It was used in the treatment of recalcitrant acne for about four decades [52]. Their use has successfully proven by many patients with severe acne and also their decreased sebum production and reduction of the marked inflammatory lesion [53, 54, 55]. The sebum-suppressive action of isotretinoin which is not related to lipid synthesis decreases individual sebocytes, but they consist of sebocytes death. For modifying gene expression the Sebocytes are 13-cis retinoic acid with ATRA to bind and activate the retinoic acid receptors [56].

Mechanism of action of Oral isotretinoin:

p53 is a transcription factor that is the key effectors of all anti-acne. Isotretinoin-induced p53-mediated sebocytes apoptosis. Isomerized is isotretinoin in sebocyte to ATRA (all-trans-retinoic acid), which is transported to the nucleus via cellular retinoic acid-binding protein 2 (CRABP2). In the nucleus, ATRA binds to retinoic acid receptor (RAR) and genes of RAR-responsive activates like TP53, which promotes the p53expression. ATRA has induced ARF expression and promotes the p14expression, which is a regulator of negative MDM2 (mouse double minute 2), the p53 the key inhibitor via p53proteasomal degradation. Signaling of increased IGF-1 is reduced by p53 and reduced the kinase AKT activity, that phosphorylation via inhibits theFoxO1 and FoxO3 activity but MDM2 is stimulated. Thus, increases the activity of p53stimulates via its induction of direct transcriptional and Its MDM2 of a negative regulator of inhibition of posttranslational. Subsequently, activates of p53 is increased, proteins of several apoptosis-promoting like TRAIL (tumor necrosis factor-related apoptosis-inducing ligand). p53-attenuated signaling reduces of IGF-1 the survivin expression, a critical caspase 3inhibitor. p53-induced BLIMP1 expression and suppresses c-Myc of FoxO3, a key transcription sebocyte differentiation factor. The outcome of the final is apoptosis of sebocyte, the primary isotretinoin mechanism induced suppression of sebum shown in fig 3.

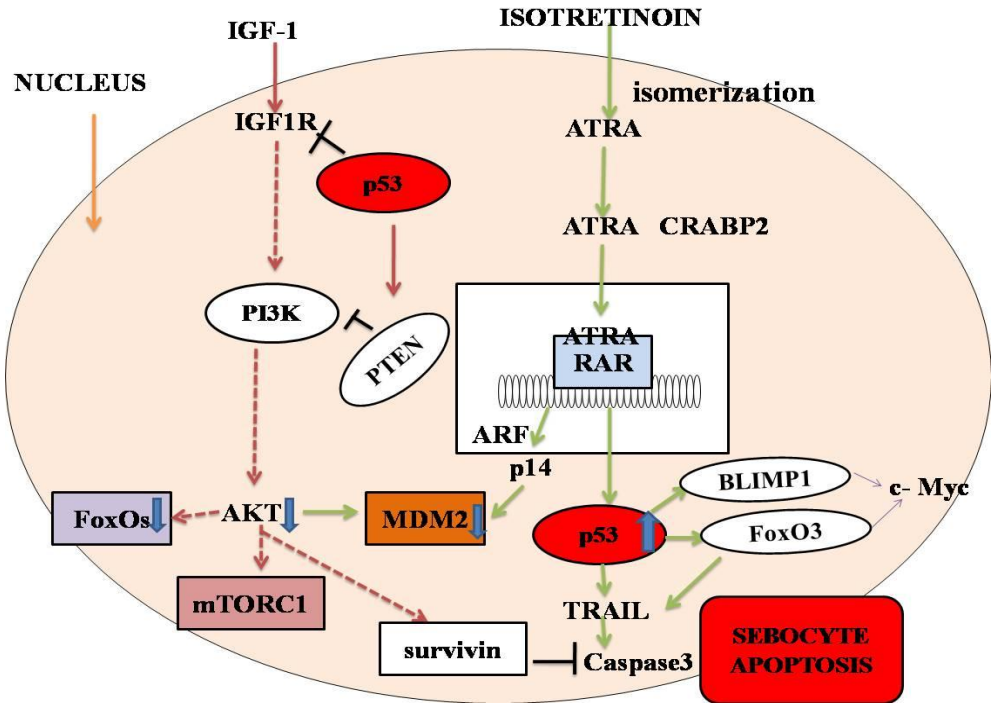

Figure No. 3: A representative diagram of Mechanism of action of isotretinoin and the involvement of transcription factors associated [57, 58].

Antiviral agents

Antiviral agents are very common to include acyclovir, famavir, and Valtrex [59]. Antiviral chemotherapy clinical benefits for the majority of symptomatic patients [60].Palliative measures like cotton underwear, saline bathing loose-fitting cold compress, on affected area keep clean and dry and should be used a topical zinc cream application [61,62] Systemic antiviral drugs can certainly control the symptoms and signs of herpes when used to treat first clinical and recurrent episodes. However, these drugs do not eradicate with the latent virus [63, 64] Antiviral drugs are used for skin conditions treatment including also herpes related [65].

Currently, three drugs are used for the treatment of genital herpes: valacyclovir, acyclovir, and famciclovir [66, 67]. Herpes simplex virus infection (HSV) causes recurring episodes of painful, small, fluid-filled blisters on the mouth, skin, lips, eyes, or genitals. This is a very contagious viral infection, spread by direct contact with sores contact with an affected area when there are no sores are present [68, 69] Acyclovir is highly active than the HSV-1 but slightly low active against the HSV-20 [70].

Mechanisms of action of anti-herpes simplex virus

The antiviral activity of acyclovir by viral thymidine kinase and intracellular conversion of acyclovir, and the monophosphate by cellular kinases subsequent conversion into active triphosphate and diphosphate. This is replication by inhibiting the herpes virus, DNA polymerase enzyme, and this active by inhibits of viral DNA synthesis. The initial activation occurs viral thymidine kinase so the whole process is highly selective for infected cells. Famciclovir and Valacyclovir are prodrugs. By compared acyclovir the penciclovir less potent 100-160 times for inhibiting the viral DNA polymerase but has a higher intracellular concentration and longer half-life. Viral DNA synthesis inhibits by penciclovir through competitive inhibition and irreversible DNA polymerase preferably than DNA chain termination. Penciclovir do not indicate the HSV-2 infections shown in fig 4[71, 72, 73].

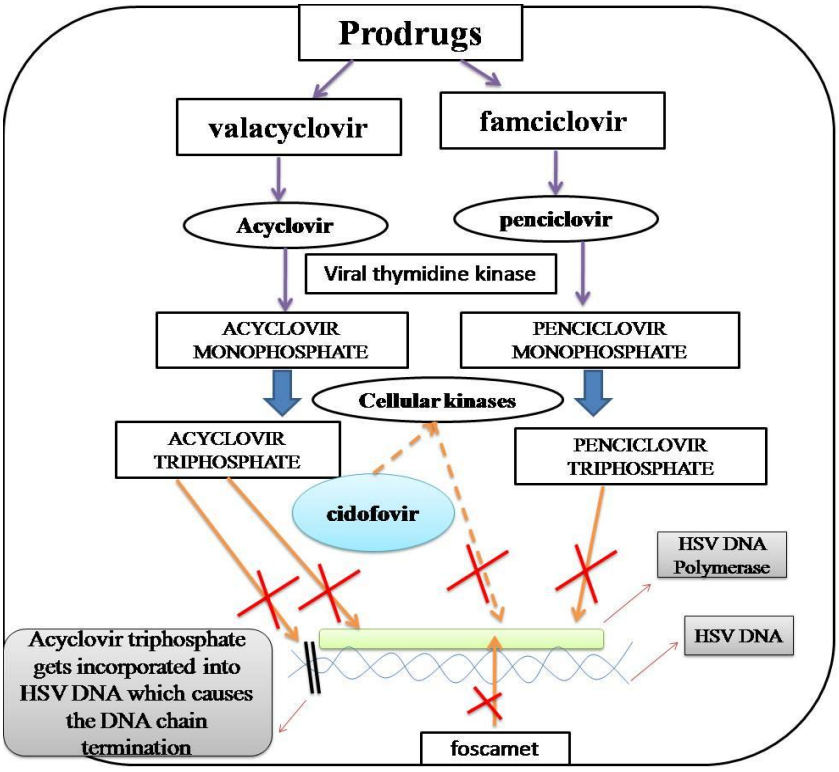

Figure No. 4: Mechanism of action of the anti-herpes simplex virus and the role of prodrugs in controlling the virtual infection [74].

Corticosteroids:

These medications can help treat skin conditions such as vasculitis and inflammatory diseases like psoriasis and eczema [75]. Topical steroids prefer by Dermatologists to avoid side-

effects, for treat skin conditions it is used including eczema and this medication come in various form such as lotion, creams, ointment [76, 77, 78].

Glucocorticoids:

It is a type of corticosteroid hormone; it was effective in suppressing and reducing inflammation in the immune system. The immune system responds with harmful substances by the way of inflammation, and also the healing process, trauma [79]. Topical glucocorticoids are a choice for treating many types of inflammatory dermatoses [80].

Mechanism of action of Lipocortin 1 in skin

LC1 Staining was present in the sweat glands of the epithelium of human and pig skin [81, 82]. The different pools have been identified as LC1 shown in fig no 5. LC1 is found in the skin of the upper and middle layers of epidermal cells within the cytoplasm [83]. LC1 movement of the cell membrane is shown active protective response in skin diseases. LC1 binding to phospholipids they decreasing the production of inflammatory prostanoid [84, 85, 86], and also LC1 movement was EGF receptor/tyrosine kinase increases in which LC1 substrate [87]. Therefore, it could be the net availability of LC1 for fact reduced [88]. Almost all these studies have mentioned concentration so far on the basal LC1 expression of skin disease. LC1 mediator of the anti-inflammatory effects in topical GC therapy [88, 89].

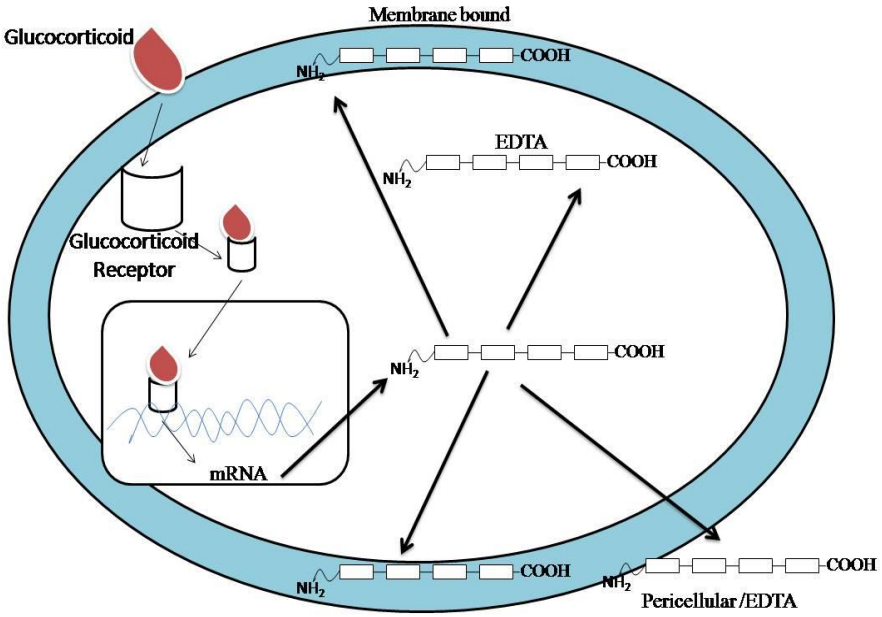

Figure No. 5: A representation of the Cellular distribution of Lipocortin 1 in the sweat gland in the skin [90].

DISCUSSION

Skin is the largest organ of the whole body. The skin protects from invasive germs and viruses and affected environmental factors like sunlight and cold. It maintains regulating body temperature and responsible for the sense of touch. Some skin diseases psoriasis, cancer, acne, rashes. Allopathic medication is good for the acutely injured and also when crisis. Patients can suffer for some common skin problems as self-limited and irrelevant. The topical medication frequently used of topical drugs such as masking of skin diseases and bacterial resistance [91]. In India, skin diseases severity growing is further emphasized by WHO World Health Organization, skin disease under non-communicable diseases. In year of 2013 10 percent prevalence rate population [92]. Some allopathic agents which used in skin diseases and their mechanism of action. Amphotericin B used in formulation Injection 10mg, 25mg, 50mg and Selective fungicide against fungal sterol and in fungal membrane binds to ergosterol, by forming amphotericin B pores leakage by alter permeability and cell death [93]. Flucytosine (5-FC) formulation used as Capsule 250mg, 500mg taken up drug by fungal cell via converted cytosine deaminase, DNA synthesis inhibition, thymidylate synthase inhibition, fluorouracil (5-FU). Clotrimazole formulation used as a lotion, cream Gel 1%, Powder, Tablet 100mg and ergosterol local irritation inhibited allergic reactions and applicable topical synthesis for leading the fungal cell impaired membrane and activity [94]. Fluconazole Terbinafine as the formulation of Tablet 50mg to 250mg. Inhibition of squalene epoxidase. Tolnaftate formulation as Cream, Lotion 1%, and squalene epoxidation inhibited. Undecylenic acid formulation used as Ointment salicylate 2.5%, Zinc undecenoate 8%. This organic acid interacts with components in the cell membrane [95]. Skin Rash is a common symptom in people suffering from coronavirus [96]. Hence a new wave of SARS and coronaviruses have opened new research avenues to look out for drugs for treating skin conditions raised due to coronavirus infections.

SUMMARY

This review showcases the molecular mechanisms involved in skin conditions and their treatments. The data were selected from research papers in databases such as EMBASE, Europe PMC, Google Scholar, PubMed, Merck Index, MedlinePlus, Indian citation index, Science Open, PubMed, Scopus, Semantic Scholar, World Wide Science, Shodhganga, Science Direct. Here we have described the mechanism of action some drugs such as Retinoids. Most cellular and molecular pathways have been discussed in this paper which

outlines the role of anti-inflammatory, anti-fungal, anti-viral medications in treatment of skin conditions. Some available marketed products from treating skin conditions are Ketoconazole (Nizoral), Clotrimazole (Lotrimin), and terbinafine.

Future prospective

The mechanism of actions of the allopathic drug must be studied deeply to understand the disease conditions which will help in formulating new derivatives for treating various diseases of the skin. New research must also be directed on understanding the mechanism of action of coronaviruses on causing skin rashes on people suffering from the virus during and post infections and similar drugs must be studied to work effectively in these conditions.

List of Abbreviations:

Ultraviolet = UV

Epidermal parasitic skin diseases = EPSD

Hookworm-related cutaneous larva migrans = HrCLM

Retinoic acid receptor called = RARs

Retinoid X receptors = RXRs

Superficial fungal infection = SFI

Reactive oxygen species = ROS

All-trans retinoic acid = ATRA

Cellular retinoic acid binding protein 2 = CRABP2

Mouse double minute 2 = MDM2

Herpes simplex virus infection = HSV

Lipocortin 1 = LC1

Conflict of interest

The author no conflict of interest expresses.

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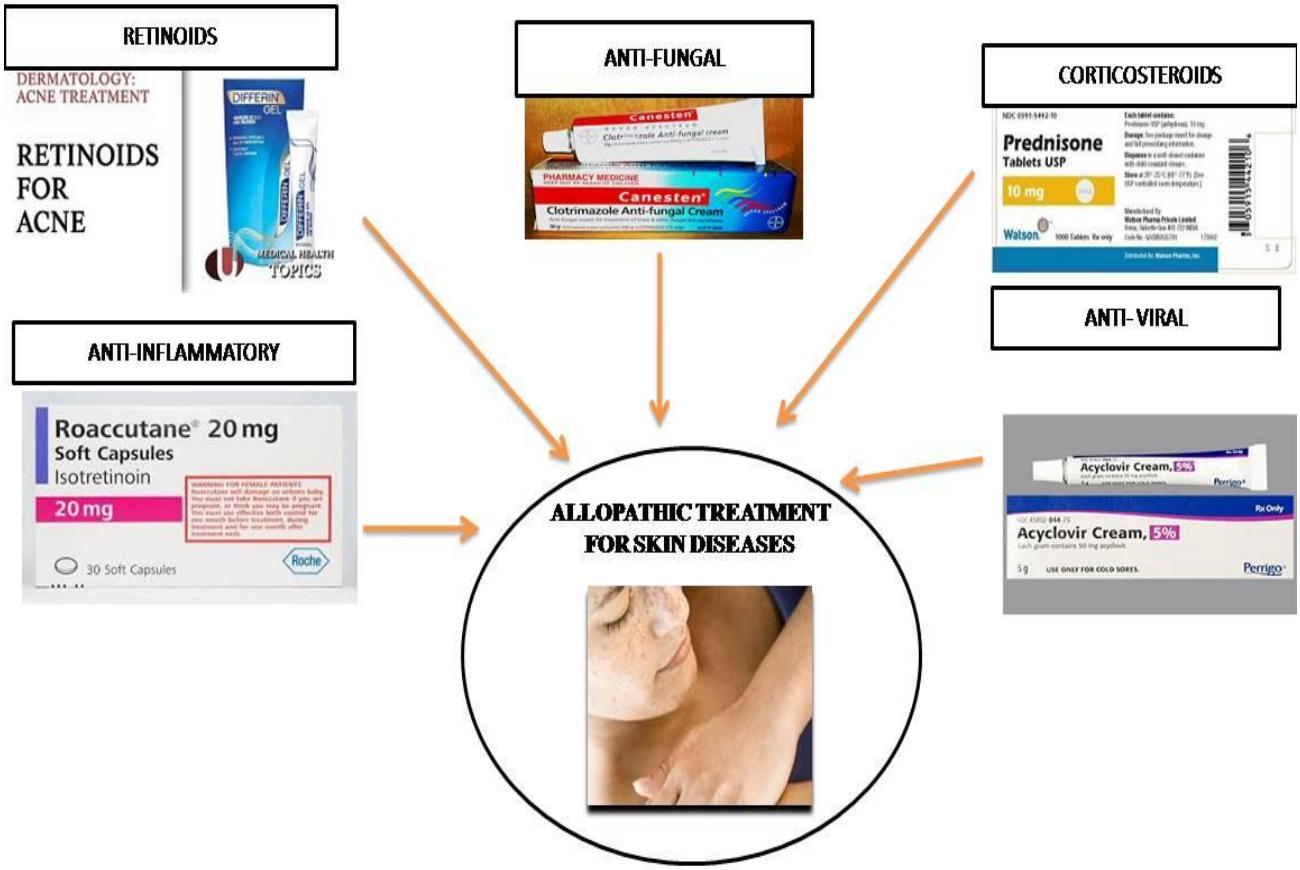
Graphical Abstract



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