



Drug nanocarrier, the future of atopic diseases: Advanced drug delivery systems and smart management of disease



Mei Shao^a, Zahid Hussain^{b,*}, Hnin Ei Thu^c, Shahzeb Khan^d, Haliza Katas^e,
Tarek A. Ahmed^f, Minaketan Tripathy^b, Jing Leng^a, Hua-Li Qin^{a,*},
Syed Nasir Abbas Bukhari^a

^a Department of Pharmaceutical Engineering, School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, 205 Luoshi Road, Wuhan, 430070, PR China

^b Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, Bandar Puncak Alam, 42300, Selangor, Malaysia

^c Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000, Cheras, Kuala Lumpur, Malaysia

^d Department of Pharmacy, University of Malakand, Chakdara, Dir (L), KPK, Pakistan

^e Centre for Drug Delivery Research, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300, Kuala Lumpur, Malaysia

^f Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

ARTICLE INFO

Article history:

Received 8 April 2016

Received in revised form 15 August 2016

Accepted 18 August 2016

Available online 20 August 2016

Keywords:

Atopic dermatitis

Advanced nanocarrier-based therapies

Liposomes

Ethosomes

Solid lipid nanoparticles

Nanoemulsion

Polymeric nanoparticles

ABSTRACT

Atopic dermatitis (AD) is a chronically relapsing skin inflammatory disorder characterized by perivascular infiltration of immunoglobulin-E (IgE), T-lymphocytes and mast cells. The key pathophysiological factors causing this disease are immunological disorders and the compromised epidermal barrier integrity. Pruritus, intense itching, psychological stress, deprived physical and mental performance and sleep disturbance are the hallmark features of this dermatological complication. Preventive interventions which include educational programs, avoidance of allergens, exclusive care towards skin, and the rational selection of therapeutic regimen play key roles in the treatment of dermatosis. In last two decades, it is evident from a plethora of studies that scientific focus is being driven from conventional therapies to the advanced nanocarrier-based regimen for an effective management of AD. These nanocarriers which include polymeric nanoparticles (NPs), hydrogel NPs, liposomes, ethosomes, solid lipid nanoparticles (SLNs) and nanoemulsion, provide efficient roles for the target specific delivery of the therapeutic payload. The success of these targeted therapies is due to their pharmaceutical versatility, longer retention time at the target site, avoiding off-target effects and preventing premature degradation of the incorporated drugs. The present review was therefore aimed to summarise convincing evidence for the therapeutic superiority of advanced nanocarrier-mediated strategies over the conventional therapies used in the treatment of AD.

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* Corresponding authors.

E-mail addresses: zahidh8589@gmail.com, zahidh85@yahoo.com (Z. Hussain), qinhuali@whut.edu.cn (H.-L. Qin).

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1. Introduction

Atopic dermatitis (AD) is a type of chronic eczematous skin inflammation characterised by an excessive infiltration of IgE, T-lymphocytes and mast cells. The common symptoms of AD include dry inflamed skin, intense pruritus, itching, skin lichenification, sleep disturbance and emotional distress [1,2]. It is a common, often long-lasting skin disease that affects a large percentage of the world's population. Recent studies demonstrated that the prevalence of AD is continuously increasing while affecting 15–30% of urban children and 1–3% of adults [3–5]. AD is not restricted to a specific age group, but it can occur in any age. It usually appears during early childhood and periodically relapses throughout the life of a patient [6].

The prime cause of AD is unclear yet; however, it is considered to have a multifactorial pathogenesis accompanying genetic defects [7–9], immune dysregulation, environmental triggers and impaired skin barrier integrity being the principal causative factors [10–12]. For many years, an abnormal T-helper cells (T_H2) adaptive immune response to largely innocuous environmental irritants was considered as the major dynamic in the development of AD [13–15]. Other studies proposed that the skin barrier defects and an abnormal immune response are highly plausible mechanisms underline atopic diseases [16–18].

To date, there is no absolute therapy for the treatment of AD owing to a complex pathogenic interplay between patient's susceptible genes, skin barrier abnormalities and immune dysregulation. Nevertheless, various pharmacological and non-pharmacological approaches including, identification and avoidance of causative allergens, skin hydration (e.g., taking baths or using moisturisers), topical anti-inflammatory or immunosuppressant therapies, antipruritic medications, and anti-bacterial measures (e.g., taking bleach baths, applying antiseptics or disinfectants) have been reported very effective either to be used alone or in combination for the treatment for mild-to-severe AD. The mild clinical cases can potentially be managed with skin care or emollient therapy only; however, moderate-to-severe patients require intensive therapy. It is worth mentioning that these approaches can achieve control over AD with varying degree; however, several challenges associated with the use of these conventional therapies which include lack of target-specific delivery [19], systemic toxicity, therapy adherence, and patient compliance are still debatable.

In last two decades, scientific focus has been changing for the development of novel target-specific delivery systems while optimising therapeutic outcome as well as to minimise off-target effects. These advanced strategies include iontophoresis [20,21], liposomes [22–25], ethosomes [26–28], SLNs [29–31], nanoemulsion [32,33] and polymeric NPs [34–37]. Iontophoresis is the process of administering ionic drug molecules across the biological membranes for biological action. This method has been well-employed for the delivery of a number of drugs such

as methylprednisolone succinate, dexamethasone phosphate and antibiotics in the treatment of atopic diseases and other dermatological disorders [20,21]. In contrast to iontophoresis, liposomes have gained remarkable attention as the small spherical vesicles which are composed of cholesterol and natural phospholipids. Owing to their ultra-small size, surface charge, high encapsulation efficiency, biocompatibility, biodegradability, and amphiphilic nature, liposomes are among the promising vesicular delivery systems for the target-specific delivery of the therapeutic payload [22–25]. Ethosome is another novel vesicular delivery system which have demonstrated remarkable features concomitant to their high deformability. The pharmacological moieties can be transferred across the physicochemical barrier of the skin via ethosomal delivery system more efficiently than the traditional liposomes [26–28]. Ethosomes-based formulations have shown greater efficiency for the target-specific delivery of drugs into the epidermis and dermis compared to the liposomal formulations [38–40]. SLNs are another type of nanocarrier that improves transcutaneous absorption of therapeutics for the treatment of skin inflammatory diseases [29–31]. Small particle size and unique physicochemical properties of the SLNs play important roles in achieving site-specific delivery of the therapeutic payload [29–31]. SLNs cause greater improvement in the permeation of drugs across the SC and their longer retention into the epidermis and the dermis compared to the conventional delivery [30,31]. Nanoemulsions have also been developed to overcome the problems of impaired penetration of drugs following the topical application. Despite the nanosized range, a special character of nanoemulsion is their positive charge which further facilitates the penetration of encapsulated drug molecules into the deeper layers of the skin [32]. The physicochemical interaction between positively charged nanoemulsion and negatively charged corneocytes of the SC result into enhanced transcutaneous permeation, longer retention time and improved bioavailability of drugs [33]. In recent years, polymeric NPs have also gained remarkable attention of the scientists both from academia and R&D sectors. The success of these nanocarriers is due to their ultra-small size, surface charge, high entrapment efficiency, biocompatibility and biodegradability [41–43]. In addition, these delivery systems can; (1) prevent the premature degradation of the labile compounds, (2) provide sustained delivery of the encapsulated drugs, (3) provide efficient triggered release of the therapeutic payload in response to change in pH, presence or absence of enzymes and other physiological stimuli [41–43], 4) increase localised delivery of the drugs and reduce their systemic toxicity, and 5) prevent off-target effect [26–28]. These novel delivery systems have also been proposed to augment percutaneous delivery of the drugs without permanent damage to the SC [44,45].

Despite numerous pharmaceutical and therapeutic benefits, nanocarriers do have a lot of drawbacks and limitations [46]. For instance, small particle size and large surface area of the nanocarri-

ers can cause particle agglomeration and making physical handling difficult. Nanocarrier-drug conjugates can also be phagocytosed by the immune guard cells whereas their intracellular degradation products may cause cytotoxic effects. Limitations to using nanocarrier-based delivery systems are also due to their low drug loading capacity and poor ability to control the size distribution index. Scarcity of technological facilities required for the development of nanocarriers of acceptable quality, also limit their utility. Despite these drawbacks and shortcoming, nanocarrier-mediated delivery systems attained remarkable recognition because of their tremendous advantages over the conventional delivery systems. The current review was therefore aimed to summarise the contents and evidence for the pharmaceutical and therapeutic advantages of the nanocarrier-mediated therapies in the treatment of atopic diseases. The therapeutic superiority of the nanocarrier-mediated systems in accomplishing site-specific delivery of drug, mitigating systemic toxicity, and to optimise therapeutic outcomes in the treatment of atopic diseases has been critically discussed.

2. Skin

Skin is the largest organ of the integumentary system that shields the internal body structures from the hostile external environment of varying pollution, humidity, radiations and the temperature [47]. There are three structural layers of the skin: the epidermis, dermis and the subcutis: each of them play distinct roles for the overall utility of the skin. Other structures such as nails, hairs, sweat glands, sebaceous glands, and apocrine glands also play important roles in maintaining skin homeostasis. Epidermis, the outermost layer of the skin, forms a shielding barrier over the body surface and is responsible for maintaining homeostasis and prevents entry of pathogens into the body. The skin also plays significant roles in heat regulation, controlling evaporation of water, excretion, and absorption [47].

Keratinocytes are the chief cells (constituting 80% of the epidermis), while Langerhans cells (LCs), Merkel cells and melanocytes are also resident in epidermal layers of the skin. Keratinocytes replicates through mitotic division and the progeny cells continuously move up from the stratum basale (basal layer of the epidermis) to the stratum corneum (SC) while undergoing structural changes during multiple stages of cell differentiation [48]. As a result of these cyclic proliferating and differentiation phases, keratinocytes develop characteristic cell-junctions (known as corneodesmosomes) between each other and synthesise lipid matrix and keratin proteins which contribute to formation of extracellular matrix (ECM) and provide mechanical strength to the skin. The degradation of corneodesmosomes results in shedding of keratinocytes – a process called desquamation. The continuous outward movement of keratinocytes build up outmost layer of the epidermis, the SC. It mainly comprised of three lipid components: fatty acids, ceramides, and cholesterol. The main function of the SC is to act as a physicochemical barrier to protect underlying body structures from chemicals and mechanical stress, prevent abnormal water loss, dehydration, and microbial infection. Another important protein playing important role in regulating integrity of the SC and preventing transepidermal water loss is filaggrin [48]. When the moisture content of the skin reduces, filaggrin is broken down into the free amino acids by specific proteolytic enzymes in the SC. These free amino acids, together with other components such as salts, lactic acid, and urea play important roles in regulating water level, keep skin moist and pliable due to their water-proofing ability.

The physicochemical barrier properties of the SC are of paramount importance to maintain internal homeostasis. The disruption of the SC increases the number of Langerhans cells, activate

T-lymphocytes and cause hypersensitivity reactions which may lead to the development of dermatological problems (e.g., psoriasis, AD, skin inflammation). It may also cause penetration of harmful substances such as allergens (e.g., house dust mite, pollens, or cat dander) into the body, which may induce stimulation of immune cascades. It is evident that the disrupted barrier function of the SC is among the prime player in the development of atopic diseases [48]. In comparison to healthy human skin, atopy skin display lesser lipid contents, phospholipids, and sterol esters in the SC [48]. The lower phospholipid contents are likely due to decreased sphingolipid content (sphingomyelin) and ceramide fraction. Thus, the disruption of SC, caused by either genetic defect or environmental factors, may provoke pathological stresses in the skin and may lead to the development of inflammatory skin disorders such as psoriasis or AD [48].

3. Dermatitis

Dermatitis (an inflammation of the skin) is a chronic, relapsing, pruritic and exudative dermatosis [3,4]. The prevalence of dermatitis is continuously increasing over the past few decades [2]. In vast majority of patient, mild forms of dermatitis are characterised by pruritus, itchy, dry and red skin. The crusty scales, painful cracking skin, and blisters oozing fluid are the hallmark features of the serious/chronic dermatitis. The main cause of dermatitis is unclear yet; however, a dysfunctional interplay between the skin integrity and the immune system is considered as the prime cause for the development of this inflammatory skin disease [3]. Numerous factors which include seasonal allergies, low humidity, exposure to harsh detergents, cold weather, and specific allergens, may cause sensitisation reactions particularly in individuals who have inherited atopic disease traits. The most common type of dermatitis is atopic dermatitis (AD), a persistent dry skin condition. In mild AD, the skin is dry, scaly, red and itchy; however, patients having severe disease might be presented with crusting and bleeding of the skin.

The pathophysiology of dermatitis underlines a complex interplay between susceptible genes, over-stimulatory immune system, and environment factors [3]. Most of the patients with dermatitis showed eosinophilia and abnormally increased serum IgE level. Moreover, increased serum levels of cytokines (IL-4, IL-5, and IL-13) and low levels of interferon-gamma (IFN- γ) is another hallmark feature of dermatitis. Marked epidermal oedema and the presence of LCs, inflammatory dendritic cells, and macrophages in the skin lesions are also evident in AD patients. The immunological display of dermatitis compared with healthy skin (uninvolved skin) is presented in Fig. 1.

3.1. Types of dermatitis

Based on the severity of skin inflammation, contributing factors and clinical spectrum, there are different types of dermatitis which include 1) allergic contact dermatitis, 2) atopic dermatitis, 3) irritant contact dermatitis, 4) neurodermatitis, 5) perioral dermatitis, and 6) seborrheic dermatitis [2]. The clinical presentation of different types of dermatitis is shown in Fig. 2.

3.1.1. Atopic dermatitis (AD)

AD (also known as atopic eczema) is a most prevalent type of dermatitis affecting both children and adults. It is not restricted to a specific age group, but it can occur in any age. It usually appears during early childhood and periodically relapses throughout the life of a patient. AD is characterised by persistent scratching, recurring rashes, itchy and dry skin, erythematous plaques, and small bumps (that look like blisters) that may ooze fluid in severe cases. The most susceptible parts of the body to develop AD-like skin lesions include elbows folds, backs of the knees, and front of the neck or face. AD

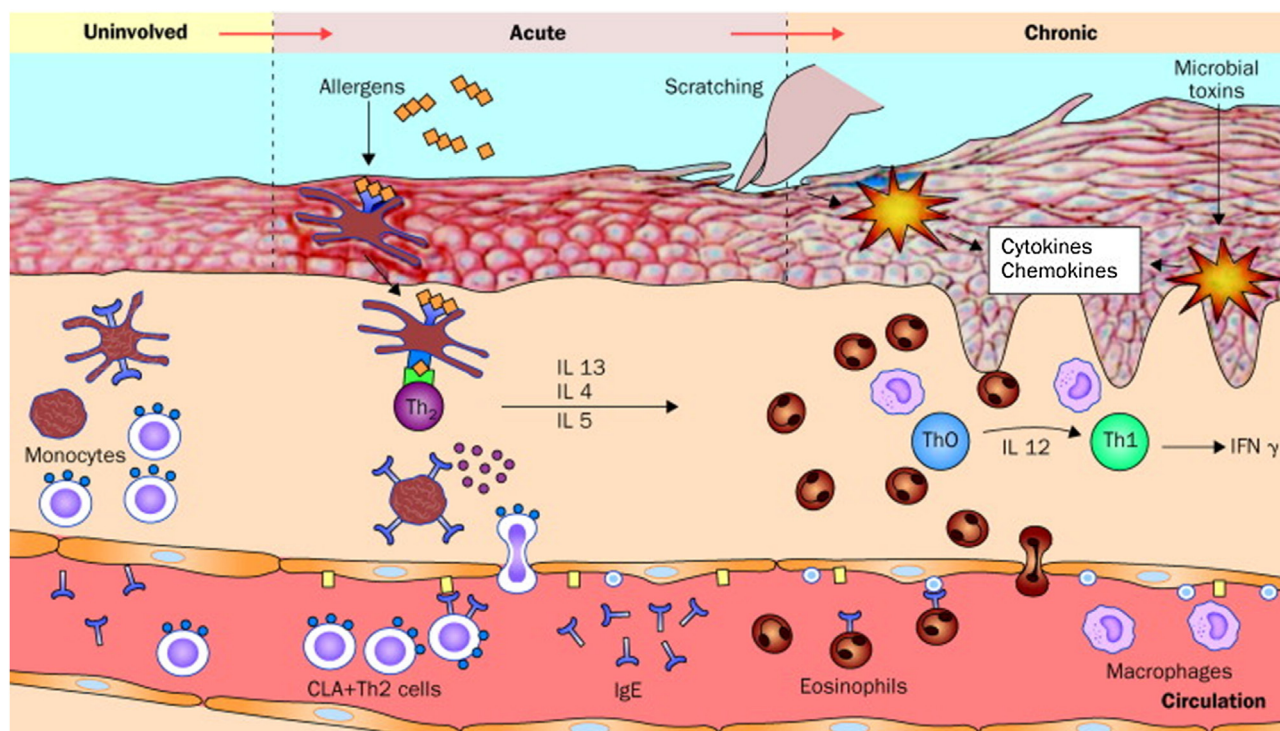


Fig. 1. Immunological pathways of dermatitis [14]. Reproduced and reprinted with the permission from Elsevier B.V. (Copyright © 2003) through Copyright Clearance Centre.



Fig. 2. Types of dermatitis based on clinical signs, symptoms and pathological causes.

tends to flare up periodically and then subside after a time, even up to several years. Genetic defect has been proposed as one of the prime causes besides the environmental (acquired allergens)

factors; though, the exact cause of AD is not well-understood yet. In AD, skin injury caused by physical scratching, exogenous allergens, or microbial toxins, is evident to activate keratinocytes to

produce pro-inflammatory cytokines [14]. These pro-inflammatory cytokines then induce various chemokines and adhesion molecules which lead to chemotaxis of leukocytes to the inflammatory sites. The cytokines produced by T_{H2} type lymphocytes (e.g., IL-4, IL-5, and IL-10) play major roles in the development of acute AD, and T_{H1} -type cytokines (e.g., IFN- γ) are most commonly involved in severe AD patients. Marked increase in IgE levels in the serum is a major hallmark feature of AD [2,3]. The clinical presentation of AD is shown in Fig. 2.

The cellular and biomolecular mechanism of AD is associated with an impaired interplay between susceptible genes, sensitising allergens, and immunological factors [14]. Most of the progress made in understanding the immuno-pathophysiology of AD is related to the raised concentration of IgE antibodies either due to the hypersensitivity reactions (intrinsic form) or sensitising allergens (extrinsic form). The immune-deficiency of T-lymphocyte is among the key factors contributing to the pathogenesis of AD [14].

4. Treatment of AD

4.1. Conventional therapies

4.1.1. Non-pharmacological approaches

Appropriate information about the disease activity, prevention of contributing factors, selected therapeutic regimen, and goals of treatment for the patients and caregivers have promising impact upon controlling the severity and progression of AD. The multi-factorial pathogenesis and the requirement of various (and sometimes rotating) non-pharmacological and pharmacological interventions demand the selection of a rational therapeutic regimen in order to achieve therapeutic outcomes and satisfactory patient compliance [51].

To date, there is no absolute consensus on whether or not patient with AD should follow a restrictive diet pattern [52,53]. It is evident that a number of food items which include eggs, cow milk, peanuts, wheat, and soy products can potentially cause or develop AD in susceptible patients. Controversies have also been reported on the role of breastfeeding in the development of AD in neonates [54,55]. The optimum skin care by regular use of emollients, use of skin hydrating regimen, and identification and eradication of specific and non-specific irritants also play striking roles to prevent disease progression. Topical moisturisers, with different composition of emollient, occlusive and humectant, are commonly used to reduce dryness of the skin and to prevent transepidermal water loss [56–59]. Typical signs and symptoms of AD such as erythema, fissuring, pruritus, and lichenification, are generally controlled by the regular application of moisturisers [60–62]. As such, the consistent use of moisturisers has become evident in preventing the development of AD in genetically susceptible infants [63].

Another exciting method to reduce the severity of symptoms of AD by providing soothing effect to the skin, is wet-wrap therapy (WWT) [64,65]. WWT is mainly used for acute symptomatic relief; however, it has also showed moderate efficacy to subside AD symptoms on areas of resistant dermatosis (e.g., thicker skin areas such as hands and feet). WWT shows anti-AD effects by maintaining skin hydration, increasing percutaneous penetration of topically applied drugs, and provide additional protective layer against intense scratching [66].

4.1.2. Pharmacological therapies

For many decades, topical corticosteroids (TCs) have been the majorly prescribed class of drugs for the management of AD in both adults and children [66–70]. They are typically prescribed for the treatment of AD patient who have failed to respond to other therapies. TCs are available in various strengths and formulations,

providing clinicians the substantial flexibility to choose rational drug regimen based on the severity and chronicity of the AD. The relative potency (class-1 (super-potent) to class-7 (least-potent)) of TCs is classified (according to USA classification system) based upon their capacity to cause vasoconstriction and blanching effect. The summary of the relative potencies of TCs and the available formulations is presented in Table 1. Despite the wide range potencies, greater choices are available in selecting suitable dose of TCs for the management of mild-to-severe forms of AD. Based on disease severity, some clinicians use a short burst of super-potent TCs to treat severe acute AD, followed by using least-potency agents [71,72]. As such, a greater caution needs to be exercised while using super-potent TCs on sensitive skin areas including face, neck, under armpits, and groin area where there is a higher probability of systemic and local side effects [73].

Other pharmacological agents used in the management of AD include topical calcineurin inhibitors (TCIs), anti-infective therapies, phototherapy, topical/systemic anti-histamines, and vitamin-D₃ analogue (Calcipotriol). TCIs have been well-recognised for alleviating AD-related symptoms in short-term (3–12 weeks) and long-term (up to 12 months) clinical trials in both adults and children [74–79]. The safety and efficacy of TCIs when applied on sensitive areas of the body (such as the face, under arms, groin area and skin folds) reveals their clinical prevalence over TCs [80–84]. Anti-infective therapy is also well-accepted in the treatment of AD that is aggravated due to infections caused by *S. aureus* [85,86]. It is estimated that skin lesions in about 76% of AD patients are colonised with *S. aureus*, which may further cause damage to the physicochemical barrier of the skin and aggravate the severity of disease [86]. Huang et al. (2009) demonstrated that the severity of AD can be reduced by taking baths containing sodium hypochlorite, which will suppress the growth and multiplication of *S. aureus* on to the infected skin lesions [86,87].

Phototherapy has also been reported an effective and well-tolerated therapeutic intervention for atopic individuals; however handful evidence regarding the safety of this method is lacking. A plethora of studies have reported that phototherapy, alone or in combination with TCs, showed promising effects in treating acute exacerbated AD [88–91]. The mechanism linked with anti-AD effects of phototherapy involves immunosuppression of key AD-responsible cells (T-lymphocytes) via inducing programmed cell death in them [92]. Scarcity of data showing anti-AD effects of topical antihistamines is also available, but due to inappropriate impact on overall disease severity, they have been precluding [93]. Moreover, the use of antihistamine also showed local side effects such as burning, stinging as well as may cause drowsiness [93,94]. Calcipotriol, a vitamin-D₃ analogue (available as topical 0.005% cream, ointment and solution), has also been used as a second-line agent in the treatment of moderate-to-severe atopic diseases [95,96]. Numerous studies have also demonstrated the therapeutic feasibility of immune-suppressants such as cyclosporine [96–99], azathioprine [100–103], IFN- γ [104,105], and methotrexate [106–109] in the management of AD [110,111].

As such, the critical review of the available evidence on the pharmacological effects of conventional therapy in the treatment of AD revealed that each of the therapies was also associated with unwanted local or systemic effects. Lack of target-specific delivery of drug molecules can be a reason for these unwanted effects. Moreover, the conventional therapies were found inefficient to deliver pharmacological moieties to the target site (into the epidermis and dermis) due to physicochemical barrier provided by the SC. In order to overcome these issues and to improve therapeutic outcomes and patient compliance, researchers both from academia and R&D (research and development) sectors have focused upon the devel-

Table 1
Relative potencies and available dosage form(s) of TCs employed in the treatment of AD.

Class	Relative potency	Drug(s)	Dosage form(s)	Formulation strength(s)
Class-I	Very high potency	Augmented betamethasone dipropionate	Ointment	0.05%
		Diffurorone diacetate	Ointment	0.05%
		Clobetasol propionate	Cream, foam, ointment	0.05%
		Halobetasol propionate	Cream, ointment	0.05%
		Augmented betamethasone dipropionate	Cream	0.05%
Class-II	High potency	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05%
		Desoximetasone	Cream, ointment	0.1%
		Amcinonide	Cream, lotion, ointment	0.05%
		Desoximetasone	Gel	0.05%
		Diffurorone diacetate	Cream	0.05%
		Fluocinonide	Cream, gel, ointment, solution	0.1%
		Mometasone furoate	Ointment	0.5%
		Triamcinolone acetonide	Cream, ointment	0.1%
		Halcinonide	Cream, ointment	0.1%
		Betamethasone valerate	Cream, foam, lotion, ointment	0.1%
		Fluticasone propionate	Cream	0.05%
		Clocortolone pivalate	Cream	0.1%
		Desoximetasone	Cream	0.05%
Class-III-IV	Medium potency	Fluocinolone acetonide	Cream, ointment	0.025%
		Flurandrenolide	Cream, ointment	0.05%
		Fluticasone propionate	Ointment	0.005%
		Triamcinolone acetonide	Cream, ointment	0.1%
		Mometasone furoate	Cream	0.1%
		Hydrocortisone butyrate	Cream, ointment, solution	0.1%
		Hydrocortisone valerate	Cream, ointment	0.2%
		Hydrocortisone probutate	Cream	0.1%
		Prednicarbate	Cream	0.1%
		Fluocinolone acetonide	Cream, solution	0.01%
		Alclometasone dipropionate	Cream, gel, foam, ointment	0.05%
		Desonide	Cream, ointment	0.05%
		Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1%
Class-V	Lower- medium potency	Hydrocortisone acetate	Cream, ointment	0.5–1%
		Dexamethasone	Cream	0.1%
Class-VI	Low potency	Fluocinolone acetonide	Cream, solution	0.01%
		Alclometasone dipropionate	Cream, gel, foam, ointment	0.05%
		Desonide	Cream, ointment	0.05%
Class-VII	Lowest potency	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1%
		Hydrocortisone acetate	Cream, ointment	0.5–1%
		Dexamethasone	Cream	0.1%

*Adopted from Ference JD, Last AR. Choosing topical corticosteroids. *Am Fam Physician*. 2009 15;79(2):135–40 [165].

opment of novel targeting strategies which hold great promise to improve and enhance the target-specific delivery of the drugs.

5. Advanced targeted therapies: drug nanocarriers

In last two decades, researchers have focused upon the development of nanocarrier-based therapies to achieve target-specific delivery of drugs while minimising their off-target effects. These nanocarriers include liposomes, ethosomes, SLNs, nanoemulsion, and polymeric NPs. In contrast to conventional therapies, advanced targeted therapies have been well-reported in improving therapeutic outcome and reducing the off-target drug effects [34–37]. The therapeutic superiority of the nanocarrier-mediated techniques has also been well-reported in terms of their greater potential for achieving site-specific delivery as well as their remarkable control on the severity and progression of the disease, in comparison to the convention therapies.

The term nanocarrier refers to the structures/devices ranging from 1 to 1000 nm; however, desired therapeutic benefits, avoidance of off-target effects, and optimal localised delivery of drugs is achieved through the use of nanocarriers <200 nm in size. They offer a large numbers of advantages over the conventional approaches which include, 1) enhanced dissolution rate and permeability of poorly water-soluble drugs [112], 2) improved cellular uptake which make them a successful delivery tool for many bioactive molecules [113,114], and 3) reduced off-target effects by achieving target-specific delivery of the therapeutic payload [115].

Due to the presence of rate limiting physicochemical barrier layer (SC) into the skin which acts as protective layers and is

impermeable to vast majority of drugs, there is a high demand for the development of novel drug delivery systems that can penetrate across the physicochemical barrier of the skin and delivery their therapeutic payload to the target tissues. Numerous studies have shown the efficiency of the nanocarrier-mediated delivery systems in delivering their payloads to the target organs and treating various dermatological disorders [116–118]. Among several nanocarrier-mediated interventions, SLNs, liposomes, ethosomes, nanoemulsion, and polymeric NPs have been well-reported for topical and transdermal applications [112,119,120].

While developing drug delivery systems for dermatological disorders (e.g., skin inflammation, AD, psoriasis, or skin cancers), different features of the compromised skin should be considered. When apply to the healthy skin, the nanocarriers-based delivery systems penetrate through the SC and hair follicle canals and release their contents (as shown in Fig. 3A); however, in infected, broken or damaged skin where the integrity of the SC is compromised, nanocarrier-based systems might cross the uppermost layers of the skin and directly enter into various layers of the skin (as shown in Fig. 3B).

Numerous physical and pharmaceutical methods have been employed to deliver drug contents across the SC which include disruption of the SC by using adhesive tapes [121], utilizing permeability enhancers to physically alter barrier properties of the skin [122,123], or using active carrier techniques (drug nanocarriers) [124]. Most of these methods were tested to evaluate the diffusion of therapeutic payload across the SC after their topical application; though among all, only nanocarrier-mediated therapies enabled to cross the intact or damaged animal or human skin [125,126]. These

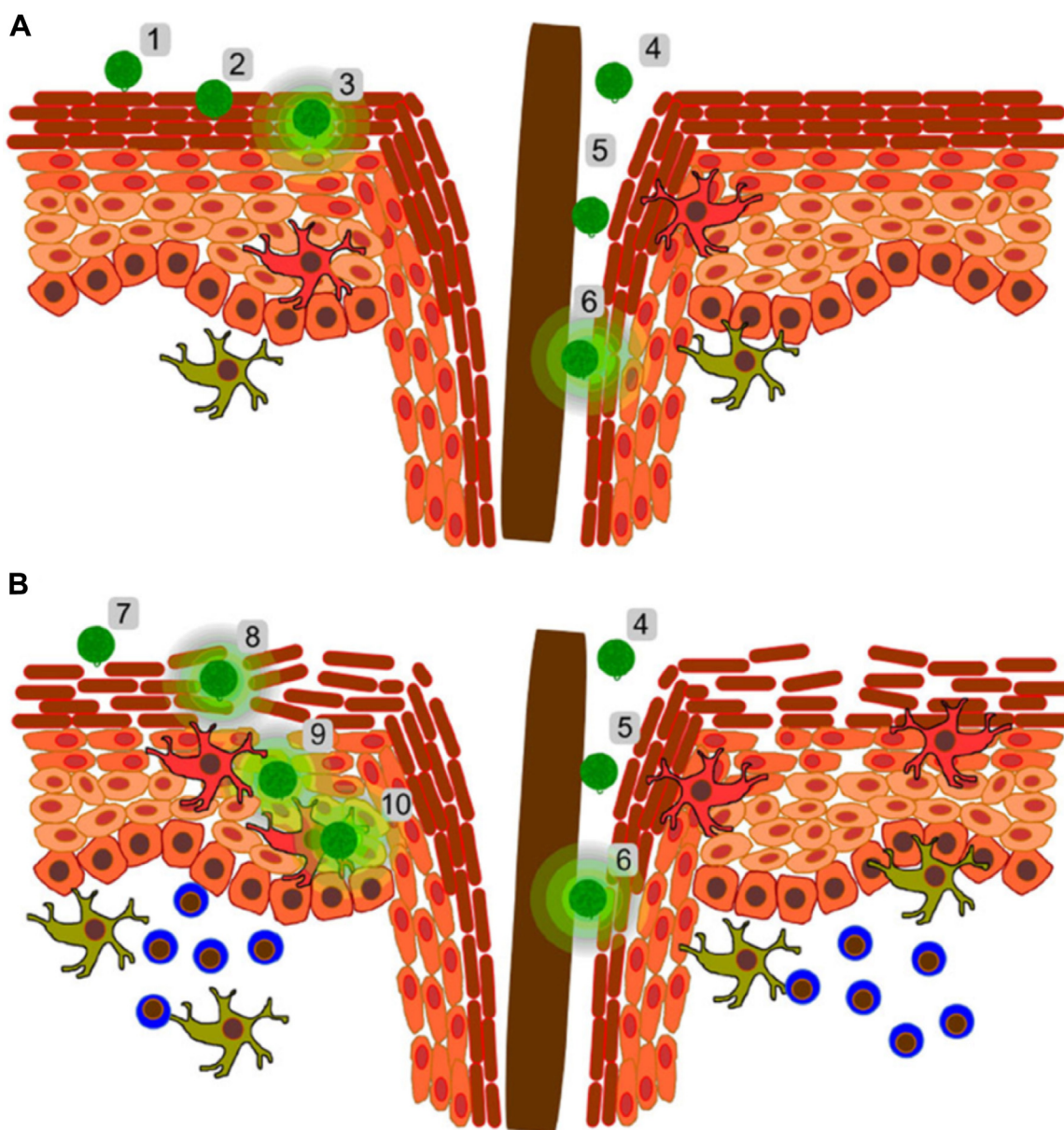


Fig. 3. Skin penetration of polymeric nanocarrier and drug release in (A) healthy skin and (B) hypothesis of nanocarrier-based system behaviour in broken and damaged skin.

(A) When the skin barrier is intact, topically applied carriers interact with the skin surface (1,4) and accumulate in the SC (2) or in the hair follicle canal (5). There, they degrade and/or release the loaded substances (3,6). (B) In inflammatory or broken skin, topically applied delivery systems may interact with damaged skin surface (7), penetrate across the broken SC (8), enter into the skin viable layers (9), or can be taken up by immune cells (10) [109]. Reproduced and adopted with the permission from Rancan et al. (2013) (Copyright © 2013).

studies have well-explained the pharmaceutical and therapeutic feasibility of the nanocarrier-based delivery systems in optimising drug permeability across the SC both in healthy and inflamed skin [126,128]. The interaction between nanocarrier-based systems and the targeted tissues and the alternation of the epidermal tight-junctions due to the swelling of the tissue were proposed as the possible mechanisms describing the pharmaceutical significance of the nanocarrier systems. The therapeutic superiority of the nanocarrier-based therapies for the treatment of AD is discussed in the following sections, in comparison to the conventional therapies.

5.1. Liposomal delivery system

Liposomes are composed of phospholipids, which self-enclose to form spheres of lipid bilayers and an aqueous core within the

bilayers. Amphiphilic in nature, the phospholipids result in the formation of polar shells in aqueous solutions due to the hydrophobic effect of the hydrophobic acyl chains with the surrounding aqueous medium. This is a thermodynamically stable architecture which further strengthened due to hydrogen bonding, van der Waals forces (which keep the long hydrocarbon tails together) and other hydrophobic interactions, which are responsible for the formation of lipid bilayers. Because of the presence of an aqueous core and a lipid bilayer, liposomes are versatile delivery systems that can incorporate hydrophilic as well as hydrophobic molecules. The solubility and the *in vivo* fate of the encapsulated drug molecules is dependent on the liposomes employed. The promising advantages of these nanocarriers include, 1) improved solubility of the encapsulated drugs, 2) prevent chemical and biological degradation of therapeutic payload under storage conditions and during

patient administration, 3) reduced off-target effects and toxicity of encapsulated drugs, thus improving the efficacy, 4) versatility when chemically modified with attached specific surface ligands for targeting, and 5) compatibility with biodegradable and non-toxic materials. These excellent properties of liposomes have led to many successful applications of these delivery systems [129–133].

The degree of success of percutaneous formulations is based on overcoming the SC barrier. Several studies have shown the significance of liposomal delivery system in enhancing the penetration of the therapeutic payload across the SC and improving the permeation flux [24,134,135]. The increased permeation of pharmacological agents in the target tissues result into greater efficacy and improved therapeutic outcomes and patient compliance. As such, Kim et al. (2009) developed elastic liposomes (EL) for the topical delivery of IL-13 antisense oligonucleotides (IL-13 ASO) [134]. They also performed animal studies to evaluate therapeutic significance of the liposome-based delivery system in reducing the severity of AD [134]. Kim and co-workers demonstrated dose- and ratio-dependent effect of IL-13-ASO-loaded EL in the inhibition of IL-13 in treated animals, in comparison to control groups. A greater decrease in the levels of IL-4 and IL-5 was observed in animals treated with IL-13-ASO-loaded EL formulation. Animals treated with IL-13-ASO-loaded EL formulation have also shown marked decrease in infiltrated inflammatory cells into various skin layers. Based on these findings, Kim and colleagues proposed that liposomes-based IL-13-ASO formulation can be used effectively in treatment of AD and other immune diseases associated with increased levels of IL-13. Though the suitability of liposomes to enhance the delivery of drugs into the deeper layers of the skin has been extensively studied, but, the underlying mechanism(s) is/are not fully understood. This can be explained based on the fact that the structure of liposomes mimics the organised lipid structure of the SC [135–137]. This structure offers an appropriate tool to achieve a precise vehiculation of liposomes that modifies water barrier properties of the skin.

The pharmaceutical significance and therapeutic feasibility of the liposomal delivery system was also evaluated by analysing ex vivo drug permeation across the skin, hydration level of skin and in vivo efficacy for the treatment of AD-like skin lesions [138–140]. Jung et al. developed liposomal hydrogel for transcutaneous delivery of adenosylcobalamin, a vitamin B₁₂ derivative [138]. The suitability of this delivery system was evaluated by examining the therapeutic effects of adenosylcobalamin in reducing the severity of AD using an NC/Nga murine AD model. Results demonstrated significant anti-AD efficacy of adenosylcobalamin-loaded liposomal hydrogel and showed remarkable reduction in dermatitis scores of AD-like skin lesions, dorsal skin thickness, parakeratosis, and total serum IgE levels in a concentration-dependent manner, in comparison to the control groups [138]. Kang et al. also reported the significance of liposomal-aided topical delivery of hirsutenone (HST), a naturally occurring immune-regulator, in the management of AD-like skin lesions [139]. They demonstrated that elastic liposomal (EL)-system showed remarkably higher permeation flux of HST across the skin, in comparison to the conventional cream. The effectiveness of liposomal-incorporated HST in the treatment of AD-like skin lesions was also assessed by using AD-induced NC/Nga mouse model (as shown in Fig. 4) [139]. HST-loaded-EL formulation showed a greater improvement in the severity index of AD-like skin lesions and other immune-related effects such as levels of cyclooxygenase-2, nitric oxide synthase, IL-4, IL-13, IgE, and eosinophils. These results were in agreement with previous studies in which liposomal delivery systems were used for the delivery of taxifolin glycoside (TXG) [140] and oregonin (ORG) [141]. The appropriateness of the liposomal delivery system was assessed in term of ex vivo drug permeation efficiency, skin hydration capacity and in vivo efficacy for the treatment of AD. These studies indicated

remarkable improvement in skin hydration levels and significant reduction in transepidermal water loss (TEWL). Moreover, the mice groups treated with TXG- and ORG-loaded EL formulations exhibited greater recovery in the barrier integrity of the SC and TEWL, in comparison to the group and vehicle groups. The anti-AD effect of EL formulations was further harmonised by showing their regulatory effects on serum IL-4, IgE, and IFN- γ [140].

5.2. Ethosomal delivery system

Ethosome is another novel vesicular delivery system that reveals remarkable features concomitant to its higher deformability. The pharmacological moieties can be transferred across the physico-chemical barrier of the skin via ethosomal delivery system more efficiently compared to the conventional liposomes [26–28,142]. Many researchers proposed that ethanol; one of the prime adjuvants in ethosomal formulations, plays a key role in enhancing transcutaneous penetration of the incorporated drugs by their rapid permeation through the skin [143,144]. In addition, propylene glycol, an extensively used adjuvant of ethosomes, was reported to work synergistically to enhance the penetration of drugs applied through the topical route [145].

Many researchers have evaluated the pharmaceutical applicability of the ethosomal delivery system in improving the permeation of drugs into the deeper skin layer (in the dermis) and their therapeutic significance in treating AD-like skin lesions [38–40]. Li et al. developed tacrolimus-loaded ethosomes and demonstrated a greater loading efficiency compared to the traditional liposomes [38]. In addition, the amount of tacrolimus retained in the epidermis and dermis after the topical application of ethosomal formulation was significantly higher, indicating a greater potential of this delivery system to accomplish target-specific delivery of drugs [38]. Li and co-workers have also demonstrated the remarkable potential of tacrolimus-loaded ethosomes in reducing the severity of AD in BALB/c mice. In this study, AD-like skin lesions were created by the topical application of 2,4-dinitrofluorobenzene [38]. A greater reduction in the number of infiltrated mast cells at the site of inflammatory reactions was demonstrated, which emphasise a remarkable efficacy of the ethosomal delivery system to alleviate skin inflammatory reactions. Goindi et al. on the other hand, also revealed the pharmaceutical and therapeutic significance of the ethosomal delivery system by conducting ex vivo and in vivo studies [39]. The permeation analysis indicated a highest permeation flux and the amount of drug retained into the skin in case of ethosome-based delivery of cetirizine, in comparison to the conventional formulation [39]. They have also assessed in vivo efficacy of cetirizine-loaded ethosomes in reducing dermatitis scores, scratching index, erythema intensity, skin hyperplasia and dermal eosinophil count [39]. Goindi and co-workers demonstrated that ethosome-based delivery systems can be used for an effective delivery of cetirizine for the treatment of AD [39]. These results were also supported by another study in which levocetirizine-loaded ethosomal delivery system was developed for the treatment of AD-like skin lesions [40]. The data obtained highlighted that ethosomal formulation was highly efficacious in reducing itching score, eosinophil count and erythema intensity compared to the conventional formulation [40].

5.3. Solid lipid nanoparticles (SLNs)

Small particle size and unique pharmaceutical properties of the SLNs signify their suitability for the site-specific delivery of drugs [146,147]. SLNs have been pharmaceutically characterised for in vitro drug release profile and percentage of drug flux across the biological membranes. SLNs showed greater improvement in the permeation of tacrolimus across the SC and higher retention of

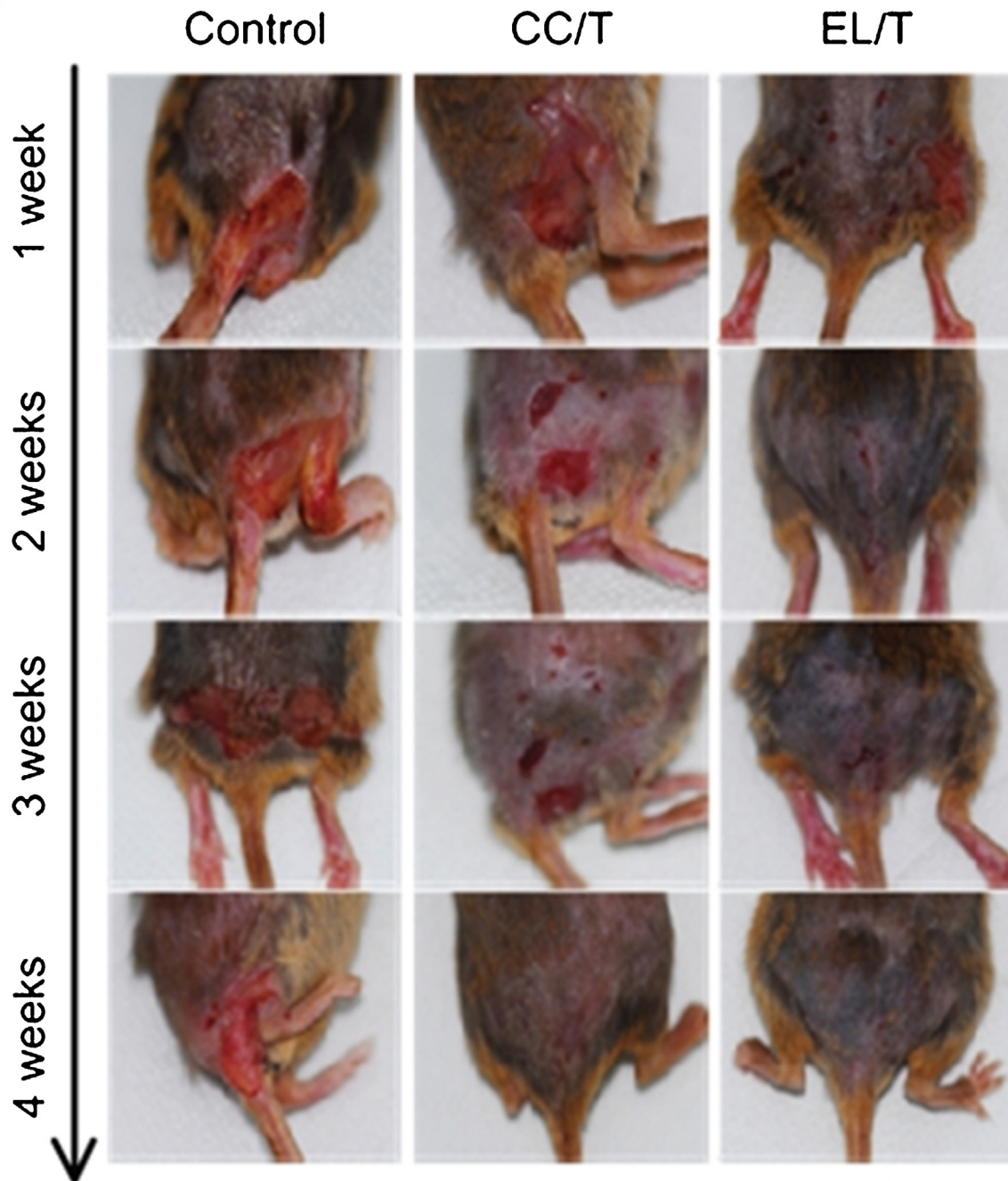


Fig. 4. Therapeutic superiority of liposome-based formulation (EL/T) in treating AD-like skin lesions in NC/Nga mice, in comparison to drug-free cream base (control) and Tat-admixed conventional cream (CC/T) [139]. Reproduced and adopted with the permission from Kang et al. (2011) (Copyright © 2011).

drugs into the epidermis and dermis, in comparison to the commercial formulation (Protopic®) [30]. SLNs also showed greater potential to target dendritic cells and thus, can down regulate various immune mediators and cytokines involved in the pathophysiology of AD [30].

The *in vivo* anti-AD efficacy of SLNs was assessed by Pople and Singh in BALB/c mice [148]. Tacrolimus-loaded SLNs showed greater control over the severity of AD symptoms, in comparison to the control and placebo groups. The topical application of tacrolimus-loaded SLNs showed greater reduction in ear thickness, total dermatitis score, and the epidermal thickness after day-1, in comparison to control groups which required comparatively longer time to produce the same effects (as shown in Fig. 5) [148]. The

animals treated with tacrolimus-loaded SLNs showed 1.24-fold greater reduction in ear thickness (inflammation) and 1.61-fold greater reduction in dermatitis scores, in comparison to the control groups. These results were in agreement with previous study published by Kim et al. [31]. They demonstrated that the permeation flux of cyclosporine was significantly higher in case of SLNs, when compared to the control group. They further highlighted the therapeutic significance of the SLNs in suppressing the signs and symptoms of AD in murine mice model. A greater reduction in T_H2 related cytokines such as IL-4 and IL-5 and decreased severity of dermatosis was observed in mice group treated with SLNs [31]. Pinaki et al. have also entailed the *in vivo* efficacy of SLNs in suppressing the dermatological symptoms such as psoriatic or

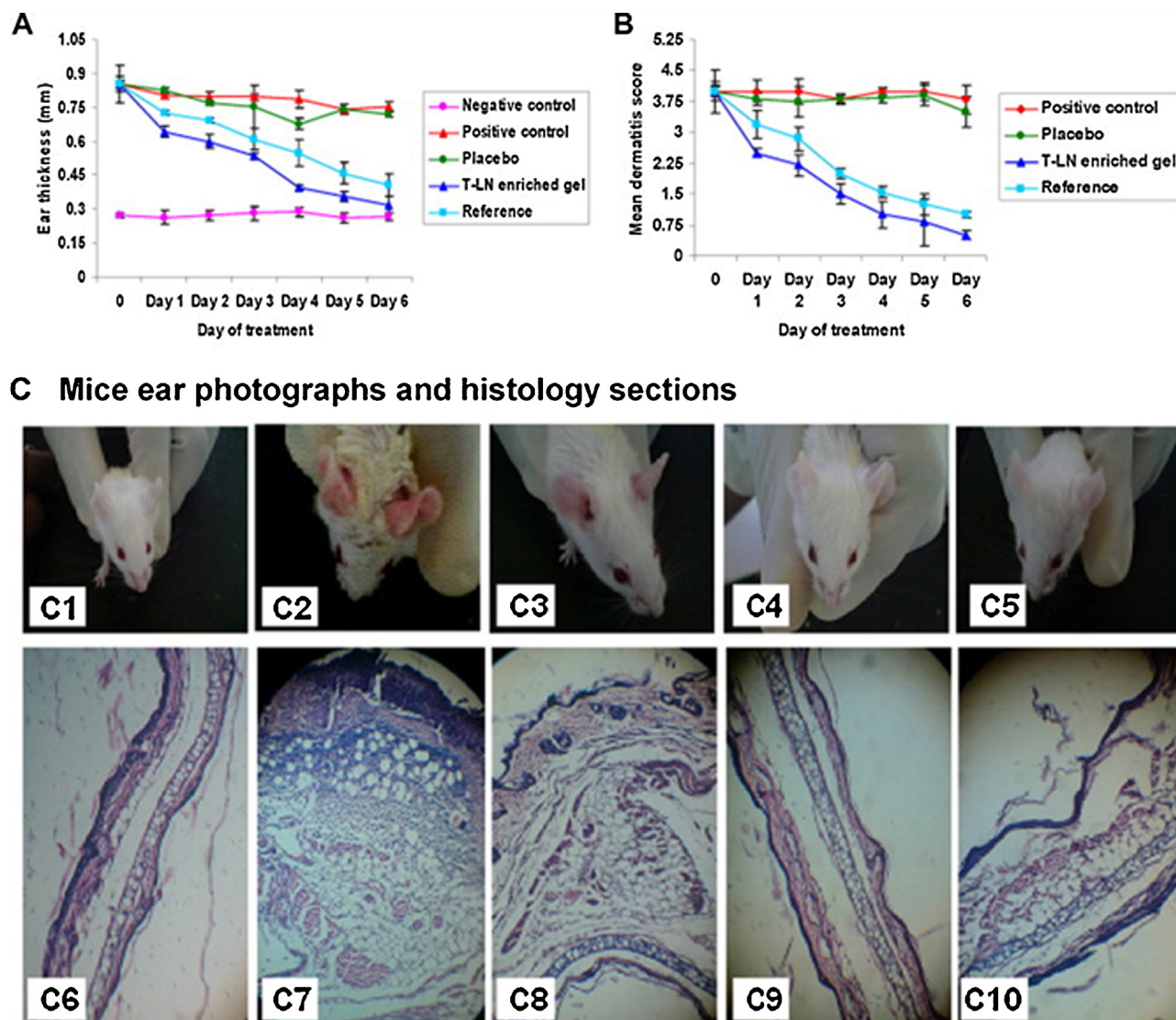


Fig. 5. Ear thickness scores (A) and mean dermatitis scores (B) in mice after treatment with test formulations. (C) The appearance of mice ears and histopathological observations; C1 and C6 show normal mice ear photographs and sections respectively. Note the marked inflammation (visible in photographs) as well as the thickening of the epidermis and dermal layers in positive control group (C2 and C7). C3 and C8 represent ears treated with placebo formulation. C4 and C9 show group treated with T-LN enriched gel while C5 and C10 represent group treated with reference. The results shown are representative of six mice in each group [148]. Reproduced and reprinted with the permission from Elsevier B.V. (Copyright © 2012) through Copyright Clearance Centre.

AD-like skin lesions [149]. The therapeutic feasibility of SLNs was highlighted in terms of higher penetrability, increased permeation flux and percentage of drug retained in target tissues, significantly lower dermatitis index, infiltrated mast cells and eosinophils, as well as lesser thickness of the SC [149]. They performed quantification of various AD-related biomarkers and have observed that SLNs showed prominent control in reducing the inflammatory cascade at the site of inflammation [149]. Some other researchers have also demonstrated the anti-AD potential of SLNs in reducing the transepidermal water loss, erythema intensity and skin dryness [150,151]. They further supported their hypothesis by showing significant increase in viscoelasticity of the SC in mice group treated with SLNs, in comparison to the control groups [150,151].

5.4. Nanoemulsion-based therapies

Nanoemulsion is an emulsion system composed of water, oils, and surfactant with an isotropic and transparent (translucent) appearance. The characteristic ultra-small (< 500 nm) size droplets

are responsible to enhance penetration of incorporated drugs into the intact or damaged skin [152]. Due to their excellent stability and translucent appearance, these formulations have gained remarkable attention of the researchers for the topical delivery of drugs. A good selection of the components (oil and surfactants) imparts greater roles in improving the pharmaceutical and therapeutic efficacy of this delivery system. Nanoemulsions have been developed to overcome problems associated with the topical delivery of drugs. Besides their nano-sized droplets, a special character of nanoemulsion is their positive charge which imparts greater roles in facilitating drug penetration into the skin [152]. Surfaces of all body tissues carry negative charge which may develop interactions with positively charged nanoemulsion and promote transcutaneous permeation of incorporated drugs [33].

As such, the pharmaceutical convenience of positively charged nanoemulsion has been explored by Hussain et al. [153]. Hussain and co-workers demonstrated that positively charged nanoemulsion showed sustained release and significantly increased permeation of amphotericin B across excised human skin. They proposed

that the increased penetration of drug was due to the interaction of the positively charged nanoemulsion with the negatively charged corneocytes of the SC [153]. Other studies have explored the therapeutic significance of the positively charged nanoemulsion in the management of skin inflammatory disorders [154,155]. Yilmaz & Borchert noticed a significant improvement in skin elasticity and the hydration level of the mice group treated with nanoemulsion-based formulation, in comparison to the control groups [154]. Yilmaz and co-worker further evaluated the anti-AD efficacy of the nanoemulsion-based formulation and demonstrated significant reduction in erythema intensity and dermatitis scores in the mice group treated with nanoemulsion, in comparison to the control groups [154]. The results were in support of Alam et al. who have highlighted anti-inflammatory and anti-AD effects of the nanoemulsion-based delivery system [156]. They observed a significant increase in the anti-inflammatory activity of the lymphocytes with increased NTPDase (Nucleoside triphosphate diphosphohydrolases) activity and showed a better control over disease severity and progression [156].

5.5. Polymeric NPs-based delivery system

In recent years, scientific focus is being driven by the polymer-based nanotechnology. The successfulness of the polymeric NPs is due to biocompatibility and biodegradability of the natural, synthetic or semi-synthetic polymers [157,158]. The pharmaceutical appropriateness of the polymeric NPs-based delivery system was demonstrated by many researchers for the target-specific delivery of the incorporated drugs [159–161]. Hussain and co-workers [159] revealed that NPs-based delivery systems could significantly reduce the permeation flux of hydrocortisone (HC) and hydroxytyrosol (HT), which can reduce systemic toxicity of these drugs. The NPs-based formulations decreased the permeation of HC and HT across NC/Nga mouse skin. NPs-based delivery of drugs has also shown promising potential to facilitate localised delivery of the incorporated drugs into the epidermis and dermis, which is the site of inflammatory reaction. Hussain and co-workers demonstrated that NPs-based formulations showed significantly higher amount of HC (approx. 2-fold) and HT (approx. 1.5-fold) retained into the epidermis, in comparison to the controls [159].

Despite the pharmaceutical appropriateness of the NPs-based delivery system, in vivo efficacy of these nanocarriers in the treatment of AD has also been highlighted by many researchers [159–164]. Hussain et al. (2013) evaluated the in vivo efficacy of the polymeric NPs-based formulation by using NC/Nga mouse model [159]. NC/Nga mice group treated with NPs-based formulation showed greater reduction in TEWL and erythema intensity compared to the control groups [159]. The anti-AD efficacy of NPs-based formulation was also assessed through the measurement of severity index (ADI) which was established according to the following criteria: (1) haemorrhage, (2) dryness, (3) oedema, and (4) excoriation, each of which were scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe) [160]. The resulting data showed a remarkable efficacy of NPs-based formulation in reducing the severity of erythema/haemorrhage, dryness/scaling, oedema, and epidermal excoriation (as shown in Fig. 6) [160]. The alleviation in the severity of dermatosis was expected to be due to blocking the underlying inflammatory reactions initiated in response to AD allergen [160].

The anti-AD efficacy of the NPs-based formulations was also assessed through histological examination of tested animals which indicated that the mice group treated with NPs-based formulation had distinctly alleviated the symptoms of AD (Fig. 7) [160]. The mice treated with the polymeric NPs-based formulation showed merely developed hair follicles which indicate restoration of the skin physiology, in comparison to the control groups

which demonstrated marked epidermal hyperplasia, parakeratosis, hyperkeratosis, acanthosis, fragmented SC, and a large number of macrophages infiltrated in the dermis. A greater reduction in the infiltration of fibroblast and fragmentation of elastic tissues was also noticed in mice group treated with NPs-based delivery systems. Other studies by the same group also revealed the therapeutic feasibility of the polymeric NPs-based formulations by evaluating the immune spectrum of treated animals, in comparison to the control groups [161]. The mice treated with nano-formulations demonstrated greater reduction in the levels of IgE, vascular endothelial growth factor- α (VEGF- α), and histamine in the serum and skin biopsies of tested mice [161]. The anti-AD efficacy of the polymeric NPs was also evaluated in preventing the expression of T_H1/T_H2 associated cytokines such as IL-4, IL-5, IL-6, IL-12, IL-13, IFN- γ , and TNF- α in AD induced mice, in comparison to the control groups [158]. These results were in agreement with Shah et al. who have also highlighted the anti-inflammatory and anti-AD efficacy of the NPs-based delivery systems [162]. As such, Kim et al. also demonstrated that NPs may increase the expressions of RIP2 (receptor interacting protein-2) and IKK β (I κ B kinase β) in normal condition [163,164]. These findings suggested that NPs-based delivery of drugs can effectively diminish allergic reaction and can be a promising therapeutic alternative for the management of atopic diseases.

6. Summary

AD, including acute and chronic milieu, is one of the prevalent skin inflammatory disorders which compel a significant burden to the patient, healthcare providers and the healthcare system. Among various therapeutic modalities, educational programs (i.e., training programs, “eczema schools”), video interventions and nurse-led programs are adjunct to the non-pharmacological approaches in the management of atopic diseases. Non-pharmacological approaches are well-accepted for the management of mild-to-moderate AD; however, pharmacological therapies are needed in the treatment of chronic AD. TCs are among the most prescribed agents; however, cautions need to be exercised while selecting TC for a specific patient. Chronic AD cases impose a substantial challenge to healthcare system and thus demand the development of novel and advanced nanocarrier-mediated targeted therapies. The nanocarrier-based therapies which include liposomes, ethosomes, SLNs, nanoemulsion and polymeric NPs are well-recognised due to target-specific delivery and longer retention of therapeutic payloads at the target site, avoiding off-target effects and their therapeutic superiority over conventional therapies in controlling severity and progression of AD. A plethora of in vivo studies have extensively demonstrated the therapeutic significance of these advanced nanocarrier-mediated approaches for the efficient management of atopic diseases and in preventing its progression.

7. Future prospects

With in-depth review of the available contents and therapeutic evidence, we have recognised that although several studies have been conducted to explore the pharmaceutical and therapeutic feasibility of the advanced nanocarrier-based delivery systems in the treatment of AD, much has yet to be executed and learned. Substantial gaps in research have been recognised, including but not limited to: methodologic research for defining AD-specific symptoms; comparative studies on various nanocarrier-based delivery systems in the management of atopic disease in order to make possible to adopt best anti-AD regimen; lack of availability of safety/toxicity profile data for the nanocarrier-mediated delivery systems; possible modification of the existing conventional ther-

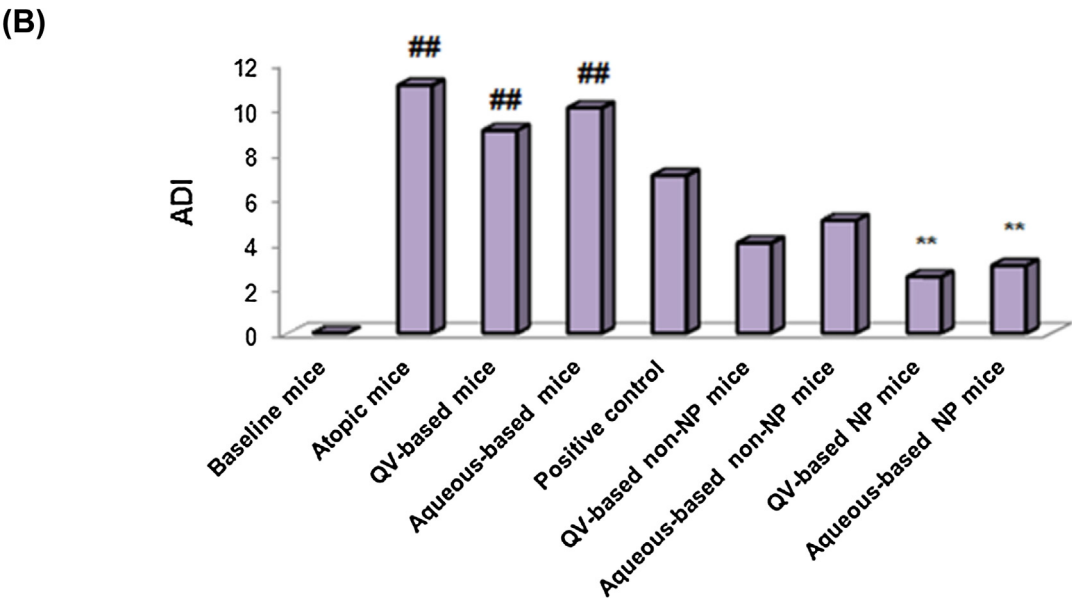
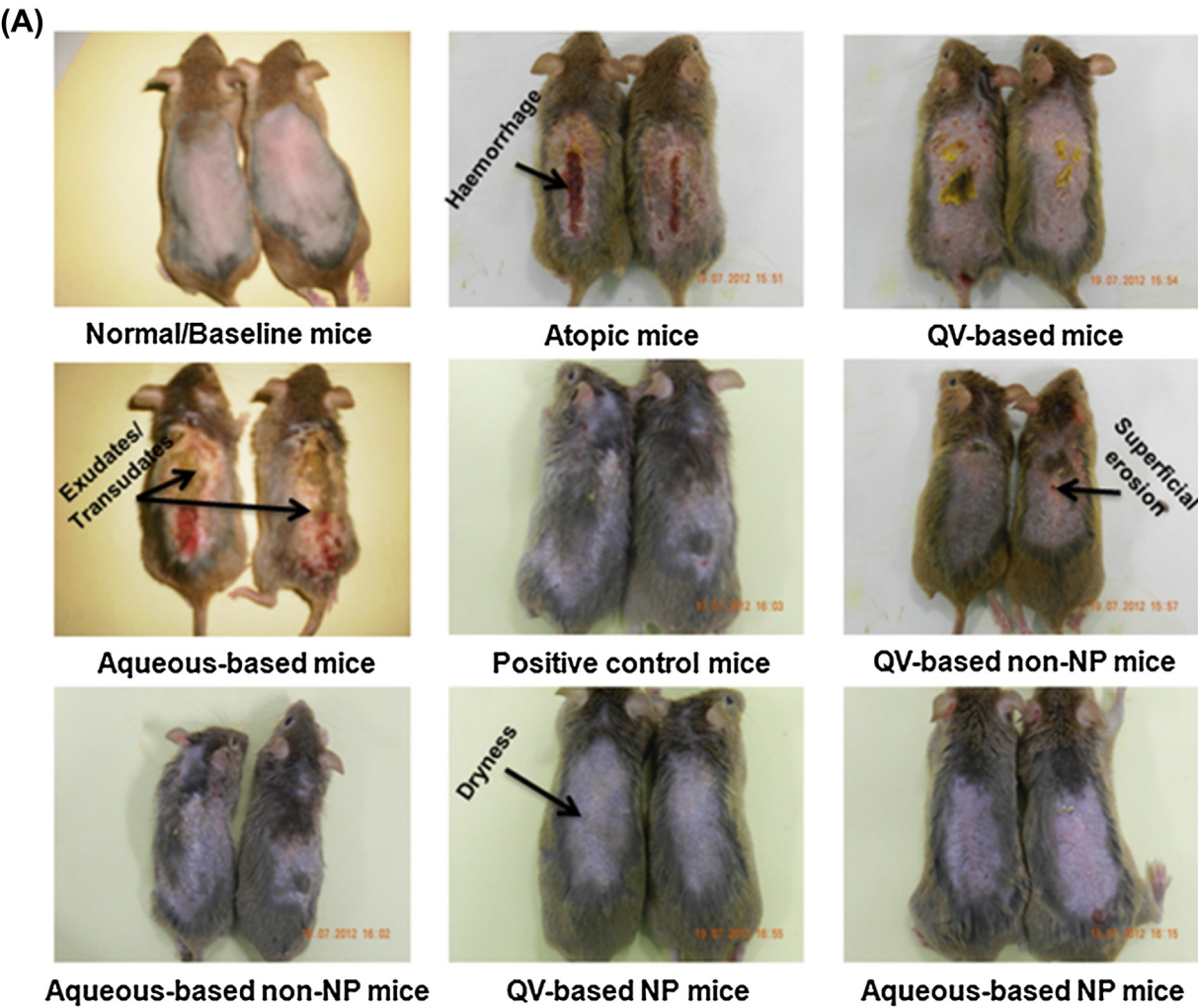


Fig. 6. Therapeutic superiority of NPs-based formulations, in comparison to control groups. QV-based mice were treated with commercial QV-cream and QV-based NP mice were treated with QV-cream based NPs formulation. Positive control mice were treated with commercial 0.5% hydrocortisone cream. Digital images (A) and ADI (B) of untreated and treated AD-induced NC/Nga mice [160]. Reproduced and adopted with the permission from Hussain et al. (2014) (Copyright © 2014).

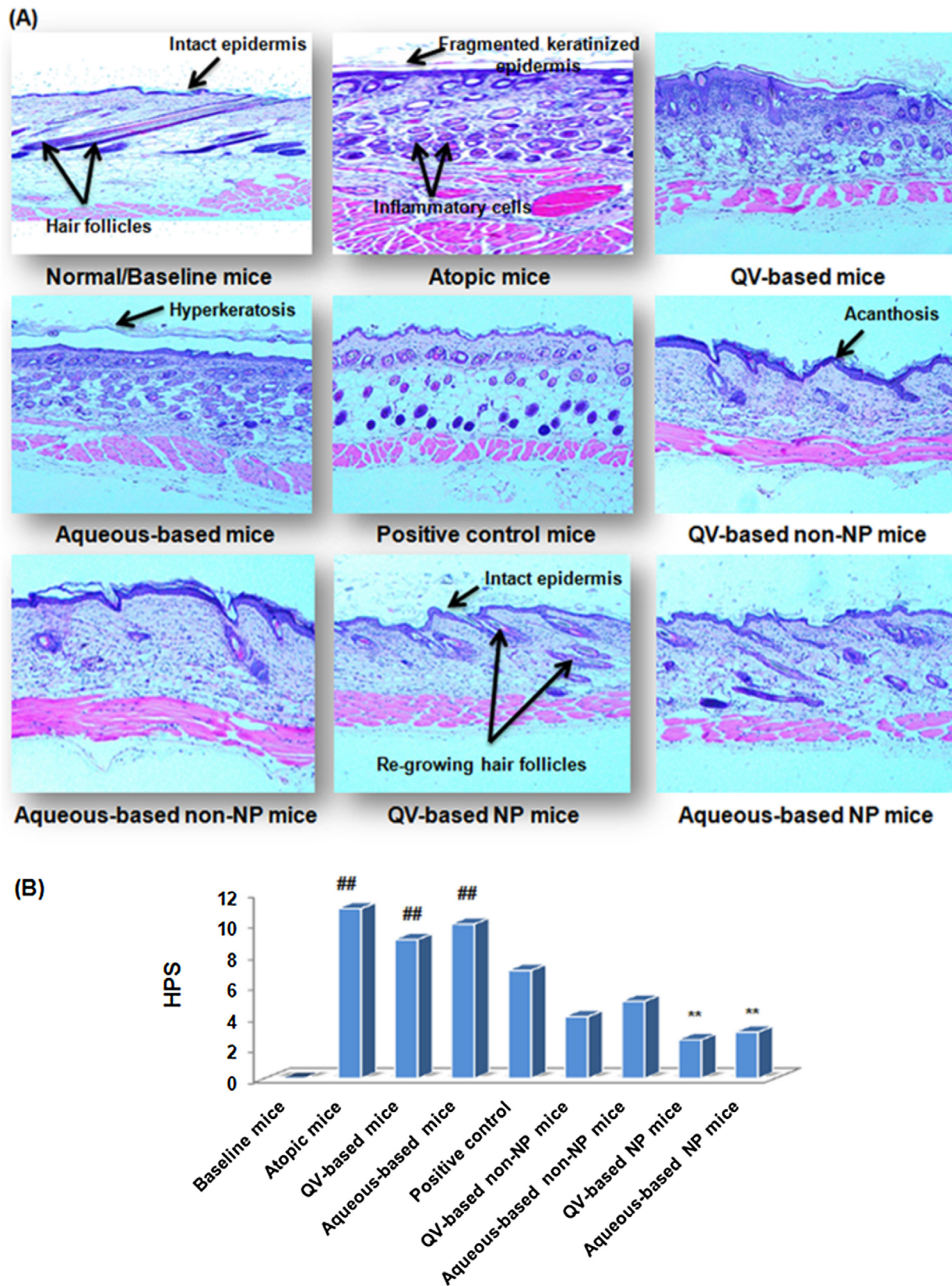


Fig. 7. Anti-AD efficacy of NP-based formulation compared to the normal/baseline and other treatment groups in terms of histological examination (A) and histopathological scores (HPS) (B). QV-based mice were treated with commercial QV-cream and QV-based NP mice were treated with QV-cream based NPs formulation. Positive control mice were treated with commercial 0.5% hydrocortisone cream. AD, atopic dermatitis; HPS, histopathological scores, NPs, nanoparticles. Reproduced and adopted with the permission from Hussain et al. (2014) [160] (Copyright © 2014).

apies or their efficacy enhancement by conjugating them with nanocarriers (via surface modification, improving loading efficiency, facilitating target-specific delivery), and evidence-based randomized research specifically exploring the therapeutic role of the advanced nanocarrier-based delivery systems on the pathophysiology of AD and other skin inflammatory diseases.

Declaration of interest

The authors report no declaration of interest in the present work.

Acknowledgements

The authors would like to acknowledge Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus Malaysia, for support and providing resources to write this review article.

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