



Nanotechnology meets atopic dermatitis: Current solutions, challenges and future prospects. Insights and implications from a systematic review of the literature

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ABSTRACT

Atopic dermatitis is a chronic, relapsing, non-contiguous, exudative eczema/dermatitis, which represents a complex, multi-factorial disorder, due to an impairment of the *stratum corneum* barrier. Currently available drugs have a low skin bioavailability and may give rise to severe adverse events. Nanotechnologies, including nanoparticles, liposomes, nano-gels, nano-mixtures, nano-emulsions and other nano-carriers, offer unprecedented solutions to these issues, enabling: i) the management of different clinical forms of atopic dermatitis, especially the recalcitrant ones, ii) a better bio-availability and trans-dermal drug targeted delivery at the inflammation site, iii) dose control, iv) significant improvements both in clinical symptoms and immune responses, v) with less adverse events being reported and a better safety profile. However, some nano-sized structures could amplify and even worsen symptoms in particularly susceptible individuals. Furthermore, most studies included in the present systematic review have been conducted *in-vitro* or *in-vivo*, with few randomized controlled clinical trials (RCTs). Future investigations should adopt this design in order to enable scholars achieving robust findings and evidence. Therefore, given the above-mentioned shortcomings, further research in the field is urgently warranted.

1. Atopic dermatitis: physiopathology and burden

Atopic dermatitis is a chronic, relapsing, non-contiguous, exudative eczema/dermatitis, which represents a complex, multi-factorial disorder, due to an impairment of the *stratum corneum* barrier [1–3]. This results in a disturbed skin function and an increase in trans-epidermal water loss (TEWL), which leads to dehydration, and in a series of inflammatory processes characterized by the production and release of several cytokines, chemokines and interleukins (including interleukin type 1 beta or IL-1 β , IL-4, IL-5, IL-6, IL-8, IL10, IL-12p70, IL-13, IL-17 and IL-17A, IL-19, IL-33 and thymic stromal lymphopoietin, or TSLP

[4,5].

These molecules and others, such as tumor necrosis factor-alpha or TNF- α and interferon- γ or IFN- γ , promote lipogenesis, activating lipids that play a major role in the skin barrier but also in delivering biochemical signals, which, in its turn, increases inflammation levels and the risk of infections.

Atopic dermatitis is also characterized by alterations in the apoptotic cascades [6]. Furthermore, an excessive amount of elastase in peripheral blood neutrophils creates an imbalance between the concentrations of the proteolytic enzyme and its endogenous inhibitors and leads to disrupted elastic fiber organization [7–9].

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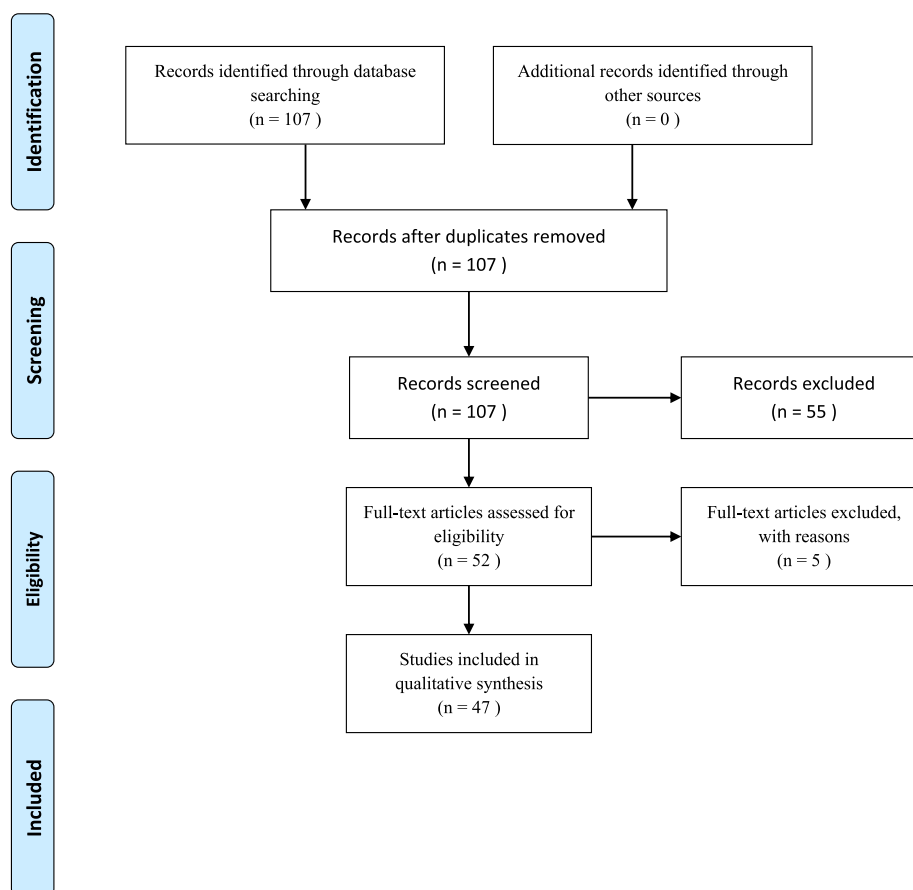


Fig. 1. Literature search strategy adopted in the present systematic review.

Summarizing, despite being not still fully understood, atopic dermatitis is traditionally regarded as a T helper type 2 lymphocytes (T_{H2})-mediated disease, whilst, recently, advancements in the field of basic science have revealed that some other immune actors may play a crucial role, like T helper type 17 lymphocytes (T_{H17}) and T helper type 22 lymphocytes (T_{H22}), as well as eosinophils and mast cells that degranulate contributing to the inflammatory microenvironment [10].

From a clinical standpoint, patients suffering from atopic dermatitis complain of dryness, erythema, scaling and fissuring [1,2]. Atopic dermatitis may occur anytime during life but its onset and development should be regarded in the contest of “atopic march”; the series of events that start from the skin and may affect mainly the respiratory system (with disorders such as rhinitis, asthma, sinusitis) and eye (conjunctivitis) [11].

Current management of atopic dermatitis comprises cyclosporine A, topical calcineurin inhibitors (tacrolimus and pimecrolimus), and corticosteroids (that can be administered in a systemic or topical way). Only recently atopic dermatitis has started to benefit from targeted therapy, due to the advent of dupilumab, an anti-IL4/13 biologic, that is capable to effectively solve also the patients resistant to systemic treatments [12,13].

Synergically with the revolution in the treatment and management of atopic dermatitis, clinicians have started to distinguish and better study the late-onset atopic dermatitis that typically is more pleomorphic and less recognized, deserving a more accurate differential diagnosis [14,15]. Each patient is different, in terms of prognosis, burden of co-morbidities [16], and contraindications to the conventional systemic treatments (hepatic or renal) or even to targeted therapy (ocular disorders). Nanotechnologies, taking into account these aspects, can pave the way to an individualized treatment and management of atopic dermatitis patients, in that drug delivery, controlled

release, dosage and skin permeation/retention play a key role [17].

2. Nanotechnology meets atopic dermatitis: current solutions

Nanotechnology-based therapeutics [18,19], including nanoparticles, nanogels, nanomixtures, nanoemulsions and other nanocarriers, have been explored as potential treatments for atopic dermatitis.

In this review, we have systematically searched PubMed/MEDLINE mining its entire content since inception, without any time or language constraint, utilizing the following string of key-words: (nanocarrier OR nanocarriers OR nanotube OR nanotubes OR nanogel OR nanogels OR nanoemulsion OR nanoemulsions OR nanostructure OR nanostructures OR nanostructured OR nanosize OR nanosized OR nanovector OR nanovectors OR nanocapsule OR nanocapsules OR nanoencapsulation OR nanoencapsulated OR liposome OR liposomes OR cubosome OR cubosomes OR nanovesicle OR nanovesicles OR transfersome OR transfersomes OR nanotechnology OR nanotechnologies OR nanobiotechnology OR nanobiotechnologies OR nanotherapeutics OR nanoformulation OR nanoformulations OR nanovehicle OR nanovehicles OR nanodrug OR nanodrugs OR nanodelivery OR nanocosmetic OR nanocosmetics OR nanocosmeceuticals OR nanoshell OR nanoshells) AND (“atopic dermatitis” OR “atopic eczema”). Medical subject headings (MeSH) terms and wild-card (i.e., truncated words) options, were used where appropriate.

The working team was multi-disciplinary, comprising of two experts in dermatology (G.D. and P.D.M.P.), an expert in research methodology (N.L.B.) and an expert in biophysics and nanotechnology (R.E.). We followed the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines [20]. Studies conducted in animals for veterinary purposes, being out of scope for the present review,

were excluded [21–24]. Review articles, if existing, were scanned for increasing the chance of getting potentially relevant articles but were excluded from the present review. Extensive, iterative cross-referencing was performed, checking the list of references of each eligible study until no new study could be found. Further details are pictorially shown in Fig. 1.

Nano-sized formulations found are described in the following paragraphs.

3. Atopic dermatitis, nanoparticles and nanocarriers

Nanoparticles and nanocarriers seem to have optimal rheological properties, antimicrobial effects and capability to restore skin conditions. These nanostructures, such as silver (Ag-NPs) and silver-lipid or poly(lactic acid) (PLA-NPs) nanoparticles [25–29] appear promising in the treatment and management of patients with atopic dermatitis.

Pandey and coworkers [30] fabricated hyaluronic acid-decorated betamethasone valerate-loaded chitosan nanoparticles (BMV-HA-CNPs, nano-size of 300 ± 28 nm, positively charged zeta potential of 58 ± 8 mV, entrapment efficiency of $86 \pm 5.6\%$ and loading capacity of $34 \pm 7.2\%$. Drug diffusion and permeation efficiency profiles appeared to be optimal and promising for atopic dermatitis management.

Rosado and colleagues [31] fabricated hydrocortisone-loaded poly(ϵ -caprolactone) nanoparticles (PCL-NPs) by modified solvent displacement method, reporting good physical-chemical properties.

Kim and collaborators [32] evaluated the efficacy of cyclosporin A-loaded solid lipid nanoparticles (CsA-SLN) prepared by hot homogenization method (size approximately of 73 nm, negative surface charge of -16 mV). The product was tested in murine models, displaying a 2-fold higher skin penetration and reducing the production and release of IL-4 and IL-5 by T helper type 2 (T_{H2}) lymphocytes.

Kang and coauthors [33] evaluated thermosensitive, solid lipid nanoparticles loaded with tacrolimus (TCR-SLNs), comparing its efficacy versus 0.1% Protopic® in a murine model. TCR-SLNs proved effective in drug delivery, allowing tacrolimus to reach the deepest skin layers.

Singh and Pople [34–36] fabricated tacrolimus-loaded lipid nanoparticles by high pressure homogenization technique. Statistically significant better drug controlled release and skin permeating profiles could be found with respect to the reference ointment, Protopic®. Immune responses were inhibited by 3.5 times, with fewer adverse events reported.

Zhuo and colleagues [37] developed hyaluronic acid-decorated tacrolimus-loaded nanoparticles (HA-TCS-CS-NPs) and tested them *in vitro*. Drug release kinetics, permeation and efficacy were proved to be satisfactory.

Yu and coworkers [38] assessed the feasibility of exploiting chitosan-based nanoparticles loaded with tacrolimus and combined with nicotinamide (FK506-NIC-CS-NPs), in order to mitigate or counteract the insurgence of adverse effects associated with high doses of FK506, potentially occurring during long-term treatment. The formulation was tested in animal models (BALB/c mice with 1-chloro-2, 4-dinitrobenzene (DNFB)-induced atopic dermatitis). FK506-NIC-CS-NPs based formulation was compared with a commercially available ointment (Protopic®). Delivery and permeation of FK506 was increased up to 92.2%, enabling to spare dose of FK506.

Siddique and coauthors [39–41] exploited nanoparticles for a targeted delivery of systemic corticosteroids at the inflammation site. In a murine model, topically applied cationic polymeric chitosan-based nanoparticles (CSNPs) loaded with anti-inflammatory hydrocortisone and antimicrobial hydroxytyrosol (HC-HT-CSNPs, size of 228.5 ± 7 nm and positive surface charge of 39 ± 5 mV) displayed optimal epidermal and dermal permeation, reaching the deepest skin layers with an efficiency 2.46-fold higher with respect to the commercial reference formulation. No evidence of toxicity could be found.

Similarly, Hussain et al. [42–44] explored the effects of

hydrocortisone-loaded chitosan-based nanoparticles (HC-CNPs) in a model of 2,4-dinitrofluorobenzene-induced atopic dermatitis in NC/Nga mice. HC-NPs resulted in down-regulated inflammatory cascades (reduced production of IgE, IL-4, IL-5, IL-6, IL-13, IL-12p70, IFN- γ , TNF- α , release of histamine, expression of prostaglandin-E2 and vascular endothelial growth factor- α , VEGF- α), in the sera and skin. At a cellular level, events such as fibroblast infiltration and fragmentation of elastic fibers were inhibited or drastically reduced.

Huang and collaborators [45] fabricated 7,3',4'-trihydroxyisoflavone based nanoparticles by planetary ball mill preparation under a solvent-free process (734THIN) using polyvinylpyrrolidone K30 as excipient. This formulation inhibited the expression of COX-2 and MMP-9 by down-regulating the "Mitogen-Activated Protein Kinase" (MAPK)-related signaling cascade.

Dessy and coworkers [46] prepared polymeric nano-particles based formulations loaded with anti-inflammatory Dead Sea Water (DSW) minerals (calcium, magnesium, sodium, potassium, zinc and strontium). Nanoparticles consisted of Poly (maleic anhydride-alt-butyl vinyl ether) 5% grafted with monomethoxy poly(ethylene glycol) 2000 MW (PEG) and 95% grafted with 2-methoxyethanol (VAM41-PEG), prepared using a combined mini-emulsion/solvent evaporation process, and had a nano-size of 300 nm. Drug delivery and release properties were found to be satisfactory.

Nagaich and Gulati [47] fabricated nanocarriers loaded with betamethasone valerate, which demonstrated a permeation profile 2.59 folds higher than commercially available betamethasone valerate gel and an extended anti-inflammatory effect (up to 16.5%).

Finally, Tessema and collaborators [48] fabricated nano-carriers loaded with oat-derived phytoceramides, including lecithin-based microemulsions and starch-based nanoparticles, using Carbopol®980 as a gel. The delivery system demonstrated appropriate physical-chemical properties.

4. Nano-capsules

Marto and coworkers [49] explored the feasibility of topically delivering a novel synthetic human neutrophil elastase inhibitor (ER143) by means of a starch-based nanoparticulate system (StNC), demonstrating good permeation and retention profiles.

MD and colleagues [50] developed an *ad hoc* nano-encapsulated delivery system for atopic dermatitis: chitosan nanoparticles loaded with betamethasone valerate (BMV-CS-NPs, nano-size of 250 ± 28 nm, positively charged zeta potential of 58 ± 8 mV). The formulation showed satisfactory entrapment efficiency and loading capacity.

5. Lipid nano-mixtures and nano-emulsions

Berardesca and coworkers [51] assessed the effectiveness of a topical skin lipid mixture containing ceramide-3 and nanoparticles alone or combined with topical corticosteroids administered until clearance or for a period of 8 weeks. Authors found improvements both in terms of skin physiology and barrier properties and clinical symptoms.

Yilmaz and Borchert [52] investigated the efficacy of positively charged oil/water nano-emulsions (PN) containing ceramide-3B and ceramide-3, cholesterol, and palmitic acid (PNSC). Creams of PNSC were compared to PN, negatively charged oil/water nano-emulsion and SC lipids (NNSC) prepared by high-pressure homogenization and stabilized with a thickener (Carbopol-940) and a commercially available cream (Physiogel®). Each formulation was tested in a sample of 14 healthy females aged 25–50 years. All products were found to increase skin properties in terms of hydration and elasticity, with PNSC being significantly more effective than PN and NNSC, suggesting a role of phytosphingosine, lipids and ceramides.

Similarly, Neubert and coworkers [53] compared different nano-formulations: a colloidal microemulsion based of novel dimeric ceramides, a ceramides-based cream with ethoxydiglycol as penetration

enhancer and a nano-formulation, finding that the former had the lowest penetration and permeation profiles, whilst the use of a penetration enhancer significantly improved the physical-chemical properties of the drug.

Bernardi et al. [54] assessed the effectiveness of rice bran oil nano-emulsions (10% rice bran oil, 10% surfactants sorbitan oleate/PEG-30 castor oil, 0.05% anti-oxidant and 0.50% preservatives formulated in distilled water) utilizing low energy emulsification methods, such as the phase diagram method. The product was found to be stable, displaying a low irritation potential, improving skin moisture and maintaining pH values within its normal range.

Baspinar and coauthors [55,56] prepared positively charged pre-dnicarbate nanoemulsions using high pressure homogenization method. The formulation was found to be stable and potentially adequate for the treatment and management of atopic dermatitis patients.

Verma and Fahr [57] utilized a lipid mixture, NAT-8539, to enhance the topical delivery of cyclosporin A (NAT-8539-CyA), with vesicles in the range 56.6–100.6 nm of diameter and ethanol between 10% and 20%. Depending on the concentration of ethanol and the nano-size of vesicles, the nano-mixture proved to be effective in reaching the deepest skin layers.

Finally, Espinoza and colleagues [58] improved the delivery of pioglitazone, a peroxisome proliferator-activated receptor agonist, by fabricating a nano-emulsion (PGZ-NE). This formulation was proved to decrease several inflammatory cytokines, such as IL-6, IL-1 β and TNF- α .

6. Liposomes, nanoliposomes and nanovesicles

Due to skin barrier defects and impairment, the *stratum spinosum* and *stratum granulosum* of atopic dermatitis patients appear to be rich in lamellar, ovoid, membrane-coating granules (MCGs), comprising of extruded, parallel disks that give rise to the formation of continuous lamellae [59–63]. Being structurally similar, liposomes can be utilized for the management of atopic dermatitis, with a hydrating effect on the *stratum corneum* [63], as well as being able to act as carriers of bioactive compounds [62,63].

The first pioneering study to investigate the effects of a liposomal preparation dates back to the nineties. Korting et al. [64] used a beta-methasone dipropionate (0.039%-loaded liposome (BDP-liposome). For this purpose, they recruited 10 patients in a double-blind, randomized, paired trial and administered BDP-liposome for two weeks versus a commercial propylene glycol-gel containing 0.064% beta-methasone dipropionate. The liposomal preparation proved effective, significantly reducing inflammation and erythema and scaling.

Based on these findings, Eroğlu and coworkers [65] prepared betamethasone valerate/diflucortolone valerate-loaded chitosan-based liposomes (nano-size of 220–350 nm), with the formulation proving to be safe and effective in ameliorating atopic dermatitis symptoms in an animal model.

Ibaraki and colleagues [66,67] explored the potential effects of a topically delivered small interfering RNA (siRNA)-based treatment using AT1002 combined with a flexible, highly permeable anti-nuclear factor-kappa B (NF- κ B) (RelA)-encapsulated 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine/cholesteryl hemisuccinate (siRelA-DOPE/CHEMS) liposome. AT1002 was chosen in that is a peptide able to open and finely modulate tight junctions [68,69]. The formulation was tested in *in-vitro* and *in-vivo* (animal and human) models.

Another peptide which may be of interest for the treatment of atopic dermatitis is Pep-1. Kang and coauthors [70] explored in a murine model (NC/Nga mice) the effects of a peptide-conjugated elastic liposomal formulation (comprising of phosphatidylcholine, Tween 80, N-[4-(p-maleimidophenyl)butyryl]-phosphatidylethanolamine or MPB-PE) of taxifolin glycoside (TXG-Pep1-EL, nano-size of 130 nm, zeta potential of 25 mV and deformability index value of 60). Authors found optimal skin delivery, permeation and retention profiles, as well as improvements in skin properties in terms of hydration, elasticity and

immune responses.

Kang et al. [71] developed oregonin-loaded elastic, highly flexible liposomes consisting of soybean phosphatidylcholine and Tween 80 (85:15 water/water %) (ORG-EL, nanosize of 130 nm and 4-fold greater deformability index than conventional liposomes). Permeation properties of the nanocarriers were excellent and were further increased by the addition of a peptide, Trans-activating transcriptional activator (Tat), which can modulate and open tight junctions (ORG-EL-Tat). Concentrations of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-4, IgE, and eosinophils in skin or blood were found to be significantly reduced.

Tat peptide (0.16 water/water %) was utilized also to facilitate skin delivery and permeation of a natural immune-modulator, hirsutenone, by means of *ad hoc* devised liposomes consisting of phosphatidylcholine and Tween 80 (85:15 water/water %) (HST-EL-Tat), prepared by thin-film hydration method, in an investigation carried out by Kang and coworkers [72]. Levels of iNOS, COX-2, IL-4, IL-13, IgE, and eosinophil were decreased in a murine model.

Augustin and colleagues [73] tested the effectiveness and the anti-septic, anti-inflammatory properties of liposomal polyvinyl-pyrrolidone (PVP)-iodine (3%) hydrogel administered for up to 4 weeks in a prospective, single-arm, uncontrolled, open-label phase II, pilot clinical trial recruiting 20 patients with atopic dermatitis. The “Global Clinical Severity” (GCS), pain, quality of life and “Eczema Area and Severity Index” (EASI) scores significantly improved. Formulation was well tolerated, with generally mild adverse events being reported.

Liposomes loaded with 18 β -glycyrrhetic acid, the major metabolite of glycyrrhizin, extracted from licorice root, and characterized by anti-microbial, anti-oxidative properties, appear to be another promising therapeutic solution for the management of atopic dermatitis [74].

Jung and coauthors [75] improved the topical skin delivery of cobalamin/vitamin B12 by preparing a liposomal hydrogel of adenosylcobalamin (Lipo-AdCbl, nano-size of 106.4 \pm 2.2 nm) by thin film hydration method. Skin permeability was increased up to 17-times in a murine model (NC/Nga mice) with ameliorated symptoms and immune responses.

Goindi and coworkers [76,77] enhanced skin delivery of cetirizine/levocetirizine dihydrochloride, a piperazine-derived second-generation anti-histaminic drug, by combining Phospholipon®90G and edge activators. The formulation was found to have good penetration and permeation profiles in a murine model, significantly reducing dermal eosinophil count, erythema and itching scores with respect to conventional ointments and creams.

Liposomes can be utilized also for gene delivery. For instance, Kim and collaborators [78] developed IL-13 antisense oligonucleotide complexed with cationic elastic liposome (IL-13-ASO-cEL). The formulation was able to suppress IL-13 production and release. by up to 70%, as well as IL-4 and IL-5.

Finally, liposomal formulations can as well act as carriers of stem cells or purified extracts from stem cells, as in the investigation by Jahn and colleagues [79]. Authors fabricated proliposomes consisting of soy phosphatidyl choline, Poloxamer-407, ethanol and sorbitol, loaded with advanced adipose stem cell derived protein extract (AAPE, nano-size of 589 \pm 3.6 nm, negatively charged zeta potential of 51.33 \pm 0.36 mV). Proliposomes were stable with good physical-chemical properties.

7. Atopic dermatitis, ethosomes, nanoethosomes, cubosomes, nanofibrils and other nanocomposites

Akhtar and colleagues [80] developed β -cylcoethosomes based on β -cycloamylose and carbomer 934P gel (nano-size of 228.33 \pm 1.23 nm), demonstrating good skin permeability, whereas Li and coworkers [81,82] prepared ethosomes loaded with tacrolimus, obtaining satisfactory pharmacological effects.

Izumi et al. [83] assessed the effect of chitin nanofibrils (CNFs) in a murine model. CNFs proved as effective as the topical application of corticosteroids. From a molecular standpoint, CNFs seem to reduce NF- κ B, COX-2, iNOS, and IgE levels.

Kwon and Kim [84] fabricated lipid cubosomes, loaded with water-soluble extracts of *Houttuynia cordata* and tested them in hairless mice. The formulation was found to decrease IgE and IL-4 expression, while stimulating IFN- γ expression.

Shershakova and coworkers [85] exploited water-soluble forms of fullerene C60 prepared by exhaustive dialysis of water-organic C60 solution against water (nano-size of 100 nm and negatively charged zeta-potential of 30 mV). In a murine model female BALB/c mice, improvements in immune responses (reduced concentrations of IgE and T_{H2} cytokines, with increased levels of T_{H1} cytokines) and skin barrier function (increased levels of Foxp3⁺ and filaggrin expression) were detected.

8. Nanotechnology and atopic dermatitis: current challenges

Despite their hope and promises, nanotechnology-based solution can have also triggering effect on the induction of allergic reactions and the clinical amplification of such symptoms. Utilizing a mouse model, Kang and collaborators [86] found that 5- but not 100-nm nano-sized Ag-NPs induce release of granule from tryptase-positive mast cells, as well as lead to increased reactive oxygen species (ROS, hydrogen peroxide and mitochondrial superoxide) levels and intracellular calcium concentrations.

Similar adverse events have been reported for titanium dioxide, silica and zinc oxide-based nanoparticles [87–90].

However, a final consensus on the safety of nanotechnological devices is yet to be established, needing more convincing investigations that expert scientists should consider and appraise carefully. Further research in this field is, therefore, warranted.

9. Future prospects

Nanotechnology-based therapeutics appear promising also in preventing atopic dermatitis. Oral oligodeoxynucleotide nanocapsules (iODN-CAPs/iSG3-CAPs) specifically targeting the gut Peyer's patches, after being administered and taken up by macrophages, are able to induce an effective immune response. If continuously administered, iODN-CAPs/iSG3-CAPs in the long-term seem to display inhibitory/suppressive effects, preventing the insurgence of skin lesions and reduced epidermal thickness and elasticity typical of atopic dermatitis. From a molecular standpoint, this formulation binds to the "Signal Transducer and Activator of Transcription 6" (STAT-6), inhibiting its phosphorylation. *STAT-6* gene is involved in the etiopathogenesis of atopic dermatitis, increasing its propensity and risk, leading to disseminated viral infections [91]. Signaling pathways and IL-4 related cascades, that are usually mediated by binding of allergens to T_{H2} cells or environmental *stimuli*, are, therefore, inhibited.

Finally, most studies included in the present systematic review have been conducted *in-vitro* or *in-vivo*, with few randomized controlled clinical trials (RCTs). Future investigations should adopt this design in order to enable scholars achieving robust findings and evidence.

10. Conclusions

Nanotechnology-based solutions appear promising in the management of atopic dermatitis, especially the recalcitrant forms, enabling: i) a better bio-availability and trans-dermal drug targeted delivery at the inflammation site, displaying better physical-chemical properties, permeation, retention and diffusion profiles, ii) dose control, iii) improvements both in clinical symptoms and immune responses, inhibiting inflammatory cascades and pathways up to 3–5 times and positively impacting on patient's quality of life, iv) with less adverse

events being reported [92–99].

However, given the above-mentioned shortcomings, further research in the field is urgently warranted.

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Declaration of competing interest

None.

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