Delivery of Natural Products Based on Nanotechnology for the Treatment of Eczema

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Abstract: Atopic dermatitis, known as eczema, presents a complex challenge rooted in environmental, genetic, and immune factors. While standard treatments like corticosteroids offer relief, they often come with side effects. The allure of natural compounds lies in their potent therapeutic effects and lower risk, yet their efficacy is hindered by stability and solubility issues. Enter nano formulation-based approaches, which strive to amplify the healing potential of these natural remedies. By packaging them in nano-sized carriers, these formulations aim to bypass limitations, enhancing their efficacy in addressing eczema symptoms. However, a critical gap exists in consolidating recent research on these innovative formulations. A focused literature review in this realm would be invaluable, shedding light on breakthroughs, limitations, and pathways for refining these solutions toward more effective eczema management.

Keywords: Eczema, atopic dermatitis, nano formulations, corticosteroids, therapeutic efficacy, stability issues, nano-sized carriers, efficacy enhancement

Introduction

The human skin, covering an expansive area of about 1.8 square meters and consisting of the epidermis, dermis, and subcutaneous tissue, serves as our body's largest organ. Its multifaceted role includes shielding us from external hazards, regulating electrolyte balance, managing body temperature through evaporation, and hosting a crucial immune system that defends against diseases[1]. Statistics underscore the widespread occurrence of skin ailments, with roughly half of adults encountering some form of skin condition during their lives. Alarmingly, around a third of these cases persist as chronic or recurring issues. These skin diseases profoundly impact individuals across age groups, from children to adults, significantly influencing their quality of life. Understanding and addressing these conditions are pivotal in safeguarding overall well- being[2]. AD, also known as eczema, is a serious skin condition characterized by eczema-like symptoms and severe skin irritation. These skin diseases usually appear around age 5 and affect approximately 30% of children and adolescents compared to 2-10% of adults. However, it is now believed that AD can occur at any time. There are many costs involved, including psychological harm to patients, risk of depression and suicide, irritation and severe pain, as well as skin cleansing supplies, appropriate clothing, lotions and creams. Interestingly, the exact cause of this disease is not fully understood, but the main findings point to the interaction of three main mechanisms: defects in skin structure, changes in the skin microbiota, and impaired Th2 immunity[3,4,5,6].

Fig 1 : Eczema.

Natural products are the source of several, and highly heterogenous, molecules such as multiple phenolic ring-bearing compounds such as flavonoids, tannins, and catechins, nitrogen-containing molecules such as alkaloids, carotenoids, and polysaccharides, and small volatile molecules such as those found in essential oil-bearing plants[2,7,8,9]. Interestingly, their anti-inflammatory properties in the treatment of skin inflammation-based diseases have been depicted, such as for vitiligo[10]. Psoriasis[11], and, more importantly, AD[9]. Recent research suggest that these molecules exert an antioxidant activity, improving cells redox status, that in turn ameliorates the inflammatory response, by suppressing the activity of key regulators in mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathways, which are key molecular inflammatory responses[8].
In recent years, nanotechnology-based solutions have emerged to address challenges in transdermal delivery, enhance targeted drug delivery, tackle solubility issues of active compounds, and boost the effectiveness of natural ingredients for treating Atopic Dermatitis (AD)[12]. Several successful examples have been explored in this review, including quercetin nanostructured lipid carriers, solid lipid nanoparticles containing capsaicin and curcumin[13,14]. Urban extracts[15], Nano capsule-incorporated films of pomegranate seed oil[16], and ethosome-based creams incorporating tea tree oil[17]. These formulations, among others detailed in this paper, showcase promising strides in leveraging nanotechnology to optimize the delivery and efficacy of natural compounds for AD treatment.

In this comprehensive review, our primary focus lies in exploring the integration of individual natural and herbal extracts, mixtures, and oils into nanotechnology-driven formulations for treating Atopic Dermatitis (AD) in recent advancements. This article not only offers a foundational understanding of the disease's pathophysiology but also elucidates the array of nanotechnology tools utilized in its treatment, providing a comprehensive overview of this area. Additionally, each natural product and nano system discussed in this review is accompanied by insights into their pharmacological properties, physical characteristics, and essential attributes, aiming to offer a holistic understanding. By emphasizing the most recent and groundbreaking developments, this review serves as a thorough exploration of innovative nanotechnology-based formulations incorporating natural products for the treatment of Eczema.
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Materials and method

A thorough investigation into the prospective role of nanotechnology-based formulations for delivering natural products in treating Atopic Dermatitis (AD) is underway. This review encompasses a comprehensive analysis of data spanning the decade between 2013 and 2023. Extensive searches were conducted across multiple databases including ScienceDirect, Scopus, PubMed, Web of Science, and Google Scholar. Various keywords were employed either individually or in combination, such as atopic dermatitis, eczema, inflammation, skin, natural products, alkaloids, phenolic compounds, flavonoids, terpenes, polysaccharides, oil, plant extract, drug delivery, and nano systems. The literature review, synthesizing recent studies, delves extensively into the utilization of numerous natural isolates, plant extracts, compounds, and oils in combating AD through nano formulation-based drug delivery approaches.

Isolated natural compounds included in nanotechnology-based formulations for the treatment of AD

Astaxanthin

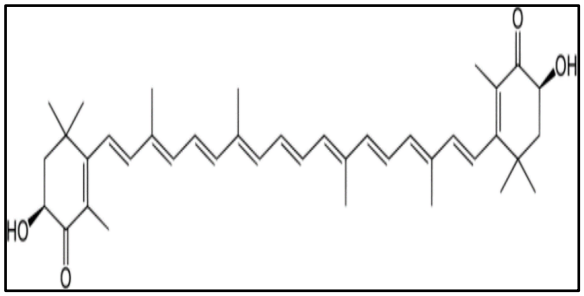

Fig 2: Molecular Structure of Astaxanthin

Natural Source, Physicochemical Features, and Bioactive Properties of Astaxanthin :

Astaxanthin, with a molecular formula C40H5204, and a weight of 596.84 g/mol, belongs to the xanthophyll carotenoid family and is notably present in various living organisms, including microalgae, crustaceans, seafood, yeast, fungi, plants, and bird feathers. Its vibrant red colour, a lipid-soluble trait, contributes to the distinct red-orange hue seen in marine animals while also serving as a shield against UV radiation. This compound's unique structure encompasses a non-polar core flanked by thirteen conjugated double bonds, coupled with two polar segments housing ionone rings featuring hydroxyl (at 3,3') and keto (at 4,4') groups, explaining its dual hydrophobic and hydrophilic nature. Astaxanthin manifests in multiple forms, including optical and geometric isomers, free or esterified versions, and associations with proteins, or lipoproteins, with the esterified form being the most prevalent in nature[18,19,20,21].

Astaxanthin boasts a diverse array of therapeutic and health-enhancing properties. Its antioxidant, anti-inflammatory, and anti-apoptotic activities contribute significantly to its potential benefits in cancer treatment, obesity management, regulation of triglycerides and cholesterol levels. Additionally, it offers advantages to human skin by functioning as an immunomodulator, exhibiting anti-diabetic properties, and acting as a protective agent for the liver and nervous system[20].

Drug Delivery Systems and Pharmacological Activity of Astaxanthin:

Astaxanthin has been shown to be a potent antioxidant that blocks inflammation at the onset of NF-kB and inhibits inflammatory factors such as interleukin-1ß (IL-18), interleukin-6 (IL- 6), and tumor necrosis factor-a (TNF).)-a). It also inhibits cyclooxygenase-1 (COX- 1) and nitric oxide (NO)[18,20]. The antidermatitis effect is also seen through inhibition of other markers of inflammation: inducible nitric oxide synthase (NOS), cyclooxygenase-2 (COX- 2) and IgE[15,21].
Different formulations have been developed to enhance stability and bioavailability of astaxanthin in topical applications which include nano emulsions (NES)[22], hydrogels/lipogels[23], liposomes (LIPS)[18], and NLCs.
Among the former, only Lee focused on the analysis of agents developed in AD[18]. Therefore, liposome formulations containing astaxanthin (L-AST) were prepared; where conjugation to a phospholipid structure improves the water solubility of this molecule and allows investigation of its effect in preventing AD by inhibiting skin inflammation[18]. This liposomal astaxanthin is prepared by mixing it with phosphatidylcholine at a ratio of 1:4 using a highly homogenizing Microfluidizer TM. The particle size measured by ELS-Z is approximately 64.5 nm. The results of this study show that signal transducer and activator of transcription 3 (STAT3) and NF-kB are indeed inhibited by L-AST, demonstrating its anti-AD potential. In fact, LIP is characterized by a bilayer membrane compared to the phospholipid cell membrane surrounding an aqueous core and is poorly distributed and biodegradable. Due to its high biocompatibility, LIP easily combines with stratum corneum cells, allowing it to penetrate deeply into the epidermal layer. They also increase the solubility, compatibility and biodegradability of the drug when combined with hydrophobic and lyophobic drugs and are used to deliver drugs to the affected area[24].

B-Carotene

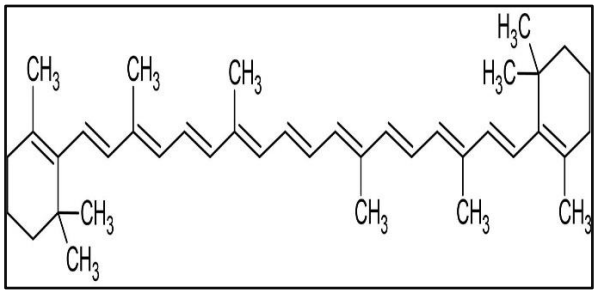

Fig 3: Molecular Structure of Beta- Carotene

Natural Source, Physicochemical Features, and Bioactive Properties of B-Carotene:

Beta-carotene, a member of the carotenoid family, serves as a precursor to vitamin A, a vital micronutrient for human health. This compound exists abundantly across various natural sources, including plants, algae, fungi, and bacteria. Among its isomers (a, β, γ, δ, ε, and 5),B-carotene stands out as the most prevalent and potent form. Renowned for its antioxidant prowess, beta-carotene plays a crucial role in supporting the immune system. Studies indicate that its consumption aids in allergy prevention and diminishes the risk of Atopic Dermatitis (AD). Its anti-inflammatory properties have rendered it effective in treating a spectrum of skin conditions, particularly AD[25].

At its core, beta-carotene consists of organic compounds characterized by polyene chains featuring lengthy conjugated double bonds that terminate in cyclic groups. Devoid of oxygen atoms, its electron-rich conjugate system underlies its remarkable antioxidant attributes[25].

Drug Delivery Systems and Pharmacological Activity of B-Carotene:

Beta-carotene exhibits anti-inflammatory effects by curbing cytokines, factors, and matrix metalloproteinase (MMP) activity in rats with oxazolone-induced Atopic Dermatitis (AD). Notably, it enhances filaggrin expression, improving skin function and fortifying the immune system. The same research group investigated oral beta-carotene administration's impact on AD-like skin, observing its effects on various factors including TNF-a, IL-18, MCP-1, TSLP, IL-6, IL-1B, IL-4, IL-5, and protease-activated receptor 2, which led to increased filaggrin expression. Moreover, beta-carotene reduced MMP activity and mRNA expression, mitigated extracellular matrix degradation, and modulated chemokines in the skin[25].

Nanofibers (NF) represent a significant class of nanomaterials extensively employed in pharmaceutical applications owing to their large area-to-volume ratio and operational efficiency, coupled with reduced water absorption and minimal checks required. Polycaprolactone (PCL), among polymer nanofibers utilized in drug delivery, stands out due to its tissue compatibility and reasonable tensile strength. Semnani and colleagues innovatively developed a PCL nanofiber mat loaded with beta-carotene using the electrospinning method. These nanofibers, with diameters ranging from 400-800 nm, exhibit optimal characteristics. In vitro studies reveal the slow degradation and controlled release of beta-carotene from the mats. These findings suggest the potential application of beta- carotene-loaded pads in treating skin conditions like AD[25].

Capsaicin

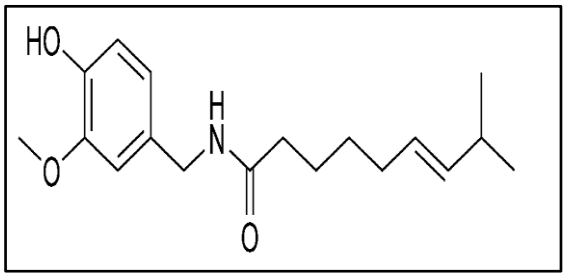

Fig 4 : Molecular Structure of Capsaicin

Natural Source, Physicochemical Features, and Bioactive Properties of Capsaicin:

Capsicum annum L., commonly referred to as pepper and belonging to the Solanaceae plant family, serves as a significant source of capsaicin (C18H27NO3). This lipophilic and pungent alkaloid, with a molecular weight of 305.40 g/mol, constitutes over 90% of all capsaicinoids present in peppers. Additionally, peppers contain other capsaicin-related compounds like dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin, all contributing to the fruit's spiciness. The pungency of capsaicin arises from an amide bond linking the acyl chain to the vanyl ring. Interestingly, capsaicin shares certain properties with another alkaloid,

piperine, prompting research into various activities encompassing irritation, nociceptive response, anti-inflammatory effects, anticancer potential, anti-obesity properties, and antibacterial activity[26].

Drug Delivery Systems and Pharmacological Activity of Capsaicin:

Capsaicin's analgesic effect primarily stems from its interaction with the transient receptor potential vanilloid I (TRPV1) ion channel, responsible for pain perception in the skin's sensory receptors. Additionally, its anti-inflammatory properties arise from its ability to inhibit pro- inflammatory mediators like COX-2 and INOS, Despite its notable nociceptive and anti- inflammatory traits, capsaicin encounters challenges due to its poor bioavailability owing to its lipophilicity and potential for skin irritation Consequently, researchers have explored novel approaches for capsaicin delivery[27]. Cassano et al. (2022)[11] aimed to enhance capsaicin's delivery by incorporating it into solid lipid nanoparticles (SLNs) alongside linoleic acid, alongside curcumin and resveratrol-derived esters, for treating Atopic Dermatitis (AD). Interestingly, results revealed that formulations with curcumin and resveratrol monooleate exhibited superior outcomes in alleviating AD-like symptoms compared to capsaicin oleate-based products. These findings are elaborated further in the article. Notably, the average size of capsaicin SLNs was 2774 120 nm, with a polydispersity index (PDI) of 0.192 ± 0.095 and almost complete encapsulation efficiency reaching 99%. SLNs offer advantages like precise skin targeting. improved dermal penetration, controlled drug release, minimized water absorption, and protection against compound degradation from hydrolytic and oxidative processes[11].

Curcumin

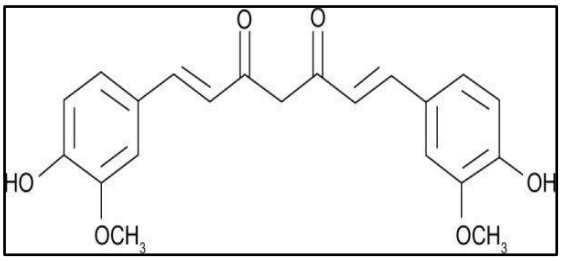

Fig 5 : Molecular Structure of Curcumin

Natural Source, Physicochemical Features, and Bioactive Properties of Curcumin:

Curcumin, sourced from the root of Curcuma longa L., commonly known as turmeric and part of the same plant family as Zingiber officinale L. (ginger), stands as a B-diketone polyphenolic compound (C21H20O6). Its formation involves a distinctive benzene ring housing a B-diketone group, a carbon-carbon double bond, and hydroxyl and methyl functional groups. This distinctive composition generates potent antioxidant compounds that specifically target inflammatory cytokines, proteins, enzymes, and transcription factors. Traditionally recognized as a yellow pigment, curcumin has been utilized for its digestive benefits in treating gastrointestinal and skin conditions. Moreover, extensive in vitro and in vivo studies have been conducted, affirming its antibacterial, antiviral, and anti-inflammatory properties. Notably, curcumin finds application in managing Atopic Dermatitis (AD) symptoms in several Asian countries[6].

Drug Delivery Systems and Pharmacological Activity of Curcumin:

Curcumin's impact on AD has been investigated both in vitro and in vivo, revealing promising outcomes. In vitro studies on the human mast cell line HMC-1 demonstrated curcumin's ability to induce TSI.P while impeding the caspase-1/NF-KB pathway. In a recent animal study utilizing aerosolized ovalbumin (OVA) exposure on mice, curcumin showcased its potential in ameliorating AD symptoms. It notably repaired epidermal thickness and impeded the infiltration of inflammatory cells into the dermis. At the molecular level, curcumin treatment suppressed the expression of Th2-promoting cytokines (TSIP/IL-33) and Th2 cytokines (II.-4/IL-5/IL-13/11-31), along with inhibiting STAT-6 phosphorylation and GATA-3 expression[6].

Another study involved gels containing solid lipid nanoparticles (SLN) loaded with tetrahydro curcumin, a curcumin-derived metabolite exhibiting medicinal properties and greater abundance than curcumin. Utilizing

microemulsion technology and high-performance homogenization, a high encapsulation efficiency (83.10%±2.29%) with a particle size of 109.2 nm was achieved for the SLN dispersion. Coating these SLNs with Carbopol hydrogel and testing them on 2,4-dinitrochlorobenzene (DNCB)-induced AD mice demonstrated their anti-inflammatory potential[28,29]. This pang system notably reduced TNF-a and IL-6 expression levels, successfully treating AD-like symptoms, even surpassing the effects of commercial Tastez Forte ointment or tetrahydro curcumin-free gel ($p<0.05$). Moreover, these tetrahydro curcumin-containing nanoparticles showed potential in improving skin hydration by enhancing transdermal permeability from the skin layer to the dermis[30,31].

Cynaroside

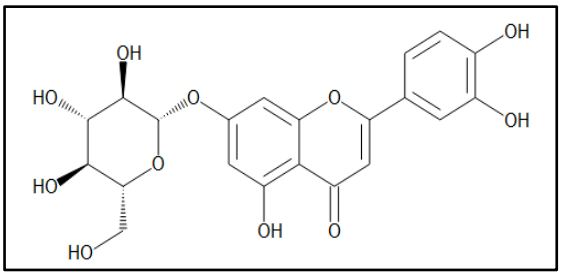

Fig 6: Molecular Structure of Cynaroside

Natural Source, Physicochemical Features, and Bioactive Properties of Cynaroside:

Cynaroside (luteolin-7-O-glucoside or luteolin; C21H20011), Pseudomonas aeruginosa, Verbascum lychnitis L., Elsholtiza bodinieri Vaniot, etc. It is a natural product found in plants such as. This is related to the glycosyloxy flavonoid luteolin. It is known for its diaphoretic, diuretic, antiseptic, anti-inflammatory and antiallergic activities. Its anticancer effects and hepatitis B protection are also known[32].

Drug Delivery Systems and Pharmacological Activity of Cynaroside:

The natural compound synaroside demonstrates anti-inflammatory effects by targeting II.-4 and IgE expression, while also controlling keratinocyte hyperproliferation through the inhibition of II.-22 and IL-6/STAT3 pathways. In vitro evaluations revealed its efficacy in reducing NO and ROS production. In vivo studies using a xylene-induced ear infection rat model exhibited inhibited edema, and reduced prostaglandin E2 (PGE2) levels in rats[33].
Zekalska et al. developed new hydrogels containing Sina glycosides as topical agents, incorporating anionic polymer alginate for its bio adhesive properties. These hydrogels, combined with glycerine, propylene glycol, and crushed squash from B. tripartita's aerial part, displayed particle sizes ranging from 22,000 to 26,000 nm. In vivo assessments on hairless mice using carrageenan-induced rat paw edema, and oxazolone-induced earache models demonstrated that 5% and 10% cynarine hydrogels effectively reduced skin and muscle swelling, along with inflammatory infiltrates. Topical application of synarın reduced the presence of T cells, mast cells, and histiocytes in the skin of inflamed and AD mice, suggesting its potential in modulating cytokine expression and IgE levels[34].

To address issues related to semaside solubility, bioavailability, and oral toxicity, Qing et al. devised biodegradable and biocompatible deblock copolymer micelles loaded with semaside. to enhance water solubility. These micelles, comprising a hydrophobic core and a hydrophilic shell encapsulating the active ingredient, employed different polymers such as MPEG-PCL, PEG-PLGA, and MPEG-PDLLA. These self-assembled micelles exhibited an average diameter of 70 nm and demonstrated controlled drug release of approximately 30% setamideside, in vitro. Additionally, prior to micelle development, Qing and colleagues explored a nanocomposite composed of nanocrystalline cellulose (NCC) to enhance pumpkin bioavailability, a material known for its biocompatibility, biodegradability, and low cytotoxicity. While these designs show promise, they have not been specifically tested for conditions like AD or other skin-related ailments[35].

Extracts, oils and plant mixtures included in nano-technology-based formulations for the treatment of AD

Linseed Oil

General consideration about Linseed Oil:

Among more than two hundred species included in the genus Linum L, the plant Linum usitatissimum L. is the oldest one. Known as flax or linseed, it has a high nutritional value: omega-3 fatty acid, such as a-linolenic acid and short chain polyunsaturated fatty acids (PUFAs), soluble and insoluble fibers, phytoestrogen-related lignans, proteins, and different antioxidants. It is found in the international food supply as a functional food. From its dried ripe seeds, a very interesting oil (Linseed oil, LSO) is extracted, comprising the following fatty acids: stearic, palmitic, linoleic, oleic, and linolenic. For this reason, flaxseed has been studied in nutrition and disease research for the health benefits of some of its bioactive compounds alpha-linolenic acid (almost 60%) and the lignan secoisolariciresinol diglycoside (SDG)[34].

Apart from its practical uses, LSO also has many beneficial properties such as anti-bacterial, anti-bacterial and anti-inflammatory, and can be used to treat arthritis, cancer, keratoconjunctivitis and various skin diseases. In fact, this herb has been used topically for years to treat skin conditions such as eczema because it contains "mucilage" that soothes and softens the skin[34].

Drug Delivery Systems and Pharmacological Activity of Linseed Oil:

Flaxseed oil helps control inflammation through eicosapentaenoic acid (EPA), which is replaced by alpha-linolenic acid, an important omega-3 fatty acid EPA acts as a competitive inhibitor of the conversion of arachidonic acid to prostaglandin E(2) (PGE2) and leukotriene B(4) (LTB4). Its potent ability to inhibit histamine and bradykinin has also been reported. This makes it very effective against diseases. The EPA has identified it as an important factor in AD Human metabolism can convert the linoleic acid in LSO to EPA. Therefore, to evaluate the application of LSO as an alternative treatment for AD, a new and better delivery method for LSO, namely emulsion, was developed. Microemulsions are used as an important tool to increase skin permeability and reduce drug permeability. It is very irritating to the skin and has a high chemical loading capacity. However, direct topical use of flaxseed oil is limited due to the low permeability of the stratum corneum. To overcome this problem, Babuta and colleagues developed a submicron microemulsion of flaxseed. Since Carbopol 971 is an oil/water emulsion, it is used to increase the viscosity of the microemulsion. Particle size and zeta potential showed an average particle size of 186 nm with small particle size, in vitra studies on the skin showed that this microemulsion improved the penetration of flaxseed and constituted a treatment for skin diseases[34,36,37,38,39,40].

Tea Tree Oil

General consideration about Tea Tree Oil :

Tea tree oil is an essential oil derived from distilling the leaves of the Melaleuca alternifolia (Maiden & Betche) Cheel plant, a member of the Myrtaceae family, similar to eucalyptus. It is characterized by its oxygenated monoterpene hydrocarbons, consisting of monocyclic and bicyclic monoterpenes. Terpinen-4-ol stands as the primary monoterpene in this oil. Additionally, tea tree oil comprises various other terpenes, including y-terpinene, a-terpinene, 1,8-cineole, p-cymene, terpinolene, a-terpineol, a-pinene, sabinene, arylene, lepene, ō-.juipen, limonene, glomerol, and viridifluorol[41,42,43].

Drug Delivery Systems and Pharmacological Activity of Tea Tree Oil:

Terpenoids like terpinen-4-ol, a-terpineol, and 1,8-cineole have demonstrated the capability to lower the levels of pro-inflammatory cells such as TNF-a, IL-18, IL-8, and IL-10. Leveraging these properties, incorporating

these essential oils into Ethylene Topical Oleosomes (ETO) explores their potential in Atopic Dermatitis (AD) treatment.

The formulation of ETO containing tea tree oil involved 2% and 3% (w/v) phosphatidylcholine and varying concentrations of ethanol (20%, 30%, and 40% w/v). The optimized ETO exhibited an encapsulation efficiency (EE) of 76.19± 3.26%, a vesicle size of 333.6 nm, and a zeta potential (ZP) of -35.3 mV. This optimized ETO was then integrated into a formulated sugar base using the phase inversion method.

Apart from exhibiting non-toxicity to keratinocytes (HaCaT cell line) in vitro, formulations based on ETO showcased superior in vivo permeability, effectively releasing the active compounds into the epidermis and dermis compared to conventional formulations. In vivo evaluation in a BALB/c mouse model demonstrated reduced leukocyte and eosinophil infiltration, decreased IgE antibody presence, and a reduction in severity score. Additionally, this ethylene oxide-based sugar formulation prevented oxidative degradation, enhancing chemical stability and skin permeability. The simplicity of the method employed for this ETO-based design suggests potential for further development and ease of application in practical use[41,42,43].

Pomegranate Seed Oil

General consideration about Pomegranate Seed Oil :

Pomegranate seed oil (PSO) is derived from the seeds of the pomegranate fruit, belonging to the Pomegranate family. This vegetable oil comprises a diverse blend of beneficial molecules, making it a subject of extensive research in various health domains, including its potential in diseases, vaccines, and chronic conditions like cancer, blood-related disorders, osteoporosis, obesity, and diabetes. Its profile includes notable anti-inflammatory and immunomodulatory properties[44].

Pomegranate seeds, constituting about 10% of the fruit's total weight, are rich in carbohydrates such as pectin and fiber, alongside vitamins E, C, and K, minerals, phenolic compounds, and flavonoids. Furthermore, they contain triterpenoids and plant sterols like 17- a-estradiol and estriol. Regarding the fatty acid composition, PSO comprises saturated fats (approximately 30-35%), monounsaturated fats (ranging from 35 to 37%), Di unsaturated fats (in quantities of 25 to 39%), and polyunsaturated fats (1 to 10%). Notably, punicic acid dominates the polyunsaturated fatty acid fraction and serves as the primary compound within PSO[45].

Drug Delivery Systems and Pharmacological Activity of Pomegranate Seed Oil :

The researchers in these studies explored pomegranate seed oil (PSO) due to its established medicinal properties as an anti-inflammatory, antioxidant, and a potential component in managing Atopic Dermatitis (AD). In one study, Cervi et al. developed a rubulan film loaded with PSO nanocarriers (NCs) using a heavy casting method for pullulan film preparation and the interfacial precipitation method to produce the NCs. Simultaneously, they prepared a panosmulsion (NE) of PSO using the spontaneous emulsification method to create a comparable pang system. In vivo analysis in mice treated with DNCB (a sensitizing agent) showed that both free PSO and rubulan films containing PSO NCs reduced AD-like lesions. However, only the rubulan film loaded with PSO NCs effectively reduced inflammation and improved redox conditions in the DNCB-treated mouse model, as seen in biochemical analysis. In vitro safety testing revealed the formulas to be safe without causing skin irritation.
The PSO-containing NCs exhibited an average diameter of 181 ± 6 nm, a low polydispersity index (PDI) below 0.2, and a zeta potential (ZP) around 43.13±0.7 mV. The hydrophilic and flexible nature of the pullulan film, a natural polymer derived from fungal fermentation, facilitated the incorporation of NCs into the polymer film, enhancing their consistency and quantity for pharmaceutical applications. Film stabilizers like pullulan have minimal impact on the skin, reduce stickiness during cosmetic use, linger on the skin surface for extended periods, and generate a hydrophilic solution. Notably, PSO has been utilized in forming hydrogels loaded with other compounds like silibinin, albeit it's worth noting its potential for irritant contact dermatitis as well[44,45].

CONCLUSION

Natural products have proven their effectiveness and quality in treating various skin conditions, especially when used in nanotechnology-based formulations Therefore this article reviews research on the development of novel nano systems for natural products for the treatment of AD, including isolates, plant extracts, plant mixture, and oil plant. Therefore, through this review, we hope to stimulate new research on natural products and drug development, as well as encourage physicians to conduct more robust research evaluation experiments to demonstrate the reliability of these methods and support their use in future clinical applications, inside. In this sense, we believe that this review is the most important source of research that addresses health problems and opens new ways to manage AD.

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