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Review

Lipid Nanoparticles and Skin: Discoveries and Advances

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Abstract: Nowadays, skin is one of the organs most commonly affected by diseases (infections, inflammations, and injuries) due to exposure to the external environment. Although topical treatment represents the most suitable administration route, it is poorly effective due to the low permeability of the drug through the skin. Skin drug delivery by lipid nanocarriers (LNs) appears to be a suitable therapeutic strategy to overcome these issues, allowing it to reach a topical or systemic effect. Several LN-based products have been developed to enhance the permeation of bioactive compounds through the skin, obtaining interesting results in both pharmaceutical and cosmetic fields. Therefore, this review aims to analyze the scientific literature regarding the use of LNs to treat major skin diseases (psoriasis, wound healing, atopic dermatitis, and acne) and esthetic skin defects (wrinkles and cellulite). Furthermore, attention has been paid to the transdermal application of LNs (topical formulations, transdermal patches, and microneedles), being a new topic in recent years.

Keywords: skin drug delivery; cosmetics; skin disorders; lipid nanoparticles

1. Introduction

The skin is the body's largest organ and it is the primary protective part against the environment [1]. It is composed of three layers: epidermis, dermis, and hypodermis [2]. Epidermis, the outermost layer of skin, provides a waterproof barrier [3]. It is constituted by a keratinized stratified squamous epithelium made up of five sublayers: basal cell layer, squamous cell layer, stratum granulosum, stratum lucidum, and stratum corneum (SC). The latter is the most superficial layer of the epidermis and it is exposed to the outside environment [4]. Therefore, its main functions are to prevent dehydration, penetration of pathogens, and injuries [5,6]. The dermis, the layer beneath the epidermis, contains connective tissue, blood and lymph vessels, nerves, and other structures, such as hair follicles and sweat glands. It is able to support the epidermis by exchanging oxygen and nutrients [7,8]. Hypodermis, the deeper subcutaneous tissue, is made of fat and connective tissue contributing to heat conservation. Therefore, the main functions of the skin include temperature regulation, sensory perception, and protection against external stimuli, such as ultraviolet (UV) light, trauma, and pathogens [9]. The skin may be affected by many disorders, infections, inflammations, and injuries. Topical treatment represents the most suitable strategy to obtain a therapeutic drug concentration in the action site reducing systemic side effects [10]. Due to the complex structure of the skin, several nanotechnological approaches have been developed in order to bypass and/or modulate the drug permeation through it. In particular, lipid nanoparticles (LNs) have emerged as promising nanocarriers for topical and transdermal drug delivery due to their advantages, including controlled drug release, increased drug skin permeation/penetration, easy scale-up, and low costs of production [11,12]. Furthermore, they have shown high biocompatibility thanks to the use of a lipid matrix (Generally Recognized As Safe, GRAS) with a composition similar to

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Academic Editor: Antonio Vassallo

Received: 5 December 2024
Revised: 20 January 2025
Accepted: 23 January 2025
Published: 27 January 2025

Citation: Santonocito, D.; Puglia, C. Lipid Nanoparticles and Skin: Discoveries and Advances. *Cosmetics* **2025**, *12*, 22. https://doi.org/10.3390/cosmetics12010022

that of the skin [13,14]. Lipid nanoparticles increase the transport of bioactive compounds through the skin by improving drug solubilization, drug partitioning into the skin, and fluidizing skin lipids. This leads to an increase in the interaction between the nanocarriers and the stratum corneum, resulting in improved skin hydration and drug permeability. LNs are colloidal carrier systems with a mean particle size ranging from 50 to 1000 nm and they are structurally classified into first (Solid Lipid Nanoparticles—SLNs) and second-generation (Nanostructured Lipid Carriers—NLCs). SLNs were obtained from the substitution of the nanoemulsion oil phase with a solid lipid, while NLCs were developed by adding a mixture of liquid and solid lipids in order to minimize the drug expulsion phenomena observed with SLNs (Figure 1) [15]. Both nanosystems possess important features, useful in cosmetic and pharmaceutical fields, for topical and transdermal delivery of drugs and active compounds.

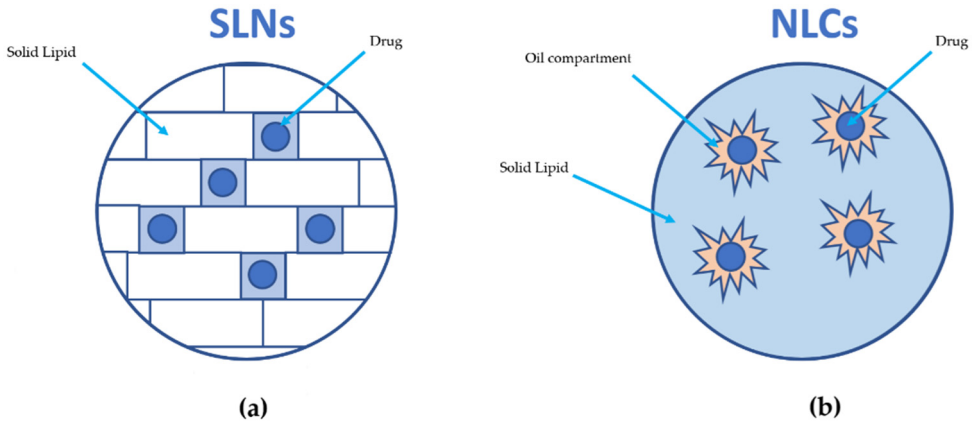

Figure 1. Lipid nanoparticle structure: (**a**) SLNs and (**b**) NLCs.

Based on the numerous benefits of LNs mentioned, this review analyzes the scientific literature regarding the use of these nanocarriers to treat skin diseases (acne, psoriasis, and infections). In addition, attention has been paid to transdermal administration, being a new topic studied in the articles published in the last decade. Therefore, the aim of this review was to collect the most recent studies to update the state-of-the-art and open new directions toward the use of LNs for cosmetic and pharmaceutical applications through the skin.

LNs: Preparation and Characterization

LNs can be produced using different methods, such as high-pressure homogenization, high shear homogenization coupled to ultrasound, and solvent evaporation technique [12,13]. The choice of method is important for the final characteristics of the product. The most common methods for producing LNs are as follows:

- The High-pressure homogenization (HPH) method represents the most used in the pharmaceutical and cosmetic fields thanks to its many benefits, like easy scale-up, absence of organic solvents, and short production time. Homogenization can be performed at hot or cold temperatures. In hot homogenization, the drug is dissolved in the molten lipid matrix and then dispersed in a hot surfactant solution, followed by homogenization. Instead, in cold homogenization, the melted lipid matrix containing the drug is rapidly cooled, using liquid nitrogen or dry ice, dispersed in a cold surfactant solution, and then homogenized;
- The Solvent evaporation method is another widely used technique to produce LNs. This method involves the lipid being dissolved in an organic solvent and then emulsified in an aqueous solution of surfactant. The solvent is then evaporated;

- The High shear homogenization coupled with ultrasound (HSH-US) is recognized as the most recent procedure to prepare LNs. This method involves the preparation of an O/W emulsion, according to the hot HPH method, followed by ultrasonication. This combination at short cycles allows us to obtain small particle sizes with low polydispersity index.

The characterization of LNs involves the measurement of nanotechnological parameters (mean particle size, polydispersity index, and zeta potential) and the evaluation of the encapsulation efficiency of the system [13]. The mean particle size and polydispersity index are measured by Photon Correlation Spectroscopy (PCS), a method based on the principle of dynamic light scattering. In particular, it calculates the hydrodynamic ray of the particles, through the Stokes–Einstein equation, by measuring the fluctuations of the scattered light due to the Brownian particle motions. The zeta potential, an indicator of the stability of a dispersed system, is determined by Electrophoretic Light Scattering (ELS), a technique which measures the electrophoretic mobility of particles in dispersion or in solution. This mobility is converted to zeta potential. The determination of the encapsulation efficiency of LNs can be measured using many methods, such as centrifugation, filtration, or tangential filtration. The latter is the most preferred method as it is able to overcome the limitations of other techniques, such as agglomeration phenomena and adhesion to the membrane surface, thanks to the filtration that occurs tangentially to the filter surface. Furthermore, it allows continuous work, constant flow, and total recovery of the product. The encapsulation efficiency is calculated by Equation (1):

$$\text{E.E. (\%)} = (\text{Mass of drug in nanoparticles})/(\text{Mass of drug fed to the system}) \quad (1)$$

2. Topical Application of LNs

The topical application is mainly preferred in treating skin disorders. It is an important administration route for drugs that require local action on the skin, thereby avoiding adverse side effects and their systemic absorption [16]. Since conventional topical treatments and systemic therapy have often shown low therapeutic efficacy and numerous side effects [17], the development of topical drug delivery systems, such as lipid nanoparticles (LNs), has shown promising results in the treatment of skin disorders (Figure 2). The excellent tolerability of LNs is due to the use of lipid matrices that possess structural similarities with the constituents of the epidermis, in particular SC [18]. Indeed, LNs are able to create a hydrophobic film on the skin, leading to a loosening of corneocyte packing. As a result, drugs entrapped in LNs can then easily cross the deeper layers of the skin (Figure 2) [19]. It has been shown that SLNs possess a deeper skin permeation than NLCs due to their high content of solid lipids; this effect was more evident when their particle size was less than 260 nm. In particular, Adid et al. demonstrated that SLNs with sizes around 100 nm are able to reach the deeper layers of the skin, nanoparticles with average sizes around 300 nm reach the upper layers of the skin, while larger SLNs with sizes around 1000 nm are unable to penetrate the skin [20]. In contrast, NLCs showed a higher drug loading and lower drug expulsion due to their imperfect structure given by the liquid and solid lipids used [21]. Therefore, LNs have emerged as promising nanocarriers for the topical delivery of bioactive compounds, exploiting their potential skin health properties for pharmaceuticals and cosmetic applications.

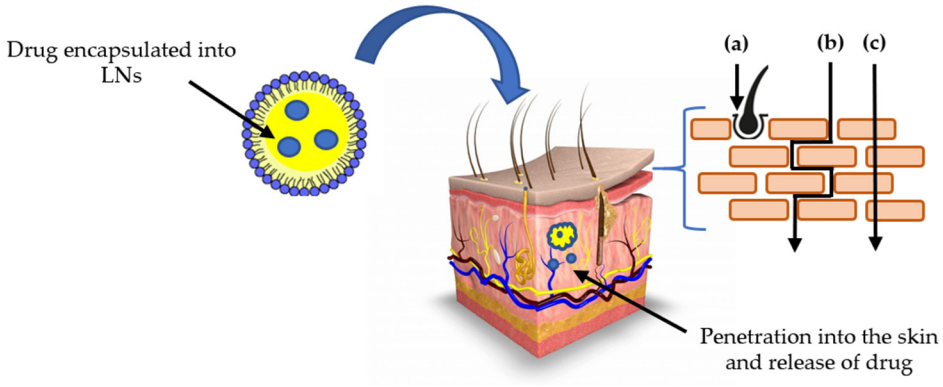

Figure 2. Nanoparticle skin penetration pathways: (**a**) transappendageal, (**b**) intercellular, and (**c**) transcellular.

2.1. Pharmaceutical Applications

2.1.1. Psoriasis Treatment

Psoriasis is a chronic inflammatory skin disorder characterized by itchy, erythematous, and squamous plaques on various parts of the body. Its etiology is multifactorial involving both genetics and environmental factors [22]. It affects more than 2% of the worldwide population with a prevalence in adults of age 20–30 years [23]. Generally, it depicts a lower occurrence in the countries located along the equator (African populations) and a higher incidence among those situated above the equator (Scandinavian people) [24]. This is probably due to different vitamin D levels and exposure to external microorganisms [25]. Based on clinical manifestations, psoriasis can be classified into five types: vulgaris, inverse, guttate, erythrodermic, and pustular psoriasis. Therefore, depending on the type and severity of the disease, different therapeutic strategies are used to control symptoms and prevent disease progression [26,27].

Current treatments include corticosteroids, phototherapy, calcineurin inhibitors, and cyclosporines. Among them, cyclosporine A (CsA), administered orally, has shown proven efficacy due to its immunosuppressive mechanism. Since its long-term use causes many adverse effects, such as hypertension and nephrotoxicity, its topical administration through the use of LNs (CsA-SLNs), which can circumvent its limitations related to high molecular weight and low hydrophilicity, seems to be advantageous [28]. In addition, LNs promote topical drug penetration due to their lipophilicity and high biocompatibility [29]. The release profile of CsA from SLNs was evaluated in vitro showing a site-specific release of the drug in the skin layers and a low transdermal release.

Methotrexate (MTX) is another important drug to manage psoriasis thanks to its anti-inflammatory and immunomodulatory activities. Generally, it is administered orally or parenterally once a week, causing many complications. Since MTX is insoluble in water, its topical application has issues in penetration to the skin that can be overcome by the use of SLNs [30]. Maiti et al. formulated MTX-loaded SLNs demonstrating the key role of drug encapsulation due to its controlled release and complete permeation through the skin (80.36%). In addition, they reported that MTX, when encapsulated into SLNs, was able to progressively inhibit the growth of keratinocytes (cytotoxic concentration was 518 mcg/mL), and was mainly distributed in organs meant for elimination (67.5% in the liver and 2.34% in the kidney, respectively) [30].

Tacrolimus (TAC), a macrolide immunosuppressive inhibitor of calcineurin, has also been studied for the treatment of psoriasis. Although its efficacy is well established, topical treatment of TAC is challenging due to its high hydrophilicity and molecular weight which compromise its skin absorption. Therefore, a nanotechnological approach has been studied to overcome these problems. In particular, Viegas et al. studied treatment with TAC and

siRNA (short interfering RNA) for TNF-α, one of the most expressed cytokines in psoriasis. NLCs were developed to co-deliver TAC and siRNA, showing controlled drug release and good permeation and retention profiles in the skin layers. Furthermore, a decrease in TNF-α expression levels and no significant toxicity on murine fibroblasts were observed [22]. In another study, siRNA was encapsulated into hybrid polymer–lipid nanoparticles (PLNs) combined with photochemical internalization (PCI) to improve the endosomal escape of TNF-α siRNA in the cytoplasm. This approach turned out to be effective as it was capable of silencing TNF-α and decreasing the redness and scaling of mouse skin [31].

Since psoriasis is a chronic inflammatory skin disease, the administration of natural anti-inflammatory compounds, such as betulin and noscapine, could represent a promising strategy for the treatment of psoriasis. Several compounds with potential anti-psoriatic activity have been loaded into LNs showing enhanced pharmacokinetic effects.

Betulin (BE) is a pentacyclic triterpenoid isolated from *Betula utilis* (*Betulaceae*) that shows interesting antipsoriatic activity due to its suppressive effect on pro-inflammatory mediators (IL-6, IL-17, and TNF-α). Since it showed low dermal permeability, poor solubility, and drug stability, its therapeutic use is limited [32]. Nanoencapsulation of BE in NLCs has shown improved skin penetration abilities and therapeutic effectiveness than free BE with a good safety profile. In addition, NLCs exhibited an optimized and sustained drug delivery, representing a promising novel topical dosage form for enhanced psoriasis management [33].

Noscapine (NOS) is a benzylisoquinoline alkaloid extracted from *Papaveraceae* plants [34]. NOS could be considered a good candidate for treating inflammatory skin diseases, like psoriasis, thanks to its several therapeutic activities, such as anti-inflammatory and antiangiogenic. Despite these benefits, its therapeutic use is limited due to its low solubility and large molecular size. For this reason, NOS-loaded SLNs (NOS-SLNs) were fabricated showing good technological parameters suitable for topical application: average particle size (245.66 $\pm$ 17 nm), polydispersity index (PDI, 0.226 $\pm$ 0.09), zeta potential (-35.74 ± 2.59 mV), and high entrapment efficiency (89.77%). In vivo studies revealed that treatment with SLN-NOS 1% significantly decreased clinical parameters, namely levels of pro-inflammatory factors (TNF-α, interleukin-17), psoriasis area, and severity index [35].

2.1.2. Wound Healing Treatment

Wound healing is a complex physiological process in which the skin barrier restores itself and closes the wound. The first step in wound healing is inflammation, a necessary process for the recruitment of the innate immune system, helping to defend the body from foreign pathogens and remove dead tissue [36]. It has been shown that several plants possess beneficial properties for wound healing. In particular, curcumin (CUR), a diferuloyl methane isolated from the rhizome of *Curcuma longa*, has the ability to suppress the release of pro-inflammatory cytokines and modulate excessive inflammation during wound healing [37]. In addition, it is able to stimulate collagen production and promote angiogenesis, accelerating tissue regeneration [38]. Topical nanoformulation containing CUR (CUR-NLCs) was investigated to test in vivo its regenerative capacity and wound healing efficiency. CUR-NLCs showed a higher potential to fasten the wound healing as it resulted in 1.15- and 1.9-fold higher wound closure compared to curcumin and control, respectively ($p < 0.0001$) [39]. This improvement can be attributed to the nanotechnological strategy used, which is able to preserve the health properties of CUR and increase its bioavailability [40]. The inflammatory properties of CUR have also been studied on its hydrogenated product tetrahydrocurcumin (THC), called "white curcumin". It was incorporated into SLNs (THC-SLNs) and administered topically as a hydrogel. Ex vivo and

in vivo studies showed enhanced anti-inflammatory activity of THC-SLNs gel ($p \leq 0.001$) and a 17-fold higher drug permeability compared to free THC gel [41].

Sesamol, a lignan extracted from sesame seeds *(Sesamum indicum* Linn.), has been investigated as a wound healing promoter thanks to its antioxidant and anti-inflammatory properties. Since free sesamol rapidly crosses skin layers reaching systemic circulation, it was encapsulated into SLNs in order to enhance its localized delivery and skin retention, as confirmed by ex vivo studies. Furthermore, its wound healing potential was significantly improved ($p < 0.001$) with a complete healing of the wound after 18 days [42]. Therefore, combining medicinal plants (e.g., *Aloe vera*, *Curcuma longa*, *Calendula officinalis*, *Camellia sinensis*) and lipid nanoparticles can revolutionize wound treatment and improve overall healthcare outcomes [43].

2.1.3. Atopic Dermatitis Treatment

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease characterized by itching and various skin manifestations, including erythema, papules–vesicles, and dry skin [44]. Its etiology includes genetic, environmental, immunological factors and food allergies. AD is characterized by intense itching, pain, and red skin can be debilitating, as well as the impact on quality of life [45]. Conventional treatment includes topical corticosteroids and immunomodulators or oral/parenteral therapy with antihistamines, immunosuppressants, or monoclonal antibodies according to disease severity [46]. Additionally, for basic management and prevention of flare-ups, daily baths followed by the application of emollients and moisturizers are recommended. Since topical corticosteroids or calcineurin inhibitors showed poor skin penetration and low skin barrier repair efficiency, nanoformulations containing these drugs have been developed to improve their penetration and deposition in the skin [47,48]. The above-mentioned THC-SLN gel was further investigated for the potential treatment of AD. Ex vivo and in vivo studies showed that THC-SLN gel greatly enhanced skin hydration (1.44 times) and reduced TNF-α and IL-6 levels than free THC gel, exhibiting its efficacy in the treatment of AD [49]. Cassano et al. formulated linolenic acid-loaded SLNs (LNA-SLNs) for the treatment of AD using curcumin, resveratrol, and capsaicin esterified with oleic acid as lipid matrices. This lipid functionalization was performed to enhance the therapeutic properties of LNA-SLNs, thanks to the antioxidant capacity of these bioactive compounds. This synergistic effect was studied in terms of encapsulation efficiency, stability, and transdermal release revealing a cumulative percentage of LNA ranging from 57 to 79%. Furthermore, LNA-SLNs composed of curcumin and resveratrol esters were able to significantly reduce IL-6 production. Therefore, these nanocarriers proved to be suitable for the administration of LNA, preserving and increasing its anti-inflammatory activity for the treatment of AD [50].

2.1.4. Alopecia Treatment

Alopecia areata is an immune-mediated disease that affects over 140 million people worldwide, with a prevalence in adults between 25 and 36 years [51,52]. It is characterized by hair loss, which occurs in different parts of the body, including the scalp, eyebrows, and eyelashes [53]. Since its etiology is not fully understood, current treatments are not curative but aim to prevent the disease's progression. The elective therapy involves the use of topically applied minoxidil [54,55] and high oral doses of corticosteroids [56,57], although numerous adverse effects (hypotension, high blood pressure, and osteoporosis) [58,59] and poor efficacy have been observed. Therefore, the development of nanoformulations capable of delivering effective amounts of drug to the therapeutic target, hair follicles, seems to be a promising strategy [60]. Topical administration of NLCs loaded with minoxidil and betamethasone showed a 10-fold higher minoxidil permeation into the hair follicles

compared to the control, avoiding systemic exposure. Furthermore, NLCs allowed to double ($p < 0.005$) the concentration of betamethasone accumulated in hair follicles after 12 and 24 h of topical treatment [61]. Similar results were observed with the nanoformulation containing cyproterone acetate (CPA) [62]; in particular, the optimal accumulation capacity in hair follicles was revealed when the NLC particle size was around 300 nm. The ability of lipid nanoparticles to promote percutaneous drug absorption and targeting into the hair follicle was further confirmed by Li et al. In particular, they fabricated tofacitinib (TFB)-loaded lipid nanoparticles which were able to promote percutaneous drug absorption into the hair follicle by reducing the progression of alopecia through the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway [63].

2.1.5. Dermatomycoses Treatment

Fungal infections of the nails, skin, and hair, commonly called dermatomycosis, affect nearly a billion people worldwide [64]. Their incidence depends on social, climatic, and economic factors [65]. The use of lipid nanoparticles containing antifungal drugs is recognized as an effective means of local therapy of skin mycoses, as they are able to improve the ability of the drug to cross the stratum corneum and reach an effective concentration at the target site [66]. El-Housiny et al. developed a fluconazole (FLZ)-loaded SLN topical gel for the potential treatment of Pityriasis Versicolor (PV), a skin fungal infection caused by the proliferation of *Malassezia* species. A randomized controlled clinical trial was carried out on 30 PV patients compared to the market product CandistanVR 1% cream. After one month of treatment, a significant improvement in therapeutic response, in terms of healing (1.4-fold) and complete eradication (4-fold), was observed compared to the market product [67]. Rapid healing of skin fungal infections was studied in vivo using SLNs loaded with sulconazole (SCZ), showing restoration of the dermal architecture of rabbit skin [68]. Furthermore, SLNs were able to improve skin deposition and skin retention of drugs, such as luliconazole and itraconazole, avoiding systemic effects and improving antifungal efficacy [69,70]. SLNs containing terbinafine (TFH) and different nail penetration enhancers (nPEs), such as N-acetyl-L-cysteine, thioglycolic acid, and thiourea were produced for the potential treatment of onychomycosis, a fungal infection of the nails. The obtained formulations (formula N2 and N8) were compared with the market product Lamifen® in terms of antifungal activity, nail hydration, and drug uptake. The optimum TFH-SLNs, formulated using thiourea as nPE, showed significantly larger microbiological zones of inhibition (~130 mm) and a higher drug uptake (~75%) in comparison with Lamifen® (70 mm and 35%, respectively) [71]. Similar results were observed with oxiconazole nitrate-loaded SLN topical gel. Furthermore, clinical improvement and greater patient compliance were observed compared to treatment with the corresponding commercial product, thanks to the reduction in side effects [72].

2.1.6. Acne Treatment

Acne vulgaris is a multifactorial skin disease of the pilosebaceous units that mainly affects the face, back, and chest of 70–80% of adolescents [73]. Since it has a significant impact on the quality of life of these young adults, several treatments have been developed based on disease severity.

The first-line treatment is topical therapy with benzoyl peroxide, salicylic acid, topical antibiotics, and retinoids [74]. The latter, especially isotretinoin (ITN), have shown significant efficacy in acne treatment, attenuating sebum production, apoptosis, and cell cycle progression. Since ITN is sensitive to oxidative degradation and its topical application causes skin irritation, it has been encapsulated into SLNs, containing α-tocopherol acetate (α-TA), to overcome these issues [75]. The synergistic activity between ITN and α-TA

showed potent efficacy and no irritation or edema in in vivo studies. In addition, it has been showing sustained drug release for 24 h with a final cumulative release of 95.8% *w*/*w* and 89.1% *w*/*w* for ITN and α-TA.

In recent decades, the elective therapy of acne has been characterized by the use of topical antibiotics [76,77]; however, the worldwide increase in antibiotic resistance, due to the frequent use of these drugs, is shifting attention towards the use of natural compounds. Among these, thymol (TH) seems to be a promising anti-acne agent thanks to its antioxidant, antimicrobial, and anti-inflammatory activities [78]. To improve its skin permeability, TH was encapsulated in NLCs (TH-NLCs) for topical use against acne. TH-NLCs were further dispersed in a carbomer gel which showed excellent skin retention and skin microbiome maintenance by eradicating pathogenic bacteria [79].

2.1.7. Melanoma Treatment

Cutaneous melanoma is a skin cancer with a mortality rate of more than 75% [80]. It is caused by excessive sun exposure, which leads to photoaging, suppression of the immune response, and ultimately photocarcinogenesis [81]. Melanoma therapy includes immunotherapy, cytotoxic chemotherapy, and targeted molecular therapy [82], although they cause serious adverse effects and, therefore, poor patient compliance. Recently, research has focused on the use of natural compounds, especially polyphenols, for their numerous health-promoting properties, such as anti-inflammatory, antioxidant, antitumor, and antiviral [83,84]. Among them, the combination therapy with curcumin and resveratrol has gained special attention for the treatment of melanoma. Since both compounds are able to inhibit the proliferation of highly aggressive melanoma cells [85,86], they were co-encapsulated in SLNs (Cur-Res-SLNs) to evaluate their synergistic anticancer efficacy and improve their skin penetration. In vitro and ex vivo assays demonstrated that Cur-Res-SLNs permeated the skin (>70%) and strongly inhibited the proliferation of SK-MEL-28 melanoma cells, suggesting their potential use for the treatment of localized melanoma [87]. The interesting ability of SLN to improve skin penetration of the drug was further evaluated by Chinembiri et al. [88].

2.2. Cosmetic Applications

2.2.1. Sunscreen Agents

To prevent skin damage caused by UV rays, it is recommended to use sunscreen and avoid intense sun exposure [89]. Although chemical sunscreens are the most commonly used, their prolonged contact time with the skin can cause unwanted effects (irritation and sensitization) due to their skin permeability and accumulation in the body [90]. To improve both the safety and efficacy of sunscreen formulations, chemical UV filters have been encapsulated in LNs in order to reduce the amount of UV filters, maintaining the SPF, thanks to the ability of LNs to act as physical UV filters [91]. Medeiros et al. fabricated a nanoformulation containing a chemical UV filter, bemotrizinol (BMZ), highlighting the importance of the nanotechnological approach. A significant enhancement in the photoprotective activity of BMZ was observed when it was incorporated into NLCs [92]. This was further confirmed by our previous study which showed an improvement in SPF (approximately 6–15%), depending on the lipid ratios used for the formulation of BMZ-NLC (12, 14, 16% *w*/*w*). In addition, we evaluated how the lipid ratio affects the technological and sensory properties of sunscreen formulation in terms of spreadability, viscosity, pH, occlusion factor, BMZ release, and sensory attributes [93].

Recently, the use of natural compounds, such as safranal, capable of protecting the skin from UV rays has increased significantly as they are environmentally safe and human-friendly. Safranal (SAF) is a secondary metabolite obtained from saffron (*Crocus sativus*) that

has antioxidant and sunscreen properties. For this reason, it has been encapsulated in SLNs (SAF-SLN cream) to develop a broad-spectrum sunscreen [94]. SAF-SLN cream showed good texture, excellent rheological properties, optimum pH, and stability with high broad-spectrum protection. SLNs were chosen as the most suitable delivery systems for safranal due to the ability of lipids to reflect UV radiation by acting as physical sunscreens [93]. This nanotechnological approach has made it possible to enhance the sunscreen properties of the cream, bypassing the limits linked to the chemical-physical characteristics of safranal and exploiting the photoprotective action of lipids.

As demonstrated by Darè et al., NLCs showed a lower cytotoxic effect than SLNs on HaCat (keratinocytes) and HFF-1 (fibroblasts) cell lines. Therefore, they were chosen for the delivery of protocatechuic acid (P0), a photoprotective agent, thanks to its ability to reduce cellular oxidative stress. The photodegradation profile of P0, free and loaded into NLCs, was evaluated demonstrating that NLCs were able to reduce the physical degradation of the P0 by 9.8-fold compared to the free compound [95]. Taniyadukkam et al. evaluated the photoprotective potential of sunscreen cream containing spinach-loaded SLNs, demonstrating the importance of SLNs in protecting active pharmaceutical ingredients (APIs) and improving skin retention and photoprotective capacity [96]. Another interesting natural photoprotective agent is Aloe Vera. Rodrigues et al. formulated an Aloe vera-loaded SLN sunscreen cream to enhance the skin penetration and stability of natural products. The optimized SLN sunscreen showed good results in terms of spreadability, viscosity, extrudability, drug content, in vitro drug release, ex vivo permeation, skin irritation test, and determination of sun protection factor (SPF). The latter was evaluated in vitro and in vivo showing an SPF on par with commercial sunscreens with values of 16.9 ± 2.44 and 14.81 ± 3.81, respectively [97].

2.2.2. Anti-Aging Agents

Skin aging is defined as a biological process affected by a mix of internal (genetic, cellular metabolism, hormonal imbalance) and external (UV and chemical exposure) factors [98]. It is characterized by a degradation of the extracellular matrix (ECM) in the skin layers, resulting in visible signs on the skin's surface, commonly called skin wrinkles [99,100]. In addition, aged skin appears dry and rough. These marks are caused by the gradual decrease in collagen and elastin production in the dermis. Many bioactive compounds, such as retinoids, have been identified as anti-wrinkle agents and incorporated into cosmetic products with the aim of preventing the formation of wrinkles and reducing those already present [101]. Retinoids are widely used as anti-wrinkles, although they show poor efficacy over time due to their high instability (light, oxygen, heat). For this reason, retinoids require appropriate drug delivery systems, such as LNs, which protect them from degradation and allow their penetration into the skin [102,103]. Furthermore, LNs are able to promote skin hydration through their adhesion to the stratum corneum thanks to their nanometric size, preventing water loss by evaporation and reinforcing the skin's lipid-film barrier [104]. Jun et al. formulated retinol-loaded NLCs (RET-NLCs) by vacuum emulsification method to increase the stability of retinol and its penetration efficiency into the skin. Retinol content was maintained stable (90% or more) after one month of storage at 25, 40, and 50 °C; in addition, RET-NLCs cream showed a higher penetration efficiency (3-fold) compared with the market product retinol 10S [101].

Other well-known anti-wrinkle agents are the bioactive compounds isolated from grape by-products, such as epigallocatechin gallate (EGCG), resveratrol, and myricetin. All compounds were encapsulated in SLNs (0.81 μg/mL) showing interesting antioxidant activity in human skin cells against t-BHP-induced oxidative stress. Moreover, the nanoformulation containing both EGCG and resveratrol was also formulated exhibiting the

highest antioxidant activity due to the synergistic effect of the two molecules. Therefore, the obtained SLNs proved to be suitable nanocarriers for these natural bioactive compounds, protecting them from external factors and improving their bioavailability [105]. Essential oils are widely used in the cosmetic field for their pleasant odor and many biological activities, such as anti-aging and photoprotective. Among them, coriander essential oil (CEO), encapsulated in SLNs, significantly increased skin collagen content and attenuated in vivo UV-induced skin photoaging decreasing MDA, COX-2, PGE-2, MMP-1, JNK, and AP-1 levels [106]. Safflower (*Carthamus tinctorius* L.) is another promising photoprotective agent to prevent symptoms associated with photoinduced skin aging, thanks to its high content of quercetin (QU) and luteolin (LU). It has been incorporated into SLN-based hydrogel in order to significantly increase the skin retention of QU and LU (19-fold) and their sunscreen ability, reaching an SPF value above 15 [107].

2.2.3. Other Topical Application of LNs

Vector-borne diseases, such as Malaria, still represent a global health concern with around 700,000 deaths annually [108]. These diseases are transmitted by different genera of mosquitoes, like *Anopheles* and *Aedes*. For this reason, the use of mosquito repellent is an effective prevention strategy, especially in endemic areas. Since synthetic repellents can cause many adverse effects [109], research is focusing on the development of alternative repellents containing green ingredients, such as *Zataria multiflora* essential oil (ZMEO) [110].

Many essential oils (EOs) have demonstrated a repellent effect, such as *Citrus reticulata*, *Mentha longifolia*, and *Cymbopogon citratus* [111]. However, since they are volatile, their use in adequate concentrations is still a challenge. Furthermore, their repellent effect allows protection for a few hours, requiring frequent applications. Long-lasting repellency can be achieved using LNs that seem to be good candidates for EO loading and its controlled release over time [112]. As previously reported, *Zataria multiflora* essential oil (ZMEO) has been encapsulated into SLNs showing that the protection time of nanoformulation (93 ± 5 min) was 3-fold longer than that of free ZMEO (29 ± 2 min). In addition, both products did not show cytotoxicity on HFFF2 (human skin normal cell line). Therefore, ZMEO-SLNs can be used as a green and potent repellent [110].

Furthermore, LNs can be topically used for the treatment of cellulite (CLT), a lipodystrophy syndrome that affects post-adolescent women worldwide [113]. It is an esthetic problem hardly accepted as is characterized by an "orange-peel" skin appearance [114]. CLT treatment includes topical applications and surgical procedures (liposuction and mesotherapy), although the latter is dangerous, invasive, and very expensive [115]. Several anti-CLT agents have been extensively studied, such as caffeine, algae, tea, etc. However, their topical treatment did not bring the desired results due to their hydrophilicity and low skin permeability [116,117]. Fouad et al. optimized caffeine-loaded SLNs (CA-SLNs) by achieving good technological parameters (particle size < 350 nm; zeta potential < −25 mV; polydispersity index < 0.5), excellent CA release ($99.44 \pm 0.36\%$), and successful CA transepidermal permeation. In addition, histological studies showed that CA-SLNs significantly reduced the mean thickness of subcutaneous fat tissue (SFT) with 4.66-fold ($p = 0.035$) and 4.16-fold ($p = 0.0001$) compared to free CA. Therefore, CA-SLNs could be a promising nanocosmeceutical for effective CLT treatment [118].

3. Transdermal Application of LNs

Transdermal drug delivery (TDD) is a non-invasive method of delivering drugs systemically by applying a drug formulation to healthy skin [119]. Specifically, the drug is able to reach systemic distribution through its penetration across the epidermis and dermis, avoiding its drug accumulation in the dermal layer. TDD has several advantages

over conventional routes of drug administration (oral and parenteral), such as increased patient compliance, maintenance of an effective drug delivery rate over time, and a constant circulation rate, reducing the risk of toxic side effects and dosing frequencies. In addition, since it avoids the gastrointestinal tract and, therefore, liver metabolism and gastrointestinal tract irritation; a significant improvement in drug bioavailability has been observed [120,121]. The most widely used methods for transdermal drug administration are topical formulations, transdermal patches, and microneedles [122] (Figure 3).

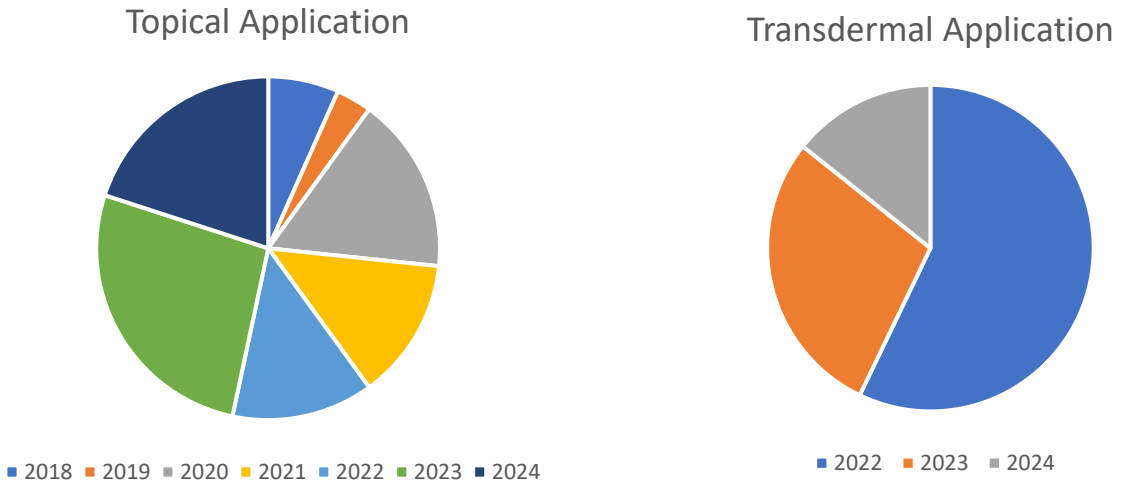

Figure 3. Number of studies per year related to topical and transdermal application of LNs according to the data reported in Table 1.

Table 1. Active compounds incorporated in topical/transdermal lipid nanoparticles.

Application	Lipid Nanoparticles	Drug	Reference
Psoriasis	SLN	Cyclosporine A	[28]
	SLN	Methotrexate	[30]
	NLC	Tacrolimus and siRNA	[22]
	Hybrid polymer lipid NPs	TNFα-siRNA	[31]
	NLC	Betulin	[33]
	SLN	Noscapine	[35]
Wound healing	SLN and NLC	Curcumin and tethadydrocurcumin	[39,41]
	SLN	Sesamol	[42]
	NLC	Medicinal plants (Aloe Vera, Calendula Offic., etc)	[43]
Atopic dermatitis	SLN and NLC	Corticosteroids and calcineurin inhibitors	[47,48]
	SLN and NLC	Curcumin and tethadydrocurcumin	[39,41]
	SLN	Linoleic acid	[49]
Alopecia	Polymer NP and NLC	Minoxidil	[61]
	NLC	Cyproterone acetate	[62]
	NLC	Tofacitinib	[63]
Dermatomycoses	SLN	Fluconazole	[67]
	SLN	Sulconazole	[68]
Acne	SLN	Isotretinoin	[75]
	NLC	Thymol	[79]
Melanoma	SLN	Curcumin and resveratrol	[87]
Sunscreen	NLC	Bemotrizinol	[92,93]
	SLN	Safranal	[94]
	SLN	Spinach ext.	[96]
	SLN	Aloe Vera	[97]
Anti-aging	NLC	Retinol	[101]
	SLN	Epigallocatechin gallate, resveratrol, myricetin	[102]
	SLN and NLC	Coriander essential oil	[106]
	SLN	Safflower	[107]

Table 1. *Cont.*

Application	Lipid Nanoparticles	Drug	Reference
Repellent	SLN	Zataria Multiflora	[110]
Cellulite	SLN	Caffein	[118]
Angina pectoris	NLC NLC	Ranolazine Raloxifene	[123] [124]
Ehrlich ascites carcinoma	SLN	Pomegranate ext.	[125]
Diabetes	SLN	Repaglinide	[126]
Reumathoid arthritis	SLN	Teriflunomide	[127]
Parkinson's disease	SLN	Curcumin	[128]

3.1. Topical Formulations

Drug delivery through the skin is still a challenge, mainly due to penetration through the stratum corneum. However, the development of LNs has made it possible to improve their permeability and bioavailability [129]. Topical NLC-based gel has been formulated for the administration of ranolazine (RZ) for the treatment of chronic stable angina pectoris. In vitro and in vivo studies demonstrated that RZ bioavailability was significantly increased when the drug was encapsulated into NLCs, highlighting the importance of the nanotechnological approach [123]. Similar results were observed by Alves et al., highlighting the role of NLCs in preventing RLX (Raloxifene hydrochloride) skin deposition and promoting drug permeation to deeper skin layers [124]. Furthermore, to improve bioavailability and reduce toxicity associated with oral drug administration, transdermal formulations have been further developed for the potential treatment of cancer, and diabetes [125,130].

3.2. Transdermal Patches

A transdermal patch is an adhesive patch designed to systemically deliver a dose of medication at a predetermined rate. It is a method of drug administration that allows the patient to easily and quickly discontinue the medication by removing the patch [121]. Since the complex anatomy of the skin and the physicochemical characteristics of the drug influence its absorption and penetration [131], the patch must be made of a biodegradable and biocompatible polymer, such as chitosan [132]. As previously reported, LNs are promising nanocarriers for transdermal delivery, enhancing permeability and bioavailability of drugs. Several studies demonstrated the combined advantages of fabricating SLNs in biodegradable chitosan-based patches for the potential treatment of many diseases, like type 2 diabetes [133]. Specifically, repaglinide-loaded SLNs (REP-SLNs) were incorporated into a chitosan solution to develop a transdermal patch (REP-SLN-TDDS), and their physicochemical properties, ex vivo drug permeability, and pharmacokinetic profiles were evaluated. REP-SLN-TDDS exhibited a "two-phase drug release" related to drug distribution, where approximately 36% of the drug was released immediately during the first 2 h, while in the second phase, it was released slowly, approximately 80% at 24 h. The drug permeability through rat skin for REP-SLN-TDDS was improved by 3.56-fold compared to conventional REP administration. Furthermore, REP-SLN-TDDS was able to sustain higher REP plasma levels over a 24 h period ($p < 0.05$) and reduce blood glucose levels ($p < 0.05$). Therefore, REP-SLN-TDDS can be considered an efficient tool for diabetes management [133]. In another study, a transdermal patch containing cephalexin-loaded SLNs (CPX-SLNs) was developed. The use of SLNs allowed for a reduction in CPX concentration (around 28%) without decreasing antimicrobial efficacy. Therefore, these innovative patches combined with LNs show great promise for the transdermal delivery of antibiotics by decreasing drug dosage and medical treatment costs [126].

3.3. Microneedles

Microneedles (MNs) are novel skin delivery tools composed of micron-size pointed projections arranged in a matrix designed to improve skin drug penetration [134,135]. In addition, they allow sustained and controlled drug delivery, painless self-administration, and localized drug administration [136]. MNs combined with LNs emerged as a promising alternative non-invasive, patient-friendly, and effective option [127]. Teriflunomide-loaded SLNs assisted by MNs (TER-SLNs-MNs) were fabricated for the management of rheumatoid arthritis showing a significant improvement of arthritic effects and a sustained TER release for nearly 96 h compared to free TER administration [127]. Prabhu et al. developed curcumin-loaded SLNs incorporated into MNs (CUR-SLNs-MNs) in order to improve CUR bioavailability and efficacy for the treatment of Parkinson's disease. CUR-SLNs-MNs treatment was found to be safe; furthermore, Parkinsonian features (e.g., motor coordination, bradykinesia, and balance ability) were significantly improved thanks to the use of MNs capable of disrupting the stratum corneum, thereby enhancing CUR skin permeation [128].

4. Conclusions

This paper reviews the current state of the art regarding the use of topical lipid-based nanocarriers (LNs) for pharmaceutical and cosmetic applications. LNs have emerged as promising nanocarriers for topical and transdermal drug delivery due to their advantages, including controlled drug release, enhanced skin penetration of the drug, low manufacturing costs, and biocompatibility of the lipids used. Several studies have been conducted to evaluate their excellent characteristics in the pharmaceutical and cosmetic fields, showing significant improvement in the desired effect. In particular, many LN-based products have been manufactured to exploit the beneficial properties of herbal drugs characterized by low bioavailability due to hydrophilicity and stability issues. Therefore, the nanotechnological approach could represent the most promising and effective device to treat skin disorders. Furthermore, they can be used as non-invasive tool to systemically deliver drugs.

Author Contributions: Conceptualization, D.S. and C.P.; investigation, D.S; writing—original draft preparation, D.S.; writing—review and editing, D.S. and C.P.; supervision, C.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Chambers, E.S.; Vukmanovic-Stejic, M. Skin Barrier Immunity and Ageing. *Immunology* **2020**, *160*, 116–125. [CrossRef]
2. Blair, M.J.; Jones, J.D.; Woessner, A.E.; Quinn, K.P. Skin Structure–Function Relationships and the Wound Healing Response to Intrinsic Aging. *Adv. Wound Care* **2020**, *9*, 127–143. [CrossRef] [PubMed]
3. Lim, K.-M. Skin Epidermis and Barrier Function. *Int. J. Mol. Sci.* **2021**, *22*, 3035. [CrossRef]
4. de Szalay, S.; Wertz, P.W. Protective Barriers Provided by the Epidermis. *Int. J. Mol. Sci.* **2023**, *24*, 3145. [CrossRef]
5. Baroni, A.; Buommino, E.; De Gregorio, V.; Ruocco, E.; Ruocco, V.; Wolf, R. Structure and Function of the Epidermis Related to Barrier Properties. *Clin. Dermatol.* **2012**, *30*, 257–262. [CrossRef] [PubMed]
6. Fallica, F.; Leonardi, C.; Toscano, V.; Santonocito, D.; Leonardi, P.; Puglia, C. Assessment of Alcohol-Based Hand Sanitizers for Long-Term Use, Formulated with Addition of Natural Ingredients in Comparison to WHO Formulation 1. *Pharmaceutics* **2021**, *13*, 571. [CrossRef]
7. Jian, L.; Cao, Y.; Zou, Y. Dermal-Epidermal Separation by Enzyme. In *Epidermal Cells: Methods and Protocols*; Humana: New York, NY, USA, 2019; pp. 27–30.

8. Thulabandu, V.; Chen, D.; Atit, R.P. Dermal Fibroblast in Cutaneous Development and Healing. *WIREs Dev. Biol.* **2018**, *7*, e307. [CrossRef] [PubMed]
9. Lee, J.; van der Valk, W.H.; Serdy, S.A.; Deakin, C.; Kim, J.; Le, A.P.; Koehler, K.R. Generation and Characterization of Hair-Bearing Skin Organoids from Human Pluripotent Stem Cells. *Nat. Protoc.* **2022**, *17*, 1266–1305. [CrossRef]
10. Sun, L.; Xiang, H.; Ge, C.; Chen, X.; Zhang, Q.; Zhang, Y.; Miao, X. A Nanocrystals-Based Topical Drug Delivery System with Improved Dermal Penetration and Enhanced Treatment of Skin Diseases. *J. Biomed. Nanotechnol.* **2021**, *17*, 2319–2337. [CrossRef] [PubMed]
11. Puglia, C.; Santonocito, D.; Bonaccorso, A.; Musumeci, T.; Ruozi, B.; Pignatello, R.; Carbone, C.; Parenti, C.; Chiechio, S. Lipid Nanoparticle Inclusion Prevents Capsaicin-Induced TRPV1 Defunctionalization. *Pharmaceutics* **2020**, *12*, 339. [CrossRef]
12. Eroğlu, C.; Sinani, G.; Ulker, Z. Current State of Lipid Nanoparticles (SLN and NLC) for Skin Applications. *Curr. Pharm. Des.* **2023**, *29*, 1632–1644. [CrossRef] [PubMed]
13. Wang, W.; Lu, K.; Yu, C.; Huang, Q.; Du, Y.-Z. Nano-Drug Delivery Systems in Wound Treatment and Skin Regeneration. *J. Nanobiotechnol.* **2019**, *17*, 82. [CrossRef] [PubMed]
14. Pinto, F.; Fonseca, L.P.; de Barros, D.P.C. Dermal Delivery of Lipid Nanoparticles: Effects on Skin and Assessment of Absorption and Safety. In *Nanotoxicology in Safety Assessment of Nanomaterials*; Springer International Publishing: Cham, Switzerland, 2022; pp. 83–114.
15. Santonocito, D.; Vivero-Lopez, M.; Lauro, M.R.; Torrisi, C.; Castelli, F.; Sarpietro, M.G.; Puglia, C. Design of Nanotechnological Carriers for Ocular Delivery of Mangiferin: Preformulation Study. *Molecules* **2022**, *27*, 1328. [CrossRef]
16. de Macedo, L.M.; Santos, É.M.d.; Militão, L.; Tundisi, L.L.; Ataide, J.A.; Souto, E.B.; Mazzola, P.G. Rosemary (*Rosmarinus officinalis* L., Syn *Salvia rosmarinus* Spenn.) and Its Topical Applications: A Review. *Plants* **2020**, *9*, 651. [CrossRef] [PubMed]
17. Parveen, S.; Ahmed, M.; Baboota, S.; Ali, J. An Innovative Approach in Nanotechnology-Based Delivery System for the Effective Management of Psoriasis. *Curr. Pharm. Des.* **2022**, *28*, 1082–1102. [CrossRef]
18. Zhai, Y.; Zhai, G. Advances in Lipid-Based Colloid Systems as Drug Carrier for Topic Delivery. *J. Control. Release* **2014**, *193*, 90–99. [CrossRef]
19. Sala, M.; Diab, R.; Elaissari, A.; Fessi, H. Lipid Nanocarriers as Skin Drug Delivery Systems: Properties, Mechanisms of Skin Interactions and Medical Applications. *Int. J. Pharm.* **2018**, *535*, 1–17. [CrossRef]
20. Mardhiah Adib, Z.; Ghanbarzadeh, S.; Kouhsoltani, M.; Yari Khosroshahi, A.; Hamishehkar, H. The Effect of Particle Size on the Deposition of Solid Lipid Nanoparticles in Different Skin Layers: A Histological Study. *Adv. Pharm. Bull.* **2016**, *6*, 31–36. [CrossRef]
21. Mishra, V.; Bansal, K.K.; Verma, A.; Yadav, N.; Thakur, S.; Sudhakar, K.; Rosenholm, J.M. Solid Lipid Nanoparticles: Emerging Colloidal Nano Drug Delivery Systems. *Pharmaceutics* **2018**, *10*, 191. [CrossRef]
22. Viegas, J.S.R.; Praça, F.G.; Caron, A.L.; Suzuki, I.; Silvestrini, A.V.P.; Medina, W.S.G.; Del Ciampo, J.O.; Kravicz, M.; Bentley, M.V.L.B. Nanostructured Lipid Carrier Co-Delivering Tacrolimus and TNF-α SiRNA as an Innovate Approach to Psoriasis. *Drug Deliv. Transl. Res.* **2020**, *10*, 646–660. [CrossRef]
23. Rendon, A.; Schäkel, K. Psoriasis Pathogenesis and Treatment. *Int. J. Mol. Sci.* **2019**, *20*, 1475. [CrossRef]
24. Parisi, R.; Iskandar, I.Y.K.; Kontopantelis, E.; Augustin, M.; Griffiths, C.E.M.; Ashcroft, D.M. National, Regional, and Worldwide Epidemiology of Psoriasis: Systematic Analysis and Modelling Study. *BMJ* **2020**, *369*, m1590. [CrossRef]
25. Singhvi, G.; Hejmady, S.; Rapalli, V.K.; Dubey, S.K.; Dubey, S. Nanocarriers for Topical Delivery in Psoriasis. In *Delivery of Drugs*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 75–96.
26. Mason, A.R.; Mason, J.; Cork, M.; Dooley, G.; Hancock, H. Topical Treatments for Chronic Plaque Psoriasis. *Cochrane Database Syst. Rev.* **2013**, *2013*, CD005028. [CrossRef] [PubMed]
27. Katari, O.; Jain, S. Solid Lipid Nanoparticles and Nanostructured Lipid Carrier-Based Nanotherapeutics for the Treatment of Psoriasis. *Expert. Opin. Drug Deliv.* **2021**, *18*, 1857–1872. [CrossRef] [PubMed]
28. Trombino, S.; Servidio, C.; Laganà, A.S.; Conforti, F.; Marrelli, M.; Cassano, R. Viscosified Solid Lipidic Nanoparticles Based on Naringenin and Linolenic Acid for the Release of Cyclosporine A on the Skin. *Molecules* **2020**, *25*, 3535. [CrossRef]
29. Souto, E.B.; Baldim, I.; Oliveira, W.P.; Rao, R.; Yadav, N.; Gama, F.M.; Mahant, S. SLN and NLC for Topical, Dermal, and Transdermal Drug Delivery. *Expert. Opin. Drug Deliv.* **2020**, *17*, 357–377. [CrossRef]
30. Maiti, D.; Naseeruddin Inamdar, M.; Almuqbil, M.; Suresh, S.; Mohammed Basheeruddin Asdaq, S.; Alshehri, S.; Ali Al Arfaj, S.; Musharraf Alamri, A.; Meshary Aldohyan, M.; Theeb Alqahtani, M.; et al. Evaluation of Solid-Lipid Nanoparticles Formulation of Methotrexate for Anti-Psoriatic Activity. *Saudi Pharm. J.* **2023**, *31*, 834–844. [CrossRef]
31. Suzuki, I.L.; de Araujo, M.M.; Bagnato, V.S.; Bentley, M.V.L.B. TNFα SiRNA Delivery by Nanoparticles and Photochemical Internalization for Psoriasis Topical Therapy. *J. Control. Release* **2021**, *338*, 316–329. [CrossRef]
32. Biswasroy, P.; Pradhan, D.; Pradhan, D.K.; Ghosh, G.; Rath, G. Development of Betulin-Loaded Nanostructured Lipid Carriers for the Management of Imiquimod-Induced Psoriasis. *AAPS PharmSciTech* **2024**, *25*, 57. [CrossRef]

33. Prakash, D.; Chaudhary, A.; Chaudhary, A. Betulin-NLC-Hydrogel for the Treatment of Psoriasis-like Skin Inflammation: Optimization, Characterisation, and In Vitro and In Vivo Evaluation. *Curr. Drug Deliv.* **2024**, *22*. [CrossRef]
34. Calaf, G.M.; Crispin, L.A.; Quisbert-Valenzuela, E.O. Noscapine and Apoptosis in Breast and Other Cancers. *Int. J. Mol. Sci.* **2024**, *25*, 3536. [CrossRef]
35. Rahmanian-Devin, P.; Askari, V.R.; Sanei-Far, Z.; Baradaran Rahimi, V.; Kamali, H.; Jaafari, M.R.; Golmohammadzadeh, S. Preparation and Characterization of Solid Lipid Nanoparticles Encapsulated Noscapine and Evaluation of Its Protective Effects against Imiquimod-Induced Psoriasis-like Skin Lesions. *Biomed. Pharmacother.* **2023**, *168*, 115823. [CrossRef]
36. Baron, J.M.; Glatz, M.; Proksch, E. Optimal Support of Wound Healing: New Insights. *Dermatology* **2020**, *236*, 593–600. [CrossRef]
37. Bonilla, P.; Hernandez, J.; Giraldo, E.; González-Pérez, M.A.; Alastrue-Agudo, A.; Elkhenany, H.; Vicent, M.J.; Navarro, X.; Edel, M.; Moreno-Manzano, V. Human-Induced Neural and Mesenchymal Stem Cell Therapy Combined with a Curcumin Nanoconjugate as a Spinal Cord Injury Treatment. *Int. J. Mol. Sci.* **2021**, *22*, 5966. [CrossRef] [PubMed]
38. Mobaraki, M.; Bizari, D.; Soltani, M.; Khshmohabat, H.; Raahemifar, K.; Akbarzade Amirdehi, M. The Effects of Curcumin Nanoparticles Incorporated into Collagen-Alginate Scaffold on Wound Healing of Skin Tissue in Trauma Patients. *Polymers* **2021**, *13*, 4291. [CrossRef]
39. Elkhateeb, O.; Badawy, M.E.I.; Tohamy, H.G.; Abou-Ahmed, H.; El-Kammar, M.; Elkhenany, H. Curcumin-Infused Nanostructured Lipid Carriers: A Promising Strategy for Enhancing Skin Regeneration and Combating Microbial Infection. *BMC Vet. Res.* **2023**, *19*, 206. [CrossRef] [PubMed]
40. Campisi, A.; Sposito, G.; Pellitteri, R.; Santonocito, D.; Bisicchia, J.; Raciti, G.; Russo, C.; Nardiello, P.; Pignatello, R.; Casamenti, F.; et al. Effect of Unloaded and Curcumin-Loaded Solid Lipid Nanoparticles on Tissue Transglutaminase Isoforms Expression Levels in an Experimental Model of Alzheimer's Disease. *Antioxidants* **2022**, *11*, 1863. [CrossRef]
41. Kakkar, V.; Kaur, I.P.; Kaur, A.P.; Saini, K.; Singh, K.K. Topical Delivery of Tetrahydrocurcumin Lipid Nanoparticles Effectively Inhibits Skin Inflammation: In Vitro and in Vivo Study. *Drug Dev. Ind. Pharm.* **2018**, *44*, 1701–1712. [CrossRef] [PubMed]
42. Deol, P.K.; Kaur, I.P.; Dhiman, R.; Kaur, H.; Sharma, G.; Rishi, P.; Ghosh, D. Investigating Wound Healing Potential of Sesamol Loaded Solid Lipid Nanoparticles: Ex-Vivo, in Vitro and in-Vivo Proof of Concept. *Int. J. Pharm.* **2024**, *654*, 123974. [CrossRef] [PubMed]
43. Jain, A.; Yadav, S.; Khan, J. Revolutionizing Wound Healing: Unleashing Nanostructured Lipid Carriers Embodied with Herbal Medicinal Plant. *Curr. Pharm. Biotechnol.* **2024**, *25*. [CrossRef]
44. Sroka-Tomaszewska, J.; Trzeciak, M. Molecular Mechanisms of Atopic Dermatitis Pathogenesis. *Int. J. Mol. Sci.* **2021**, *22*, 4130. [CrossRef] [PubMed]
45. Fishbein, A.B.; Silverberg, J.I.; Wilson, E.J.; Ong, P.Y. Update on Atopic Dermatitis: Diagnosis, Severity Assessment, and Treatment Selection. *J. Allergy Clin. Immunol. Pract.* **2020**, *8*, 91–101. [CrossRef] [PubMed]
46. Li, H.; Zhang, Z.; Zhang, H.; Guo, Y.; Yao, Z. Update on the Pathogenesis and Therapy of Atopic Dermatitis. *Clin. Rev. Allergy Immunol.* **2021**, *61*, 324–338. [CrossRef] [PubMed]
47. Kumar, P.; Ashawat, M.S.; Pandit, V.; Singh Verma, C.P.; Ankalgi, A.D.; Kumar, M. Recent Trends in Nanocarriers for the Management of Atopic Dermatitis. *Pharm. Nanotechnol.* **2023**, *11*, 397–409. [CrossRef] [PubMed]
48. Cláudia Paiva-Santos, A.; Gama, M.; Peixoto, D.; Sousa-Oliveira, I.; Ferreira-Faria, I.; Zeinali, M.; Abbaspour-Ravasjani, S.; Mascarenhas-Melo, F.; Hamishehkar, H.; Veiga, F. Nanocarrier-Based Dermopharmaceutical Formulations for the Topical Management of Atopic Dermatitis. *Int. J. Pharm.* **2022**, *618*, 121656. [CrossRef] [PubMed]
49. Saini, K.; Modgill, N.; Singh, K.; Kakkar, V. Tetrahydrocurcumin Lipid Nanoparticle Based Gel Promotes Penetration into Deeper Skin Layers and Alleviates Atopic Dermatitis in 2,4-Dinitrochlorobenzene (DNCB) Mouse Model. *Nanomaterials* **2022**, *12*, 636. [CrossRef]
50. Cassano, R.; Serini, S.; Curcio, F.; Trombino, S.; Calviello, G. Preparation and Study of Solid Lipid Nanoparticles Based on Curcumin, Resveratrol and Capsaicin Containing Linolenic Acid. *Pharmaceutics* **2022**, *14*, 1593. [CrossRef]
51. Zhou, C.; Li, X.; Wang, C.; Zhang, J. Alopecia Areata: An Update on Etiopathogenesis, Diagnosis, and Management. *Clin. Rev. Allergy Immunol.* **2021**, *61*, 403–423. [CrossRef]
52. Freire, P.C.B.; Riera, R.; Martimbianco, A.L.C.; Petri, V.; Atallah, A.N. Minoxidil for Patchy Alopecia Areata: Systematic Review and Meta-analysis. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 1792–1799. [CrossRef]
53. Strazzulla, L.C.; Wang, E.H.C.; Avila, L.; Lo Sicco, K.; Brinster, N.; Christiano, A.M.; Shapiro, J. Alopecia Areata. *J. Am. Acad. Dermatol.* **2018**, *78*, 1–12. [CrossRef] [PubMed]
54. Randolph, M.; Tosti, A. Oral Minoxidil Treatment for Hair Loss: A Review of Efficacy and Safety. *J. Am. Acad. Dermatol.* **2021**, *84*, 737–746. [CrossRef] [PubMed]
55. Cardoso, C.O.; Tolentino, S.; Gratieri, T.; Cunha-Filho, M.; Lopez, R.; Gelfuso, G. Topical Treatment for Scarring and Non-Scarring Alopecia: An Overview of the Current Evidence. *Clin. Cosmet. Investig. Dermatol.* **2021**, *14*, 485–499. [CrossRef] [PubMed]
56. Nowaczyk, J.; Makowska, K.; Rakowska, A.; Sikora, M.; Rudnicka, L. Cyclosporine With and Without Systemic Corticosteroids in Treatment of Alopecia Areata: A Systematic Review. *Dermatol. Ther.* **2020**, *10*, 387–399. [CrossRef] [PubMed]

57. Rastaghi, F.; Kaveh, R.; Yazdanpanah, N.; Sahaf, A.-S.; Ahramiyanpour, N. Efficacy and Adverse Effects of Corticosteroid Pulse Therapy in Alopecia Areata. *Dermatol. Pract. Concept.* **2023**, *13*, e2023255. [CrossRef] [PubMed]
58. Bleecker, E.R.; Menzies-Gow, A.N.; Price, D.B.; Bourdin, A.; Sweet, S.; Martin, A.L.; Alacqua, M.; Tran, T.N. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, 276–293. [CrossRef]
59. Rice, J.B.; White, A.G.; Scarpati, L.M.; Wan, G.; Nelson, W.W. Long-Term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin. Ther.* **2017**, *39*, 2216–2229. [CrossRef] [PubMed]
60. Fang, C.L.; Aljuffali, I.A.; Li, Y.C.; Fang, J.Y. Delivery and targeting of nanoparticles into hair follicles. *Ther Deliv.* **2014**, *5*, 991–1006. [CrossRef]
61. Matos, B.N.; Lima, A.L.; Cardoso, C.O.; Cunha-Filho, M.; Gratieri, T.; Gelfuso, G.M. Follicle-Targeted Delivery of Betamethasone and Minoxidil Co-Entrapped in Polymeric and Lipid Nanoparticles for Topical Alopecia Areata Treatment. *Pharmaceuticals* **2023**, *16*, 1322. [CrossRef] [PubMed]
62. Ghasemiyeh, P.; Azadi, A.; Daneshamouz, S.; Heidari, R.; Azarpira, N.; Mohammadi-Samani, S. Cyproterone Acetate-Loaded Nanostructured Lipid Carriers: Effect of Particle Size on Skin Penetration and Follicular Targeting. *Pharm. Dev. Technol.* **2019**, *24*, 812–823. [CrossRef] [PubMed]
63. Li, Q.; Wang, Y.; Guo, Q.; Cao, J.; Feng, Y.; Ke, X. Nanostructured Lipid Carriers Promote Percutaneous Absorption and Hair Follicle Targeting of Tofacitinib for Treating Alopecia Areata. *J. Control. Release* **2024**, *372*, 778–794. [CrossRef]
64. Urban, K.; Chu, S.; Scheufele, C.; Giesey, R.L.; Mehrmal, S.; Uppal, P.; Delost, G.R. The Global, Regional, and National Burden of Fungal Skin Diseases in 195 Countries and Territories: A Cross-Sectional Analysis from the Global Burden of Disease Study 2017. *JAAD Int.* **2021**, *2*, 22–27. [CrossRef]
65. Qin, Q.; Su, J.; Liu, J.; Chen, R.; Wei, W.; Yuan, Z.; Lai, S.; Duan, R.; Lai, J.; Ye, L.; et al. Global, Regional, and National Burden of Fungal Skin Diseases in 204 Countries and Territories from 1990 to 2021: An Analysis of the Global Burden of Disease Study 2021. *Mycoses* **2024**, *67*, e13787. [CrossRef] [PubMed]
66. Fathi, N.; Lotfipour, F.; Dizaj, S.M.; Hamishehkar, H.; Mohammadi, M. Antimicrobial Activity of Nanostructured Lipid Carriers Loaded Punica Granatum Seed Oil against Staphylococcus Epidermidis. *Pharm. Nanotechnol.* **2020**, *8*, 485–494. [CrossRef]
67. El-Housiny, S.; Shams Eldeen, M.A.; El-Attar, Y.A.; Salem, H.A.; Attia, D.; Bendas, E.R.; El-Nabarawi, M.A. Fluconazole-Loaded Solid Lipid Nanoparticles Topical Gel for Treatment of Pityriasis Versicolor: Formulation and Clinical Study. *Drug Deliv.* **2018**, *25*, 78–90. [CrossRef] [PubMed]
68. Samee, A.; Usman, F.; Wani, T.A.; Farooq, M.; Shah, H.S.; Javed, I.; Ahmad, H.; Khan, R.; Zargar, S.; Kausar, S. Sulconazole-Loaded Solid Lipid Nanoparticles for Enhanced Antifungal Activity: In Vitro and In Vivo Approach. *Molecules* **2023**, *28*, 7508. [CrossRef]
69. Passos, J.S.; Martino, L.C.d.; Dartora, V.F.C.; de Araujo, G.L.B.; Ishida, K.; Lopes, L.B. Development, Skin Targeting and Antifungal Efficacy of Topical Lipid Nanoparticles Containing Itraconazole. *Eur. J. Pharm. Sci.* **2020**, *149*, 105296. [CrossRef] [PubMed]
70. Kaur, M.; Singh, G.; Shivgotra, R.; Singh, M.; Thakur, S.; Jain, S.K. Prolonged Skin Retention of Luliconazole from SLNs Based Topical Gel Formulation Contributing to Ameliorated Antifungal Activity. *AAPS PharmSciTech* **2024**, *25*, 229. [CrossRef] [PubMed]
71. Abobakr, F.E.; Fayez, S.M.; Elwazzan, V.S.; Sakran, W. Effect of Different Nail Penetration Enhancers in Solid Lipid Nanoparticles Containing Terbinafine Hydrochloride for Treatment of Onychomycosis. *AAPS PharmSciTech* **2021**, *22*, 33. [CrossRef] [PubMed]
72. Mahmoud, R.A.; Hussein, A.K.; Nasef, G.A.; Mansour, H.F. Oxiconazole Nitrate Solid Lipid Nanoparticles: Formulation, in-Vitro Characterization and Clinical Assessment of an Analogous Loaded Carbopol Gel. *Drug Dev. Ind. Pharm.* **2020**, *46*, 706–716. [CrossRef]
73. Hazarika, N. Acne Vulgaris: New Evidence in Pathogenesis and Future Modalities of Treatment. *J. Dermatol. Treat.* **2021**, *32*, 277–285. [CrossRef] [PubMed]
74. Valente Duarte De Sousa, I.C. New and Emerging Drugs for the Treatment of Acne Vulgaris in Adolescents. *Expert. Opin. Pharmacother.* **2019**, *20*, 1009–1024. [CrossRef] [PubMed]
75. Gupta, S.; Wairkar, S.; Bhatt, L.K. Isotretinoin and α-Tocopherol Acetate-Loaded Solid Lipid Nanoparticle Topical Gel for the Treatment of Acne. *J. Microencapsul.* **2020**, *37*, 557–565. [CrossRef] [PubMed]
76. Auffret, N.; Claudel, J.P.; Leccia, M.-T.; Ballanger, F.; Dreno, B. Novel and Emerging Treatment Options for *acne vulgaris*. *Eur. J. Dermatol.* **2022**, *32*, 451–458. [CrossRef]
77. Xu, H.; Li, H. Acne, the Skin Microbiome, and Antibiotic Treatment. *Am. J. Clin. Dermatol.* **2019**, *20*, 335–344. [CrossRef] [PubMed]
78. Folle, C.; Marqués, A.M.; Díaz-Garrido, N.; Espina, M.; Sánchez-López, E.; Badia, J.; Baldoma, L.; Calpena, A.C.; García, M.L. Thymol-Loaded PLGA Nanoparticles: An Efficient Approach for Acne Treatment. *J. Nanobiotechnol.* **2021**, *19*, 359. [CrossRef]
79. Folle, C.; Marqués, A.; Díaz-Garrido, N.; Carvajal-Vidal, P.; Sánchez López, E.; Suñer-Carbó, J.; Halbaut, L.; Mallandrich, M.; Espina, M.; Badia, J.; et al. Gel-Dispersed Nanostructured Lipid Carriers Loading Thymol Designed for Dermal Pathologies. *Int. J. Nanomed.* **2024**, *19*, 1225–1248. [CrossRef] [PubMed]
80. Arnold, M.; Singh, D.; Laversanne, M.; Vignat, J.; Vaccarella, S.; Meheus, F.; Cust, A.E.; de Vries, E.; Whiteman, D.C.; Bray, F. Global Burden of Cutaneous Melanoma in 2020 and Projections to 2040. *JAMA Dermatol.* **2022**, *158*, 495. [CrossRef] [PubMed]

81. Long, G.V.; Swetter, S.M.; Menzies, A.M.; Gershenwald, J.E.; Scolyer, R.A. Cutaneous Melanoma. *Lancet* **2023**, *402*, 485–502. [CrossRef] [PubMed]
82. Bhatia, S.; Tykodi, S.S.; Thompson, J.A. Treatment of Metastatic Melanoma: An Overview. *Oncology* **2009**, *23*, 488–496.
83. Alsadi, N.; Yahfoufi, N.; Nessim, C.; Matar, C. Role of a Polyphenol-Enriched Blueberry Preparation on Inhibition of Melanoma Cancer Stem Cells and Modulation of MicroRNAs. *Biomedicines* **2024**, *12*, 193. [CrossRef]
84. Isacescu, E.; Chiroi, P.; Zanoaga, O.; Nutu, A.; Budisan, L.; Pirlog, R.; Atanasov, A.G.; Berindan-Neagoe, I. Melanoma Cellular Signaling Transduction Pathways Targeted by Polyphenols Action Mechanisms. *Antioxidants* **2023**, *12*, 407. [CrossRef]
85. Tang, Y.; Cao, Y. Curcumin Inhibits the Growth and Metastasis of Melanoma via MiR-222-3p/SOX10/Notch Axis. *Dis. Markers* **2022**, *2022*, 3129781. [CrossRef] [PubMed]
86. Pourhanifeh, M.H.; Abbaszadeh-Goudarzi, K.; Goodarzi, M.; Piccirillo, S.G.M.; Shafiee, A.; Hajighadimi, S.; Moradizarmehri, S.; Asemi, Z.; Mirzaei, H. Resveratrol: A New Potential Therapeutic Agent for Melanoma? *Curr. Med. Chem.* **2021**, *28*, 687–711. [CrossRef]
87. Palliyage, G.H.; Hussein, N.; Mimlitz, M.; Weeder, C.; Alnasser, M.H.A.; Singh, S.; Ekpenyong, A.; Tiwari, A.K.; Chauhan, H. Novel Curcumin-Resveratrol Solid Nanoparticles Synergistically Inhibit Proliferation of Melanoma Cells. *Pharm. Res.* **2021**, *38*, 851–871. [CrossRef] [PubMed]
88. Chinembiri, T.; Gerber, M.; du Plessis, L.; du Preez, J.; Hamman, J.; du Plessis, J. Topical Delivery of Withania Somnifera Crude Extracts in Niosomes and Solid Lipid Nanoparticles. *Pharmacogn. Mag.* **2017**, *13*, 663. [CrossRef]
89. Saginala, K.; Barsouk, A.; Aluru, J.S.; Rawla, P.; Barsouk, A. Epidemiology of Melanoma. *Med. Sci.* **2021**, *9*, 63. [CrossRef]
90. Heo, S.; Hwang, H.S.; Jeong, Y.; Na, K. Skin Protection Efficacy from UV Irradiation and Skin Penetration Property of Polysaccharide-Benzophenone Conjugates as a Sunscreen Agent. *Carbohydr. Polym.* **2018**, *195*, 534–541. [CrossRef]
91. Souto, E.B.; Jäger, E.; Jäger, A.; Štěpánek, P.; Cano, A.; Viseras, C.; de Melo Barbosa, R.; Chorilli, M.; Zielińska, A.; Severino, P.; et al. Lipid Nanomaterials for Targeted Delivery of Dermocosmetic Ingredients: Advances in Photoprotection and Skin Anti-Aging. *Nanomaterials* **2022**, *12*, 377. [CrossRef]
92. Medeiros, T.S.; Moreira, L.M.C.C.; Oliveira, T.M.T.; Melo, D.F.; Azevedo, E.P.; Gadelha, A.E.G.; Fook, M.V.L.; Oshiro-Júnior, J.A.; Damasceno, B.P.G.L. Bemotrizinol-Loaded Carnauba Wax-Based Nanostructured Lipid Carriers for Sunscreen: Optimization, Characterization, and In Vitro Evaluation. *AAPS PharmSciTech* **2020**, *21*, 288. [CrossRef] [PubMed]
93. Santonocito, D.; Puglia, C.; Montenegro, L. Effects of Lipid Phase Content on the Technological and Sensory Properties of O/W Emulsions Containing Bemotrizinol-Loaded Nanostructured Lipid Carriers. *Cosmetics* **2024**, *11*, 123. [CrossRef]
94. Sanju, N.; Vineet, M.; Kumud, M. Development and Evaluation of a Broad Spectrum Polyherbal Sunscreen Formulation Using Solid Lipid Nanoparticles of Safranal. *J. Cosmet. Dermatol.* **2022**, *21*, 4433–4446. [CrossRef]
95. Daré, R.G.; Costa, A.; Nakamura, C.V.; Truiti, M.C.T.; Ximenes, V.F.; Lautenschlager, S.O.S.; Sarmento, B. Evaluation of Lipid Nanoparticles for Topical Delivery of Protocatechuic Acid and Ethyl Protocatechuate as a New Photoprotection Strategy. *Int. J. Pharm.* **2020**, *582*, 119336. [CrossRef] [PubMed]
96. Taniyadukkam, V.; Jose, J.; Maliyakkal, N.; Beeran, A.A.; Almoyad, M.A.A.; Aleya, L.; Bandiwadekar, A. Development and Evaluation of Sunscreen Cream Containing Solid Lipid Nanoparticles of Spinacia Oleraceae. *Environ. Sci. Pollut. Res.* **2023**, *30*, 51782–51791. [CrossRef]
97. Rodrigues, L.R.; Jose, J. Exploring the Photo Protective Potential of Solid Lipid Nanoparticle-Based Sunscreen Cream Containing Aloe Vera. *Environ. Sci. Pollut. Res.* **2020**, *27*, 20876–20888. [CrossRef]
98. Kim, J.C.; Park, T.J.; Kang, H.Y. Skin-Aging Pigmentation: Who Is the Real Enemy? *Cells* **2022**, *11*, 2541. [CrossRef] [PubMed]
99. Shin, J.-W.; Kwon, S.-H.; Choi, J.-Y.; Na, J.-I.; Huh, C.-H.; Choi, H.-R.; Park, K.-C. Molecular Mechanisms of Dermal Aging and Antiaging Approaches. *Int. J. Mol. Sci.* **2019**, *20*, 2126. [CrossRef] [PubMed]
100. de Miranda, R.B.; Weimer, P.; Rossi, R.C. Effects of Hydrolyzed Collagen Supplementation on Skin Aging: A Systematic Review and Meta-analysis. *Int. J. Dermatol.* **2021**, *60*, 1449–1461. [CrossRef] [PubMed]
101. Jun, S.-H.; Kim, H.; Lee, H.; Song, J.E.; Park, S.G.; Kang, N.-G. Synthesis of Retinol-Loaded Lipid Nanocarrier via Vacuum Emulsification to Improve Topical Skin Delivery. *Polymers* **2021**, *13*, 826. [CrossRef] [PubMed]
102. Pawłowska, M.; Marzec, M.; Jankowiak, W.; Nowak, I. Retinol and Oligopeptide-Loaded Lipid Nanocarriers as Effective Raw Material in Anti-Acne and Anti-Aging Therapies. *Life* **2024**, *14*, 1212. [CrossRef] [PubMed]
103. El Moukhtari, S.H.; Garbayo, E.; Amundarain, A.; Pascual-Gil, S.; Carrasco-León, A.; Prosper, F.; Agirre, X.; Blanco-Prieto, M.J. Lipid Nanoparticles for SiRNA Delivery in Cancer Treatment. *J. Control. Release* **2023**, *361*, 130–146. [CrossRef]
104. Della Sala, F.; Borzacchiello, A.; Dianzani, C.; Muntoni, E.; Argenziano, M.; Capucchio, M.T.; Valsania, M.C.; Bozza, A.; Garelli, S.; Di Muro, M.; et al. Ultrasmall Solid-Lipid Nanoparticles via the Polysorbate Sorbitan Phase-Inversion Temperature Technique: A Promising Vehicle for Antioxidant Delivery into the Skin. *Pharmaceutics* **2023**, *15*, 1962. [CrossRef] [PubMed]
105. Pereira, A.; Ramalho, M.J.; Silva, R.; Silva, V.; Marques-Oliveira, R.; Silva, A.C.; Pereira, M.C.; Loureiro, J.A. Vine Cane Compounds to Prevent Skin Cells Aging through Solid Lipid Nanoparticles. *Pharmaceutics* **2022**, *14*, 240. [CrossRef] [PubMed]

106. Salem, M.A.; Manaa, E.G.; Osama, N.; Aborehab, N.M.; Ragab, M.F.; Haggag, Y.A.; Ibrahim, M.T.; Hamdan, D.I. Coriander (*Coriandrum sativum* L.) Essential Oil and Oil-Loaded Nano-Formulations as an Anti-Aging Potentiality via TGFβ/SMAD Pathway. *Sci. Rep.* **2022**, *12*, 6578. [CrossRef] [PubMed]
107. Aanisah, N.; Sulistiawati, S.; Djabir, Y.Y.; Asri, R.M.; Sumarheni, S.; Chabib, L.; Hamzah, H.; Permana, A.D. Development of Solid Lipid Nanoparticle-Loaded Polymeric Hydrogels Containing Antioxidant and Photoprotective Bioactive Compounds of Safflower (*Carthamus tinctorius* L.) for Improved Skin Delivery. *Langmuir* **2023**, *39*, 1838–1851. [CrossRef]
108. Achee, N.L.; Grieco, J.P.; Vatandoost, H.; Seixas, G.; Pinto, J.; Ching-NG, L.; Martins, A.J.; Juntarajumnong, W.; Corbel, V.; Gouagna, C.; et al. Alternative Strategies for Mosquito-Borne Arbovirus Control. *PLoS Negl. Trop. Dis.* **2019**, *13*, e0006822. [CrossRef]
109. Sharma, R.; Rao, R.; Kumar, S.; Mahant, S.; Khatkar, S. Therapeutic Potential of Citronella Essential Oil: A Review. *Curr. Drug Discov. Technol.* **2019**, *16*, 330–339. [CrossRef] [PubMed]
110. Kelidari, H.R.; Moemenbellah-Fard, M.D.; Morteza-Semnani, K.; Amoozegar, F.; Shahriari-Namadi, M.; Saeedi, M.; Osanloo, M. Solid-Lipid Nanoparticles (SLN)s Containing Zataria Multiflora Essential Oil with No-Cytotoxicity and Potent Repellent Activity against Anopheles Stephensi. *J. Parasit. Dis.* **2021**, *45*, 101–108. [CrossRef]
111. Kamaraj, C.; Satish Kumar, R.C.; Al-Ghanim, K.A.; Nicoletti, M.; Sathiyamoorthy, V.; Sarvesh, S.; Ragavendran, C.; Govindarajan, M. Novel Essential Oils Blend as a Repellent and Toxic Agent against Disease-Transmitting Mosquitoes. *Toxics* **2023**, *11*, 517. [CrossRef]
112. Mapossa, A.B.; Focke, W.W.; Tewo, R.K.; Androsch, R.; Kruger, T. Mosquito-repellent Controlled-release Formulations for Fighting Infectious Diseases. *Malar. J.* **2021**, *20*, 165. [CrossRef]
113. Hernandes, A.N.; Boscariol, R.; Balcão, V.M.; Vila, M.M.D.C. Transdermal Permeation of Caffeine Aided by Ionic Liquids: Potential for Enhanced Treatment of Cellulite. *AAPS PharmSciTech* **2021**, *22*, 121. [CrossRef]
114. Scarano, A.; Petrini, M.; Sbarbati, A.; Amore, R.; Iorio, E.L.; Marchetti, M.; Amuso, D. Pilot Study of Histology Aspect of Cellulite in Seventy Patients Who Differ in BMI and Cellulite Grading. *J. Cosmet. Dermatol.* **2021**, *20*, 4024–4031. [CrossRef] [PubMed]
115. Sadick, N. Treatment for Cellulite. *Int. J. Womens Dermatol.* **2019**, *5*, 68–72. [CrossRef] [PubMed]
116. Khalil, L.M.; El-Refaie, W.M.; Elnaggar, Y.S.R.; Abdelkader, H.; Al Fatease, A.; Abdallah, O.Y. Non-Invasive Caffeinated-Nanovesicles as Adipocytes-Targeted Therapy for Cellulite and Localized Fats. *Int. J. Pharm. X* **2024**, *7*, 100236. [CrossRef] [PubMed]
117. Cikoš, A.-M.; Jerković, I.; Molnar, M.; Šubarić, D.; Jokić, S. New Trends for Macroalgal Natural Products Applications. *Nat. Prod. Res.* **2021**, *35*, 1180–1191. [CrossRef] [PubMed]
118. Fouad, S.A.; Badr, T.A.; Abdelbary, A.; Fadel, M.; Abdelmonem, R.; Jasti, B.R.; El-Nabarawi, M. New Insight for Enhanced Topical Targeting of Caffeine for Effective Cellulite Treatment: In Vitro Characterization, Permeation Studies, and Histological Evaluation in Rats. *AAPS PharmSciTech* **2024**, *25*, 237. [CrossRef]
119. Alkilani, A.Z.; McCrudden, M.T.C.; Donnelly, R.F. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the Stratum Corneum. *Pharmaceutics* **2015**, *7*, 438–470. [CrossRef]
120. Qu, F.; Geng, R.; Liu, Y.; Zhu, J. Advanced Nanocarrier- and Microneedle-Based Transdermal Drug Delivery Strategies for Skin Diseases Treatment. *Theranostics* **2022**, *12*, 3372–3406. [CrossRef] [PubMed]
121. Wong, W.F.; Ang, K.P.; Sethi, G.; Looi, C.Y. Recent Advancement of Medical Patch for Transdermal Drug Delivery. *Medicina* **2023**, *59*, 778. [CrossRef] [PubMed]
122. Waghule, T.; Singhvi, G.; Dubey, S.K.; Pandey, M.M.; Gupta, G.; Singh, M.; Dua, K. Microneedles: A Smart Approach and Increasing Potential for Transdermal Drug Delivery System. *Biomed. Pharmacother.* **2019**, *109*, 1249–1258. [CrossRef]
123. Unnisa, A.; Chettupalli, A.K.; Alazragi, R.S.; Alelwani, W.; Bannunah, A.M.; Barnawi, J.; Amarachinta, P.R.; Jandrajupalli, S.B.; Elamine, B.A.; Mohamed, O.A.; et al. Nanostructured Lipid Carriers to Enhance the Bioavailability and Solubility of Ranolazine: Statistical Optimization and Pharmacological Evaluations. *Pharmaceuticals* **2023**, *16*, 1151. [CrossRef]
124. Alves, G.L.; Teixeira, F.V.; da Rocha, P.B.R.; Krawczyk-Santos, A.P.; Andrade, L.M.; Cunha-Filho, M.; Marreto, R.N.; Taveira, S.F. Preformulation and Characterization of Raloxifene-Loaded Lipid Nanoparticles for Transdermal Administration. *Drug Deliv. Transl. Res.* **2022**, *12*, 526–537. [CrossRef] [PubMed]
125. Teaima, M.H.; Badawi, N.M.; Attia, D.A.; El-Nabarawi, M.A.; Elmazar, M.M.; Mousa, S.A. Efficacy of Pomegranate Extract Loaded Solid Lipid Nanoparticles Transdermal Emulgel against Ehrlich Ascites Carcinoma. *Nanomedicine* **2022**, *39*, 102466. [CrossRef] [PubMed]
126. Nasrollahzadeh, M.; Ganji, F.; Taghizadeh, S.M.; Vasheghani-Farahani, E.; Mohiti-Asli, M. Drug in Adhesive Transdermal Patch Containing Antibiotic-Loaded Solid Lipid Nanoparticles. *J. Biosci. Bioeng.* **2022**, *134*, 471–476. [CrossRef] [PubMed]
127. Abd-El-Azim, H.; Abbas, H.; El Sayed, N.S.; Fayez, A.M.; Zewail, M. Non-Invasive Management of Rheumatoid Arthritis Using Hollow Microneedles as a Tool for Transdermal Delivery of Teriflunomide Loaded Solid Lipid Nanoparticles. *Int. J. Pharm.* **2023**, *644*, 123334. [CrossRef]

128. Prabhu, A.; Jose, J.; Kumar, L.; Salwa, S.; Vijay Kumar, M.; Nabavi, S.M. Transdermal Delivery of Curcumin-Loaded Solid Lipid Nanoparticles as Microneedle Patch: An In Vitro and In Vivo Study. *AAPS PharmSciTech* **2022**, *23*, 49. [CrossRef]
129. Khan, M.F.A.; Ur. Rehman, A.; Howari, H.; Alhodaib, A.; Ullah, F.; Mustafa, Z.u.; Elaissari, A.; Ahmed, N. Hydrogel Containing Solid Lipid Nanoparticles Loaded with Argan Oil and Simvastatin: Preparation, In Vitro and Ex Vivo Assessment. *Gels* **2022**, *8*, 277. [CrossRef] [PubMed]
130. Anantaworasakul, P.; Chaiyana, W.; Michniak-Kohn, B.B.; Rungseevijitprapa, W.; Ampasavate, C. Enhanced Transdermal Delivery of Concentrated Capsaicin from Chili Extract-Loaded Lipid Nanoparticles with Reduced Skin Irritation. *Pharmaceutics* **2020**, *12*, 463. [CrossRef]
131. Souto, E.B.; Fangueiro, J.F.; Fernandes, A.R.; Cano, A.; Sanchez-Lopez, E.; Garcia, M.L.; Severino, P.; Paganelli, M.O.; Chaud, M.V.; Silva, A.M. Physicochemical and Biopharmaceutical Aspects Influencing Skin Permeation and Role of SLN and NLC for Skin Drug Delivery. *Heliyon* **2022**, *8*, e08938. [CrossRef]
132. Altememy, D.; Javdani, M.; Khosravian, P.; Khosravi, A.; Moghtadaei Khorasgani, E. Preparation of Transdermal Patch Containing Selenium Nanoparticles Loaded with Doxycycline and Evaluation of Skin Wound Healing in a Rat Model. *Pharmaceuticals* **2022**, *15*, 1381. [CrossRef]
133. Ali, H.S.; Namazi, N.; Elbadawy, H.M.; El-Sayed, A.A.; Ahmed, S.A.; Bafail, R.; Almikhlafi, M.A.; Alahmadi, Y.M. Repaglinide–Solid Lipid Nanoparticles in Chitosan Patches for Transdermal Application: Box–Behnken Design, Characterization, and In Vivo Evaluation. *Int. J. Nanomed.* **2024**, *19*, 209–230. [CrossRef] [PubMed]
134. Zhang, W.; Zhang, W.; Li, C.; Zhang, J.; Qin, L.; Lai, Y. Recent Advances of Microneedles and Their Application in Disease Treatment. *Int. J. Mol. Sci.* **2022**, *23*, 2401. [CrossRef]
135. Khalid, R.; Mahmood, S.; Mohamed Sofian, Z.; Hilles, A.R.; Hashim, N.M.; Ge, Y. Microneedles and Their Application in Transdermal Delivery of Antihypertensive Drugs—A Review. *Pharmaceutics* **2023**, *15*, 2029. [CrossRef] [PubMed]
136. Wang, J.; Zeng, J.; Liu, Z.; Zhou, Q.; Wang, X.; Zhao, F.; Zhang, Y.; Wang, J.; Liu, M.; Du, R. Promising Strategies for Transdermal Delivery of Arthritis Drugs: Microneedle Systems. *Pharmaceutics* **2022**, *14*, 1736. [CrossRef]