Scientia Pharmaceutica

Review

A Narrative Review of the Potential Roles of Lipid-Based Vesicles (Vesiculosomes) in Burn Management

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Abstract: Burn injuries can have a lasting effect on people's quality of life, as they negatively impact their physical and mental health. Then, they are likely to suffer psychological problems as a result. A serious problem is that deep burns are more challenging to treat due to their slow healing rate and susceptibility to microbial infection. Conventional topical medications used for burn treatment are sometimes ineffective because they cannot optimize their ability of transcutaneous absorption at the targeted site and accelerate healing. However, nanotechnology offers excellent prospects for developing current medical wound therapies and is capable of addressing issues such as low drug stability, water solubility, permeability, and bioavailability. The current review focuses on lipid-based vesicles (vesiculosomes) as an example of advanced delivery systems, showing their potential clinical applications in burn wound management. Vesiculosomes may help overcome impediments including the low bioavailability of active agents, offering the controlled release of drugs, increased drug stability, fewer side effects, and reduced dosing frequency, which will ultimately improve therapeutic efficacy and patient compliance. We discuss the application of various types of vesiculosomes such as liposomes, niosomes, ethosomes, cubosomes, transfersomes, and phytosomes in burn healing therapy, as these demonstrate superior skin penetration compared to conventional burn topical treatment. We also highlight their noteworthy uses in the formulation of natural products and discuss the current status as well as future perspectives of these carriers in burn management. Furthermore, the burn treatment options currently available in the market are also summarized.

Keywords: burn; liposomes; cubosomes; noisomes; phytosomes; ethosomes; transfersomes; drug delivery systems

Citation: Abdul Rasool, B.K.; Al Mahri, N.; Alburaimi, N.; Abdallah, F.; Shamma, A.S.B. A Narrative Review of the Potential Roles of Lipid-Based Vesicles (Vesiculosomes) in Burn Management. *Sci. Pharm.* **2022**, *90*, 39. https://doi.org/10.3390/scipharm90030039

Academic Editor: Natasa Skalko-Basnet

Received: 28 April 2022
Accepted: 27 June 2022
Published: 29 June 2022

1. Introduction

1.1. Burn Degrees

A burn is typically thought to be an injury caused by extreme heat, friction, radiation, chemicals, electric sources, or hot/cold liquids or solids. Complicated responses to burn injuries are associated with hypermetabolism, morbidity, and mortality. Additionally, burn injuries can be one of the most devastating injuries a person can suffer because they have a long-term influence on people's quality of life and harm their physical and emotional health. Sometimes, severely burned patients are likely to have psychological issues. Additionally, mortality from burn injuries has previously been very high, but advances in treatment have improved patient survival in the past few decades. This reduction in mortality is due to burn centers and changes in treatment protocols. Nonetheless, the survival of burn patients has resulted in a massive economic drain on both government and patients worldwide due to the very high cost of burn patient care [1]. To classify a burn, the tissue depth affected is taken into account. Accordingly, burn wounds are classified internationally into three stages: first-degree burns, which are superficial and only affect the skin surface;

second-degree burns, which affect the first and second layers of the skin; and third-degree burns, where all the skin layers are involved. In addition, fat tissue is burned in the third degree, killing the skin [2]. The features and management of burn degrees are discussed in Table 1 [3].

Table 1. Burn degrees along with their features and management.

Burn Class	Features	Symptoms	Management
First degree	○ Mild burn (cover <10% of the total body surface area); ○ Hospitalization is rare.	○ Pain; ○ Redness of the top layer of the skin (epidermis); ○ No blisters.	○ Immerse the burned area in running water for 5–10 min; ○ Cold compresses; ○ Cooling topical gels such as aloe vera gel; ○ Topical antibiotics, e.g., bacitracin ointment; ○ Pain killers, e.g., acetaminophen and ibuprofen.
Second degree	○ Moderate burn (cover around 10% of the total body surface area); ○ Hospitalization may be needed.	○ Redness and pain; ○ Affects the first (epidermis) and second layers (dermis) of the skin; ○ Swelling and blistering.	○ Same treatment as the first-degree burn; ○ Stronger local antibiotics, e.g., silver sulfadiazine 1% cream; ○ Bandaging and dressing of the broken open burn; ○ Lifting limbs to reduce swelling.
Third degree	○ Sever burn (cover >10% of the total body surface area); ○ Life-threatening; ○ Hospitalization is compulsory; ○ Patient rehabilitation.	○ All the skin's layers are involved; ○ Black, brown, yellow, or white skin; ○ Swelling; ○ Leathery and dry skin; ○ Lack of pain because of nerve ending destruction.	○ Removing dead tissue and damaged skin from the burned area; ○ Excessive fluid replacement (IV admixture fluids) to avoid dehydration and hypovolemic shock; ○ Intravenous and oral antibiotics to prevent infection and septicemia; ○ Local antibiotic ointments or creams; ○ A warm, humid environment for the burn; ○ High-protein diet; ○ Nutritional supplements; ○ Pain killers; ○ Tetanus shot; ○ Functional and cosmetic reconstruction; ○ Skin grafts by replacing damaged tissue with healthy skin from other unaffected parts of the body; ○ If the patient does not have enough healthy skin for grafting, a temporary source of skin graft can be obtained from donors or using artificial skin grafts.

1.2. Skin Substitutes

A skin substitute is a material used to cover burn wounds and replace the function of the skin either temporarily or permanently. Patients who need extensive post-burn reconstructions, as well as those who are acutely burned, require skin substitutes. Depending on the composition of these products, they can be classified into various groups, as presented in Table 2 [4].

Table 2. Classification of biological and synthetic skin substitutes.

Class	Characteristics	Types	Composition	Example
Class I	Materials for impermeable dressings and short-term dressings.	(a) Single-layer substances	○ Biological naturally occurring dressings;	○ Amniotic membrane; ○ Potato peel;
			○ Alternative for synthetic dressing.	○ Polymer sheet; ○ Polymer foam; ○ Polymer spray.
		(b) Double-layer substances	○ Skin substitutes include bovine type I collagen and nylon mesh embedded with fibroblasts.	○ TransCyte®.
	Durable single-layer skin replacements.	Epidermal replacements	○ An epidermal sheet derived from male neonatal epidermal keratinocytes and a bovine type I collagen matrix.	○ Apligraft®; ○ Cultured Epithelial Autograft (CEA).
Class II		Skin substitutes	○ Sheets are made of bovine collagen; ○ Porcine collagen sheet; ○ Bovine dermal matrix; ○ Human dermal matrix.	○ Kollagen®. ○ Matriderm®. ○ Alloderm®.
Class III	Alternatives to composite skin.	Grafted skin	○ Skin transplantation from another person.	○ Allograft; ○ Xenograft.
		Skin tissue engineering	○ Template for dermal regeneration.	○ Integra®; ○ Biobrane®.

1.3. Current Local Treatment of Burns

Burn injury treatment includes disinfection and debridement, in addition to the regular changing of topical antimicrobial dressings. There is indeed no consensus on the best antimicrobial agents or dressings to prevent or manage infection or help wound healing. The main purpose of using topical treatments is to protect the burn wound surface from contamination and promote wound healing [5]. Additionally, topical treatment is non-invasive, self-administered, may be removed from the skin after usage, and has high patient compliance since it allows medicine to be applied directly to the afflicted region, boosting therapeutic efficacy, decreasing undesired side effects, and limiting burn wound

complications. Nevertheless, the major concern with current topical treatment is that most medications only penetrate the skin to a limited extent due to the skin's barrier function and should be supported with adequate basic wound care [6].

Burn wounds are treated with topical agents and wound dressings depending on their stage and extent. To determine the optimal treatment, other factors must be considered such as wound quality and status, e.g., wound contamination and infection, patient skin allergies, treatment availability and cost, and the patient's preference [7]. Local treatments of burn wounds that are currently available in hospitals and pharmacies include: (a) conventional topical antimicrobial preparations (creams, ointments, dressings, solutions, and cleansers); (b) biologic grafts; and (c) semibiologic skin substitutes. It is evident that current antimicrobial therapies are not suitable for treating deep burns due to their poor skin penetration properties; furthermore, they exhibit many limitations and serious adverse effects. More details about the current topical antimicrobial therapies for burns are shown in Table 3 [8].

Table 3. Current topical antimicrobial treatment for burn wounds.

Antimicrobial Agents	Dosage Form	Clinical Indications	Side Effects	Contraindications
Silver sulfadiazine (1% cream) with or without cerium	Cream (1%)	All types of burns (small, medium, and large wound surface areas).	Skin allergies, neutropenia, and leukopenia.	Pregnancy, lactating, infants, and allergies to sulfonamides.
Nanocrystalline silver (Acticoat®, Aquacel Ag®)	Dressings	All sizes of burns (small, medium, and large wound surface areas).	Systemic silver absorption, and skin staining.	Burn near eyes, Pregnancy, and allergic to silver.
Bacitracin	Ointment 500 IU/g	All sizes of burn wounds, including face, perineum, graft sites. An alternative if allergic to sulfonamides.	Yeast growth, skin allergies.	Bacterial resistance, allergic reaction, and signs of reepithelialization.
Mupirocin	Ointment Cream (2%)	Face, perineum, and small and medium surface area burns. An alternative if allergic to sulfonamides.	Yeast growth, skin hypersensitivity.	Bacterial resistance, allergic reaction.
Mafenide	Cream (8.5%) Solution (5%)	Small wound surface area, ears, and nose burn.	Pain, epithelial regeneration inhibition, and metabolic acidosis.	Large burn area of burn (>40% of the total BSA); allergic to sulfonamides.
Chlorhexidine	Skin cleanser	Only superficial burns.	Skin hypersensitivity.	Deep burns.
Povidone-iodine	Liposomal ointment	Small, and medium surface area burns	Pain, skin hypersensitivity, iodine toxicity, renal failure.	Infants, pregnancy, lactation, and thyroid diseases.
Acetic acid	Diluted solution	Antiseptic, *Pseudomonas aeruginosa* infections	Inhibits epithelialization at high concentrations.	Superficial burns.
Bismuth-impregnated petroleum gauze	Dressings	Preferred dressing for skin graft donor sites and use in children.	No adverse effects are reported.	Allergic reactions.
Sodium hypochlorite Dakin's solution®	Solution (0.025%)	Difficult burn wounds and other antibiotic-resistant bacteria.	Pain.	Allergic reactions.

1.4. Vesicular Drug Delivery Systems

As discussed earlier, the major concern with current topical treatment is that most medications only penetrate the skin to a limited extent due to the skin's barrier function. Scientists have therefore proposed novel formulation approaches to improve burn therapies' effectiveness and permeation deep into the skin. The incorporation of drug molecules into vesicular lipid delivery systems is one of these approaches. Liposomes, niosomes, ethosomes, transfersomes, and cubosomes are examples of these delivery systems [9]. For ease of explanation, we call these systems vesiculosomes in our present study. Liposomes are the parent carrier, were discovered in 1961 by a British scientist named Dr. Alec Bangham, and are the oldest form of these lipoparticles. Later, a variety of vesiculosome carriers were prepared for burn and wound therapy based on the structural modification of liposomes. Additionally, treating a burn with conventional treatments can take a long time. As a result, studies have been conducted to prove the need for advanced pharmaceutical preparations that will help treat burns faster and reduce cost. Further explanations of the advantages and limitations of lipid-based vesicular drug delivery systems (DDSs) are displayed in Table 4 [10].

Table 4. The main advantages and limitations of lipid-based vesicular DDSs.

Advantages	Limitations
○ Can entrap both hydrophilic and hydrophobic compounds; ○ Improve drug bioavailability; ○ Delay the elimination of rapidly metabolized drugs (drugs of short half-life); ○ Prolonged drug lifespan in the body; ○ Targeted drug delivery can be accomplished; ○ Enhance drug stability; ○ Reduce drug toxicity and side effects.	○ Drug leakage leads to burst drug release; ○ Poor loading efficiency for hydrophilic drugs; ○ Expensive technique; ○ Liposomes possess a short biological half-life; ○ Unstable chemical properties; ○ Purity problems of the phospholipids.

Thus, based on the previously reported research work, it seems that many drug formulation problems can be addressed with vesiculosomes to improve drug therapeutic efficacy and patient compliance. Vesiculosomes also improve the skin penetration of various medications compared to traditional burn topical treatment.

Accordingly, the current literature review is designed to clarify the use of vesicular DDSs in the management of burn injuries. A variety of pharmacological targets and treatment pathways are now being tested in clinical trials with exciting new developments. Therefore, we hope to provide the reader with brief general information about burn care services, in addition to a comprehensive overview of advanced lipid-based vesicular DDSs, their applications for burn wound treatment, and the current status in the pharmaceutical market, along with prospects for the future of the field. In addition, herbal products loaded into vesiculosomes are highlighted, as they have proven potential effectiveness in burn treatment as well.

2. Methodology

In June 2021, numerous meetings were conducted online through the Zoom app, as well as on-campus, to discuss the article's topic. There was continuous discussion among the authors throughout this period until the topic and the outlines of the article were decided in July 2021.

In September 2021, the study proposal was submitted to the Research Unit of Dubai Pharmacy College for Girls for approval. The Research Evaluation Committee revised and

approved the research proposal in October 2021. Once the proposal was approved, we began seeking references from previous studies and research work to build our article.

Meanwhile, from November 2021 to March 2022, we all worked together to write the review and prepare illustrations including the figures, tables, graphical summary, and video abstract. The relevant citations (with content related to burn and vesicular DDSs) were selected based on their year of publication (between 2010 and 2022), whereas references published before 2010 were excluded unless the information was required. References were searched from a variety of databases, including Google Chrome, Google Scholar, Google Patents, PubMed, Embase, and other related search engines. The selected references were research articles, review articles, and websites, and all were written in the English language. Another criterion for selecting a reference was the quality of the journal in which the research was published. Our main objective was to select articles that had been published in high-quality, peer-reviewed, indexed, international journals with good impact factors.

Furthermore, several keywords were used in the review, including burn, liposomes, cubosomes, noisomes, phytosomes, ethosomes, transfersomes, and other related search terms such as drug delivery systems, wound, and antimicrobials. Finally, in April 2022, the manuscript preparation was completed and submitted for consideration for publication.

3. Vesiculosomes in Burn Management

3.1. Liposomes

Liposomes are spherical vesicular particles with an aqueous center encased by one or more concentric phospholipid bilayers (Figure 1). Since the 1970s, liposomes have been explored as potential DDSs because of their numerous advantages, such as their ability to incorporate hydrophilic and hydrophobic active pharmaceutical agents (APIs), reduce the risk of severe adverse effects of toxic drugs such as chemotherapeutics [10], target drugs to a specific site of action, improve drug bioavailability, control the release pattern of medication over a long duration, and minimize the frequency of the dose, thus improving patient compliance [11].

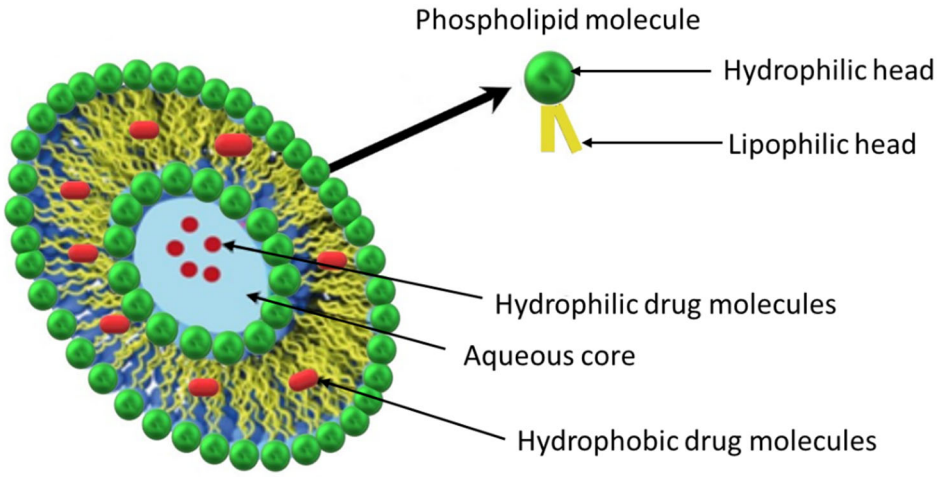

Figure 1. Sketch of liposome components.

Liposomes have been applied in various pharmacotherapeutic areas to improve therapeutic drug performance from different routes of administration including oral, topical, parenteral, ocular, and nasal [12–15]. However, in burn management, most effort has been dedicated to local antimicrobial medication due to the increasing rate of antibiotic resistance upon using conventional topical preparations [16].

Recently, many lipid-based vesicular systems have been intensively searched to enhance skin regeneration and overcome infections in burn wounds, with optimistic outcomes [17]. Scientists have found that liposomal vesicles could penetrate the skin via the

intracellular pathway and deliver drugs into the outer layer of the skin—to the epidermis and dermis—and provide the sustained release of the drug [18].

On the other hand, phage therapy has gained considerable popularity as a method for treating illness and chronic wound infections [19]. For almost a century, phage therapy has been widely reconsidered as an alternative to antibiotics to treat bacterial infections using naturally occurring viruses (phages). Later on, bacterial resistance to antibiotics resulted in a renewed interest in reconsidering this practice. Phage therapy is typically used to infect and lyse bacteria at the infection site using phages. Additionally, advances in biotechnological approaches have further enhanced the range of potential phage therapeutics to include bioengineered phages and their purified lytic proteins that target multidrug-resistant bacteria [20].

Moreover, the phage is loaded into the liposomes to improve their therapeutic outcomes. For example, a liposome-entrapped phahomoge cocktail to treat bacterial infections not responding to antibiotics caused by Staphylococcus aureus-induced diabetic wound infection was investigated by Chhibber and his assistants [21]. They proved that the phage cocktail-loaded liposomes showed faster-wound healing and longer persistence than free phage therapy in mice. The same strategy also served as an efficient tactic for treating burn wound infections of *Klebsiella* not responding to conventional antibiotic therapy in mice. Furthermore, the liposome-loaded phage cocktail protected the test animals from death even after a 24 h delay in therapy establishment with a higher reduction in bacterial load in major organs and the blood [22].

Additionally, the treatment is suggested according to the area of the burn as well as skin permeation properties. For instance, madecassoside has manifested high efficacy in treating skin diseases such as dermatitis and psoriasis. Nevertheless, the topical wound-healing effect of madecassoside was hindered by its poor skin permeability. Therefore, in a previous study, madecassoside liposomal double-emulsion and film dispersion liposomal preparations were developed to improve its transdermal permeation and wound-curing effect. As a result, it was found that the liposomal double-emulsion was superior to the madecassoside film dispersion liposomes, and both approaches had outstanding performance thanks to polyethylene glycol modification [23]. The development of polysaccharide-coated liposomes loaded with epidermal growth factor was another attempt to treat deep burns. The modified liposomes were coated with a layer of sodium alginate followed by another layer of chitosan using the layer-by-layer technique. The prepared biopolymer-coated liposomes were cationic nano-sized vesicles of high drug entrapment efficiency, and remarkably prolonged the drug release. Moreover, the liposomes accumulated in the epidermis and improved the transcutaneous permeation of the epidermal growth factor; hence, this can be considered a candidate approach for local drug delivery to promote wound healing [24].

Further trials to develop the innovative liposomes were performed to combine the advantages of the conventional liposomes and the additional benefits of topical administration. The presence of the surfactant edge activator gives deformable liposomes a lot of flexibility, allowing them to traverse the compact dead stratum corneum and reach the viable epidermis. One of these studies was conducted by Choi et al. [25] who linked the N-termini of the epidermal growth factor, platelet-derived growth factor A, and insulin-like growth factor I with low-molecular-weight protamine, which was then conjugated with hyaluronic acid and integrated into the deformable liposomes. They discovered that the novel liposomes had a reasonably high skin drug absorption, with roughly 11% of the drug deposited in the entire skin and 8% in the dermis; thus, it was regarded as quite efficient.

Moreover, the continual increase in antibiotic resistance against pathogenic microorganisms with the high susceptibility of burn wounds to infections and the difficulty in the systematic administration of antibiotics has resulted in the development of advanced topical antimicrobial preparations for burn infections, and has become a fertile field of innovation for researchers and pharmaceuticals. Indeed, topical liposome delivery systems have a large share in this field. Therefore, when antimicrobials are incorporated into liposomes in a hydrogel platform, they synergistically enhance burn wound healing and exert

immediate and prolonged effects. For example, chitosan hydrogels loaded with mupirocin antibiotics in liposomes have been proposed as an enhanced burn therapy. Though the vesicle size significantly impacted the drug release, the liposomes incorporated into hydrogels showed a prolonged release of mupirocin [26]. Thus, nano-sized liposome-based antimicrobial medicines delivered locally in adequate quantities and over a long time could improve antimicrobial activity and reduce the effective strength required, perhaps via the putative mechanisms of increased permeation through the microbial cell membrane. For instance, previous research has suggested fusogenic liposomes carrying fusidic acid as a potential option for addressing the infectious challenges of severe and resistant cases such as burns [27,28]. Furthermore, silver sulfadiazine liposomes have been examined as a feasible treatment strategies that could act as prolonged-release drug depots, and may merit further consideration in providing localized treatment for infected burns [29].

Several modifications were introduced to the liposome components and structure to improve their stability and performance as drug carriers. Sterically stabilized, ligand-targeted, and mucoadhesive liposomes are examples of modified liposomes [30–32] where various techniques to create sterically stabilized liposomes were used, such as "ethanol-injection solvent evaporation".

The fabrication approach of surface-modified mucoadhesive lipid nanovesicles is a novel trend in the application of liposomes for wound treatment. Among the mucoadhesive polymers used for liposome coating is chitosan. Chitosan-coated liposomes (chitosomes) have been fabricated to enhance the bioavailability [33] and stability [34] of drugs and also to control drug release [35] over a prolonged duration. Chitosomes are formed by ionic interaction between the positively charged amino groups of chitosan and the negatively charged phosphate groups on the surface of liposomes. The outcomes of the mentioned research are supported by other findings where chitosan has been reported to be effectively utilized in burn wound infections due to its antimicrobial activity, wound-healing support, and ability for slow drug release into wounds [36]. Zadeh and Zamin [37] successfully loaded mafenide acetate, one of the most effective antibiotics in treating burn infections, into the chitosomes. They reported that chitosomes can overcome mafenide acetate drawbacks by increasing penetration through the burned skin, reducing dose frequency, and reducing drug toxicity, thereby providing a more concentrated form of the drug in the burned tissue than aqueous solutions and creams can. Experiments have also evidenced liposome stability improvement with coatings of chitosan polymer, since traditional liposomes suffer from stability issues such as aggregation, fusion, degradation, and drug leakage during storage [38].

On the other hand, anti-infective liposomal preparations were found to be unable to provide a moist environment to encourage fast wound healing in the local treatment of burn injuries. Therefore, anti-infective-loaded liposomes were incorporated into a hydrogel base with a high water-binding capacity. This concept was implemented by Homann et al., who conducted a randomized controlled trial on forty-three patients with partial-thickness burn wounds to investigate the efficacy of polyvinyl–pyrrolidone–iodine liposomal hydrogel compared with conventional silver-sulfadiazine cream on burn healing. The results indicated that the liposomal hydrogel treatment provides fast wound healing and promising cosmetic improvement [32]. Further examples of liposome-based formulations and their application in burn therapy are displayed in Table 5.

Table 5. Examples of liposome-based formulations and their application in burn therapy.

Drug	Therapeutic Activity	Prepared Formulation	Model Used	Outcomes	Reference
Silver Sulfadiazine	Prevents and treats wound infection in patients with second- and third-degree burns.	Topical wound dressing containing liposome-entrapped silver sulfadiazine.	Sacrificed rats: colony-forming units of *P. aeruginosa* were injected into the muscle tissue of the rats.	One application of liposomal-entrapped antibiotics resulted in a therapeutic effect that would normally require multiple administrations of conventional therapy.	[39]
Usnic acid	Antimicrobial, anti-inflammatory antiviral, and antitumor activities.	Gelatin-based dressings containing usnic acid-loaded liposomes.	Male pigs	According to the data, topical wound dressing for second-degree burn treatment promotes faster-wound healing than silver sulfadiazine ointment.	[40]
Amphotericin B	Broad-spectrum antifungal agent of choice for burn patients.	Experimental liposomal amphotericin B in commercial products.	In vitro	Liposomal amphotericin B exhibited superior in vitro antimicrobial activity against Aspergillus fumigatus compared to the free drug as well as superior physical stability.	[41]
Epidermal growth factor (EGF)	EGF enhances wound healing by stimulating epidermal and dermal regeneration and promoting cell growth.	EGF-loaded liposomes in chitosan gel formulations.	Rats	An experiment was conducted on rats to investigate the effect of formulations on healing second-degree burn wounds. The histochemical results showed that the EGF–liposomal gel formulations had the highest epithelialization rate.	[42]
Bupivacaine	Postoperative analgesia	Bupivacaine-loaded liposomes.	A clinical study in burn patients.	The administration on the surgical site (autograft harvesting) produced postsurgical analgesia in burn patients.	[43]

3.2. Cubosomes

Cubosomes are lipid-based nanosystems. They were discovered in 1980 as analogous to conventional vesicular systems such as liposomes and niosomes, and are composed of amphiphilic lipids in specific quantities. In cubosomes, the hydrophobic region of the amphiphilic molecules can self-assemble in the polar solvent into thermodynamically stable arrays to form the bicontinuous cubic liquid crystalline phase of lengths on a nanometer scale (Figure 2) [44].

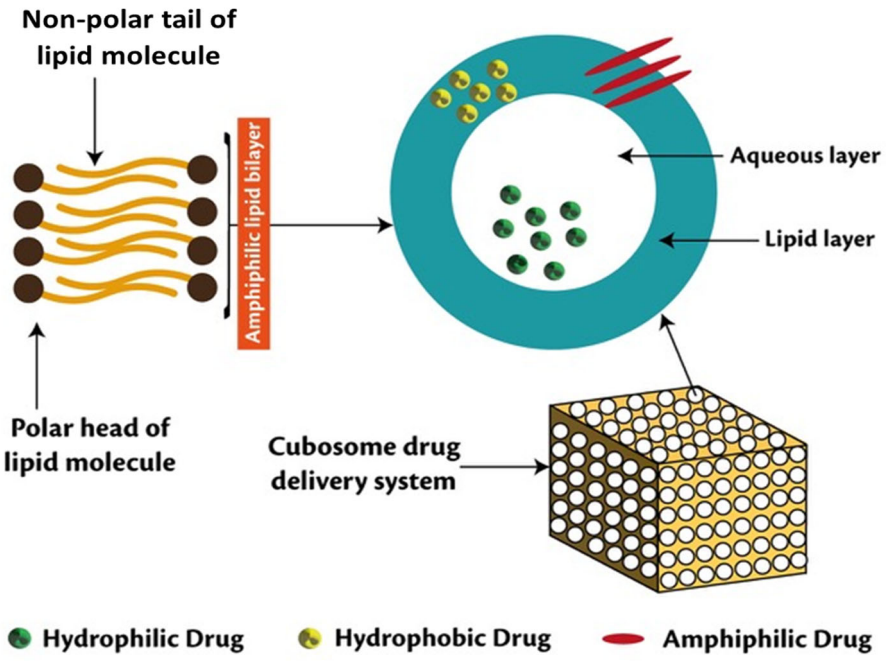

Figure 2. Primary structural components of cubosomes.

The novel cubosomal delivery system has become attractive and extensively encompassed in pharmaceutical formulations due to its appreciated advantages, including: (i) cubosomes possessing the ability to target and control drug release; (ii) suitable carriers for hydrophilic, hydrophobic, and amphiphilic drugs; (iii) biocompatibility and biodegradability; and (iv) applicability in both mucosal and topical drug delivery due to their bioadhesive properties [45]. Moreover, cubosomes are easily formed at almost any dilution level in the aqueous vehicle, and drug leakage is less concerning than liposome leakage. Cubosomes are considered great delivery vehicles for a wide range of medicines; however, their manufacturing on a large scale is problematic because of their unusual phase behavior and vicious qualities [46].

In the previous research, cubic nano-sized lipid vesicles showed a wide range of applications, such as improving oral drug bioavailability [47,48], reducing systemic side effects [49], decreasing ocular irritancy, and increasing local drug bioavailability [50]. In addition, they showed the site-targeting of radiological and chemotherapeutic agents [51] and transdermal drug delivery [52]. However, only limited research works have been published on the use of cubosomes in the treatment of burn wounds. One of these studies was conducted by Morsi et al. (2014), who developed silver sulfadiazine-loaded cubosome dispersions with the emulsification method using monoolein as a lipid phase and the nonionic surfactant of poloxamer 407 with or without polyvinyl alcohol in a mucoadhesive hydrogel base. Their results demonstrated that the antibiotic-loaded cubogel was non-irritant to the skin, had minimal cytotoxicity in the dermal cell lines, improved wound contraction, and could be used in deep second-degree burns compared to the commercial product Dermazin® cream [53].

Certainly, the rapid growth of microbial resistance to conventional antibiotics poses a serious global threat of growing concern in wound treatment. Thus, scientists have accelerated their contributions to discover new antimicrobials with new modes of action to be less susceptible to bacterial resistance. As a result, massive laboratory and clinical research efforts are underway to introduce and evaluate next-generation antibiotics. Currently, several antimicrobial peptides are being evaluated as novel anti-infective drugs and innovative products to treat complicated skin infections related to burn wounds through immune-modulating effects, wound healing promotion, and skin scar prevention [54]. For example, cubosomes loaded with the human cathelicidin antimicrobial peptide LL-37 have demonstrated a high antibacterial effect against the tested bacteria *Escherichia coli*, and function as an antimicrobial unit through their adsorption and destruction of the bacterial membrane [55]. Additionally, Boge and his group prepared another novel cubosome loaded with three antimicrobial peptides (AP114, DPK-060, and LL-37), and again the highest association efficacy (>60%) in the cubosomes observed among the three peptides was with LL-37. Moreover, the cubosomes further protected LL-37 from elastase proteolytic degradation, resulting in significantly better antibacterial activity than the free peptide [56]. Later on, the same group of researchers studied three different protocols for preparing the antimicrobial peptide LL-37 loaded-cubosomes for antimicrobial topical drug delivery. The preparation protocols were designed based on the step (pre-, post-, and hydrotrope-loading) of the peptide incorporation into the cubosomes. Their results showed that the highest peptide loading was achieved when the cubosomes were prepared by sonication (pre-loading). Additionally, the peptide was strongly associated inside the cubosomes and was more stable, since its bactericidal effect was persistent after incubation with the proteolytic enzyme compared to the free LL-37 [57].

3.3. Niosomes

Due to the defects of the liposome delivery systems, new non-ionic surfactant vesicles, known as niosomes, were introduced. L'Oreal created and patented the first niosome formulations in 1975 [58]. They were biodegradable, relatively safe, more stable, and inexpensive, hence offering advantages over conventional liposomes. Niosomes improve medication behavior in three ways: the drug clearance is delayed, the drug is protected from the biological environment, and the drug's action is limited to the target site [59]. Furthermore, niosomes are flexible and easily modified due to the functional groups on their hydrophilic heads, and the storage and handling of the surfactants do not necessitate special conditions [60]. Additionally, toxic effects on tissues are reduced when the drugs have a local effect; thus, the use of niosomes for drug administration via transdermal, parenteral, and ocular pathways has been extensively investigated [61,62].

Regarding niosomes' transdermal absorption, no particular mechanism can adequately explain the capacity of niosomes to enhance medication transfer to deep layers of the skin. Niosome adsorption at the cell surface occurs with little or no internalization of either aqueous or lipid phases; it can occur due to attracting physical forces or specific receptors binding to ligands on the vesicle membrane and direct drug transport from the vesicles to the skin. On the other hand, niosomes can also amalgamate with the cell membrane, resulting in a thorough mixing of the niosomal content with the cytoplasm. Another proposal is that niosomes can be absorbed by the cell via endocytosis. Then, the cytoplasmic lysozyme destroys or digests the niosome membrane structure, releasing the entrapped substance into the medium [63].

Numerous studies have recently been published that explore the application of niosomes for drug delivery in treating burn wounds. Silver sulfadiazine is a powerful antibacterial used to treat burns and is available in the market in topical cream dosage form [64]. Several advanced techniques have been investigated to reduce silver sulfadiazine toxicity and improve its therapeutic effectiveness. For instance, silver sulfadiazine-loaded niosomes were fabricated by the thin-film hydration technique and then integrated into carbopol 934 gel base. As a result, burn wound healing was more successful with the niosomal gel

than with the commercial cream. Additionally, the in vitro permeation tests revealed that the release of the drug from both niosomes and the niosomal gel was significantly delayed, thus reducing the dosage frequency [65].

In another study, niosomes embedded in chitosan gel were prepared as a novel vehicle for the topical administration of moxifloxacin. The niosomal gel formulations displayed pseudo-plastic flow behavior and a prolonged drug release profile. Additionally, the niosomal formulation was superior against *P. aeruginosa,* while incorporating moxifloxacin niosomes into chitosan gel had a more significant antibacterial impact against *S. aureus* than free moxifloxacin gel [66]. A positive point is that the chitosan gel base, as shown in other studies, shows excellent promise for localized microbial infection in treating burns, providing a synergistic antimicrobial effect in the preparation [67].

In addition, scientists have explored different approaches for burn wound management. One of these is the mitochondrial production inhibition of reactive oxygen species (ROS) during the inflammatory stage of skin injury which can damage the tissue and delay wound healing. Methylene blue was effective in burn wound treatment, decreasing mitochondrial ROS production and the antioxidant effects. Farmoudeh et al. formulated methylene blue-containing niosomes using an ultra-sonication technique and included them in the gel-based formulation. They reported that the optimized formulation displayed promising results in rats. After three days of treatment, the level of malondialdehyde (an end product of lipid peroxidation) was significantly decreased in the niosomal gel-treated group. In contrast, the superoxide dismutase (an endogenous antioxidant) level was increased. Moreover, histological observations demonstrated effective and fast burn treatment with methylene blue niosomal gel [68].

Moreover, pentoxifylline (PTX) in systemic dosing has been shown to promote wound healing. PTX helps salvage the damage by enhancing the rate of epithelization, reducing the necrotic area, and preventing burn wounds from deepening [69]. Nevertheless, the usage of PTX topically appears to increase the clinical efficacy of drugs by concentrating the drug near the site of infection. According to an in vivo study performed on mice using PTX–niosomal creams, the wound recovery time was reduced by two days. The size of the wounds was also considerably smaller than the control group of the mice. The niosomal creams also increased epithelization and collagen production compared to the PTX cream conventional dosage form, resulting in quicker wound closure [70].

Notably, advanced research has been conducted to explore the utilization of niosomal delivery systems in burn therapy. Some examples of niosomal formulations along with their characteristics and outcomes for burn treatment are displayed in Table 6.

Table 6. Characteristics and outcomes of niosomal formulations in burn treatment.

Drug	Therapeutic Activity	Preparation Technique	Formulation Concepts	Study Outcomes	Study Design	References
Sulfadiazine sodium	Antibiotic	Film hydration method	The vesicular size increased with the amount of alcohol. Large-sized vesicles were obtained with ethanol, followed by propylene glycol and glycerol.	The drug permeation increased with an alcohol concentration.	Ex vivo permeation through rabbit ear skin.	[71]
C. officinalis	Antioxidant, antimicrobial, and promotes wound healing.	Thin-film hydration method	Anthocyanins-loaded niosomes were incorporated into a mucoadhesive gel formulation.	The bioactivity of *C. officinalis* methanolic extract significantly increased after loading into the phytoniosome formulation.	In vitro cell lines	[72]
Silver sulfadiazine	Topical antibacterial	Solvent injection method	The niosomes with Span 60 gave the highest entrapment efficiency and exhibited considerable retardation in vitro drug release.	A sustained release once-a-day niosomal formulation to improve patient compliance was developed.	In vitro antimicrobial study	[73]
hBD-1 and HNP-1	Antimicrobial peptides (AMPs)	Mechanical shaking/ homogenization	The AMP niosomal topical gels were prepared, and the antimicrobial activity was investigated against *Staphylococcus aureus* clinical strains in vitro and in vivo.	The niosomal gel containing recombinant hBD-1 (1 µg/mL) increased the healing rate of infected wounds in rats.	Animal studies (rats)	[74]
Tannic acid	Antibacterial and antibiofilm activities		Optimized formulation using response surface methodology	Niosomes were found as an ideal candidate for designing a new delivery method for the antibacterial agent.	In vitro antimicrobial study	[75]
Phenytoin sodium	Wound-healing activity	Solvent evaporation–film hydration method	The phenytoin-loaded niosomes were incorporated in sodium alginate gel.	In contrast to the vehicle-treated control group, the niosome-treated lesions were fully healed by the ninth day of the in vivo study.	Guinea pigs with induced wounds	[76]
Hypericum perforatum	Wound-healing and anti-inflammatory activities	Film hydration technique	Optimized formulation using response surface methodology.	By the seventh day of the in vivo study, the niosomal gel treatment group showed increased angiogenesis and fibroblastic proliferation.	Adult mongrel dogs	[77]

3.4. Ethosomes

Recent advances in the development of improved and innovative transdermal and dermal therapies have been made possible by ultra-deformable lipid vesicles such as ethosomes. Ethosomes are soft and flexible lipid vesicles, developed in 1996 by Elka Touitou based on the structural modification of the parent vesicles, liposomes. Ethosomes are composed of phospholipids, a high concentration of ethanol, and water [78]. Because of their high ethanol content, they can interact with the polar heads of the phospholipids present in the stratum corneum and permeate into the deep layers of the skin [79].

Lipid nanovesicles can deliver drugs to the target site and improve their stability and absorption. Nanoethosomes are lipidic vesicles that have become attractive permeation enhancers for transdermal drug administration in burn treatment. Nanoethosomes are ultimately included in various topical preparations such as creams, gels, and ointments. For example, Razavi et al. [80] produced silver sulfadiazine nanoethosomal gel formulations to reduce the bacterial infection of burn wounds and healing time. As a result, the ethogel promoted the antibacterial activity of silver sulfadiazine with a faster wound contraction rate in Wistar rats than the untreated animals.

Moreover, ethosomes have been widely used in the transdermal delivery of non-steroidal anti-inflammatory drugs (NSAIDs) for pain management in burns [81]. The anti-inflammatory and analgesic activity of flurbiprofen was significantly increased by its inclusion in the ethosomes vesicles. The loaded ethosomes were stable at the refrigerator temperature and could maintain the sustained release of flurbiprofen for 24 h [82]. Nanoethosomal formulations loaded with other NSAIDs such as naproxen sodium [83], diclofenac sodium [84], ketoprofen [85], and aceclofenac [86] were also explored.

More findings have been approved that suggest that the incorporation of bioactive materials inside the lipid core enhances their permeation properties and protects the active entity from pH and enzymatic degradation [87]. Here is an example for illustration: thymosin β-4 (Tβ-4) is a macromolecular peptide medication that increases the rate of dermal healing, tissue repair, and skin regeneration; however, its usage is limited due to poor membrane permeability and unstable physicochemical characteristics. Therefore, scientists have tried to overcome these obstacles by loading Tβ-4 into the ethosomal delivery system. The results were promising; hence, the ethosomal gel system loaded with protein/peptide drugs provoked the percutaneous absorption of the drug, speed up wound recovery, and improved the therapeutic effect [88]. In another work, tamoxifen citrate was loaded into ethosomes and compared to conventional liposome formulation. Tamoxifen citrate is an anti-estrogenic agent that has been utilized in burn wounds and scar treatment. The prepared lipid vesicles were evaluated in vitro for their permeation properties in human cadaver skin. The confocal scanning microscopy results indicated a higher penetrability of the ethosomal vesicles than liposomes, which were restricted only to the upper epidermal layer [89].

Although recent advances in ethosomal DDSs have shown significant results in reducing the drawbacks of conventional therapies, some limitations are still associated with ethosomal formulations, such as physical instability and a poor yield of production [90].

3.5. Transfersomes

Since the 1990s, the word transfersomes, a trademark of IDEA AG®, Munich, Germany, has been the topic of various patents and literary information. It represents the first generation of ultra-deformable vesicles. Furthermore, IDEA AG has announced the granting of a new US patent that explicitly covers Diractin® (ketoprofen in transfersome® gel, formerly known as IDEA-033). Thus, it provides an appreciated foundation for the future marketing of IDEA's innovative targeted analgesics in the United States [91]. Transfersomes are analogs of liposome vesicles but contain the "edge activator" surfactant in their lipid composition, which is responsible for their ultra-deformable and flexible structure (Figure 3).

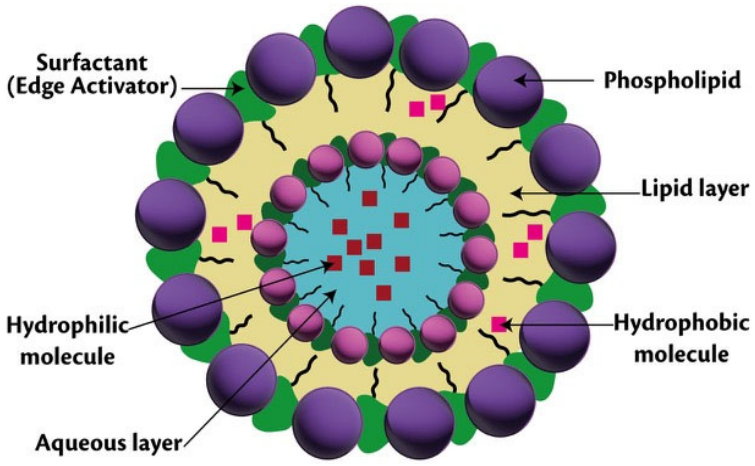

Figure 3. The basic structural components of the deformable transfersome.

Transfersomes have demonstrated potential for delivering both lipophilic and hydrophilic APIs via the transdermal route [92]. Furthermore, the elastic structure and accel properties of the transfersomes allow them to have more significant skin penetration properties compared to traditional liposomes, even reaching the blood circulation [93].

Transfersomes were developed as a new modern technology in drug transdermal delivery for systemic drug percutaneous administration [93,94]. On the other hand, transfersomes were among the most effective medication delivery methods for topical use compared to traditional topical systems. They offer drug penetration to deep skin layers due to their extraordinarily elastic and malleable structure. For example, lidocaine is a local anesthetic that reduces pain or discomfort caused by skin irritations such as burns. To avoid painful local anesthetic injections, Omer et al. developed a topical gel loaded with lidocaine. The transfersomal gel of lidocaine was fabricated using HPMC K15 as a gelling agent with permeation enhancers. Their results revealed the enhanced skin permeation effect and local anesthetic action of lidocaine-loaded transfersomes [95]. Based on transfersomes' significant penetration characteristics, they have become attractive as drug carriers in burn wound treatment. In a previous study, Chaudhari and his group attempted to improve patient compliance by reducing the administration frequency by formulating a transfersomal cream of acriflavine. The transfersomes were prepared by the thin-film hydration method and thoroughly evaluated in vitro. The candidate transfersomal formula showed high loading efficiency and prolonged drug release over 24 h [96]. Further research is being undertaken regarding applying transfersome drug delivery systems to burn treatments, as summarized in Table 7.

Table 7. Examples of transfersome drug delivery systems for burn treatment.

Drug	Vesicles Formers	Therapeutic Activity	Dosage Form	References
Human Growth Hormone	Lecithin soybean phospholipid	Reduction in wound healing time.	Transdermal suspension	[93]
Tocopherol Acetate	Soy phosphatidylcholine (Lipoid S75)	Antioxidant activity and wound healing properties. A simple and low-cost technique for speeding up the healing of infected tough wounds.	Topical suspension	[97,98]
Recombinant Human Epidermal Growth Factor	Phosphatidylcholine and sodium deoxycholate	Accelerates chronic wound healing.	Transdermal suspension	[99]
Mangiferin	Soy lecithin and mucine	Antioxidant and anti-inflammatory.	Bioadhesive topical preparation	[100]

3.6. Phytosomes

Phospholipid complexation patented technology was developed by INDENA, an Italian pharmaceutical and nutraceutical company, in 1989 by combining polyphenolic plant active constituents with phospholipids containing phosphatidylcholine, now known as phytosomes [101]. One of their marketed products is Oleaselect®, a commercialized product that is made up of phytosomes and is based on the polyphenols in olive oil. In comparison to normal oil, antioxidant, antihyperlipidemic, and anti-inflammatory effects, as well as cardiovascular protection, were reported to be improved when it was administered as a phytosomal formulation [102].

In comparison with ordinary herbal extracts, phytosome technology is believed to enhance pharmacological and pharmacokinetic properties and increase drug bioavailability. Phytosomes, also known as photo-phospholipid complexes, are vesicular drug systems generated by hydrogen bonding between hydrophilic portions of phospholipids and phytoactive components of plant extract. Moreover, phytosomes appear to increase the absorption of active constituents from both oral and topical dosage forms and consequently reduce the dose required. However, phytoconstituents from phytosomes are quickly removed, which is a disadvantage [103,104]. Indeed, soya-lecithin phosphatidylcholine, phosphatidylserine, and phosphatidylethanolamine are the most often used phospholipids, and the best phospholipid-to-phytoconstituent ratio is 1:1 [105]. In this field, many studies are being conducted to develop therapeutically effective phytosomal products. *Gingko biloba* extract, loaded into phytosomes, significantly increased the absorption of its flavonoid and terpene active components, and enhanced brain and vascular protection in human volunteers [106].

Several herbal extracts have been studied for their ability to relieve burns and other skin ailments due to their medicinal benefits, including their antibacterial and anti-inflammatory properties, and capabilities to promote wound healing and blood clotting. Most plant extracts used in pharmaceutical applications are pharmacologically active due to their flavonoids or polyphenol rings, which have high molecular weights and are therefore poorly soluble and imperfectly absorbed through the skin. Therefore, the nano-sized phytosomal delivery system is needed to enhance the penetration of these compounds across biological barriers due to their distinctive physicochemical properties, thereby increasing their bioavailability [107,108]. Table 8 provides examples of phytosomal products prepared for treating burns and other types of wounds.

Table 8. Phytosome-based herbal formulations for burn/wound treatment.

Scientific Name	Dosage Form	Model Used	Magnitude of Results	Reference
Aloe vera	Mucilage (98%)	Clinical studies (patients with second-degree burns)	Aloe therapy proved effective for partial burn injuries (total burn surface area <25%). Burn wound healing and pain relief in the tested patient (who received aloe treatment) were faster than in the control group patients (who received silver sulfadiazine cream 1%). Pain relief was effective by the 5th–12th day of treatment, and 24 out of 25 total patients healed completely by the 40th day of treatment.	[109]
	Phytosomal gel	Ex vivo permeation study using rat skin	The formulation was optimized by a factorial design experiment. The skin permeation and flux profile of the phytosomal gel were superior compared to aloe vera extract mucilage. The phytosomal gel showed stability for three months.	[110]
	l-Carnosine/Aloe vera-loaded dual nanophytosomes	In vitro model using human umbilical vein endothelial cells (HUVECs)	The nanophytosomal preparation was effective in protecting the HUVECs against methylglyoxal (MGO)-induced toxicity for 72 h of incubation. Moreover, the formula showed efficient free radical scavenging potency. Thus, it could be used in the treatment of microvascular dysfunction in diabetics with uncontrolled hyperglycemia.	[111]
Sinigrin glucosinolate (seeds of *Brassica nigra*)	Sinigrin–phytosome complexes	Ex vivo permeation study using the abdominal skin of Caucasian female patients after plastic surgery	The phytosomes delivered a statistically significantly higher concentration of sinigrin into the stratum corneum–epidermis compared to the control (free sinigrin).	[112]
Brassica oleracea	Leaf aqueous extract-loaded phytosomes	In vitro assessment	HPLC was accurate, fast, and cost-effective for the estimation of allyl isothiocyanate in black mustard extract-loaded phytosomes.	[113]
Camellia sinensis	Leaf ethanolic extract-loaded phytosomes	Male Balb-c mice	Analgesia and the anti-inflammatory activity of green tea phytosomes that contained diclofenac were enhanced and prolonged in a dose-dependent manner when compared to diclofenac alone.	[114]

Table 8. *Cont.*

Scientific Name	Dosage Form	Model Used	Magnitude of Results	Reference
Calendula officinalis	Gold nanoparticle-loaded phytosomes	In vitro cell culture studies	Fluorescence imaging showed that gold nanoparticle-loaded phytosomes penetrated deep into the cells and accumulated around the nucleus. They also exhibited antioxidant and wound healing properties.	[115]
Moringa oleifera	Leaf aqueous extract-loaded phytosomes	In vitro normal human dermal fibroblast cell migration and cytotoxicity tests	Comparatively to the controls, the phytosomes exhibited significantly higher cell migration and proliferation rates. Moreover, the phytosomes had no cytotoxic effects at concentrations up to 1.5 mg/mL, exhibiting significant potential as a therapeutic wound dressing.	[116]
Crocetin from Nyctanthes arbor-tristis	Crocetin-loaded phytosomal gel	Incision and excision wounds inflicted on Wister albino rats	With the phytosome-loaded gel, both wound models showed good wound healing potential, as the epithelization period was significantly reduced from 26 to 9 days when compared to the control group. Additionally, the entrapment of crocetin into phytosomes increased its stability.	[117]
Onosma echioides (Root bark)	Naphthoquinone-enriched extract-loaded phytosomes	Incision and excision wounds inflicted on Wister albino rats	The formulation-treated animals showed improved wound healing effects for wounds concerning both wound contraction and tensile strength compared with the control group. A reduction in lipid peroxidation and an increase in catalase activity were also indicative of reduced oxidative stress in the granulation tissue.	[118]
Woodfordia fruticosa (Flower extract)	Phytosomal gels	In vitro antioxidant activity assay	The phytosomal gel outperformed crude extract in terms of solubility, antioxidant activity, and in vitro drug release.	[119]

4. Natural Products

The materials employed in wound dressing can significantly impact wound healing quality and affect the wounded tissue's occlusion [120]. Some of these materials are attained from natural resources, such as medicinal plants, and have been used extensively for skin damage treatment due to burns [121]. Moreover, since ancient times, traditional remedies have been favored for burn management because they are more effective, less expensive, have fewer side effects, and are abundantly available. A variety of herbal therapies used in the treatment of burns are presented in Table 9.

Table 9. Uses of natural herbs in burn treatment.

Herbs	Main Constituents	Dosage Forms	Administration Routes	Clinical Evidence	References
Aloe vera	Soluble sugars, polysaccharides, lignin, glycoproteins, and antiseptic agents.	Solutions, creams, mucilage, gels, and dressings.	Topical, oral	It has anti-inflammatory, anti-bacterial, and wound-contracting properties, as well as contributing to cell proliferation, collagen formation, and angiogenesis.	[122–124]
Hippophae rhamnoides	Flavonoids, tannins, vitamins (C, E, K), organic acids, glycerides of palmitic, triterpenes, stearic acid, oleic acid, and amino acids.	Aqueous leaf extract, seed oil	Topical, oral	It has antioxidant and anti-inflammatory properties, as well as the ability to promote wound contraction and epithelization and increase wound hydroxyproline and the content of protein.	[125,126]
Angelica Sinensis	Ferulic acid is the major active component, in addition to the essential oils, and water-soluble ingredients.	Ethanol extracts	In vitro tests	Stimulates the proliferation of human skin fibroblasts, collagen synthesis, and TGF-b production in vitro.	[127,128]
Catharanthus roseus (Vinca rosea)	Alkaloids, and tannins.	Leaf ethanol extract	Topical	Stimulates wound healing and wound contraction, and has antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.	[129,130]
Calendula officinalis (Marigold)	Triterpenoids, and Flavonoids.	Gels, aqueous and alcoholic extracts	Topical	Proliferates and migrates fibroblasts in vitro; stimulates collagen synthesis and angiogenesis. Moreover, it has antimicrobial activity.	[131,132]

Table 9. *Cont.*

Herbs	Main Constituents	Dosage Forms	Administration Routes	Clinical Evidence	References
Sesamum indicum	Sesamolin, Sesaminol, and antioxidants.	Solution	Intraperitoneal, intramuscular injections	Enhances wound tensile strength, wound contraction, and hydroxyproline levels in rats using various wound models.	[133,134]
Morinda citrifolia (noni)	Phenols, esters, acids, alcohols, anthraquinones, flavonoids, triterpenoids, saccharides, carotenoid esters, ketone and lactone molecules, lignans, and nucleosides.	Ethanol extract of plant leaves mixed with water	Oral	Reduces wound area and epithelialization time and improves hydroxyproline content in rat excision wounds.	[135,136]
Camellia sinensis	Polyphenols, flavonoids, tannins, caffeine, and amino acids	Ethanolic plant extract in pure Vaseline ointment	Topical	Incision wounds in Wistar rats were reduced in healing time and wound area.	[137,138]
Rosmarinus officinalis L. (rosemary)	Most bioactive constituents include terpenoids and polyphenols, e.g., carnosol, rosmarinic, and carnosic acids.	Aqueous and essential oil extracts	Topical, intraperitoneal injection	In diabetic mice with full-thickness wounds, reduces inflammation and promotes wound contraction, re-epithelialization, angiogenesis, and collagen production.	[139–141]

On the other hand, advanced DDSs have been considerably explored for traditional medications to improve transcutaneous absorption and drug deposition to the deep layers of the skin. Fruitful research works have been conducted in this field by incorporating plant extracts and natural remedies inside drug carriers. For example, bee pollen is a male reproductive organ generated by entomophilous plant blossoms, commonly known as flower pollen. Flower pollens are an essential part of the bee's nourishment; they can be used for immediate needs or saved for later consumption. In one study, the phenolic pollen extract was loaded into a proliposomal delivery system that enhanced liposomes' physical stability and the entrapment ability of poor water-soluble extracts. The proliposomes were produced by the high-pressure homogenization technique. This new technique could dramatically enhance the pollens extract's solubility, in vitro bioaccessibility, and antioxidant activity [142]. Extrusion and ultrasonication techniques are also used for the nano/micro-downsizing of vesiculosomes [143], as shown in Figure 4.

Further research on liposomes loaded with propolis, a natural bee product, has been conducted [144]. Propolis has both antimicrobial/antifungal and antioxidant characteristics, which is helpful in burn wound infection treatment. The study outcomes showed the superior effectiveness of the propolis extract-loaded liposomal preparation compared with the extracted sample.

Honey is another common natural remedy, which has long been used as a traditional medicine for a variety of medical purposes. It is well-known for its antiparasitic, anti-inflammatory, and pain-relieving properties. It is also helpful against respiratory tract

infections. In addition, honey-containing topicals have been prepared and evaluated for burn wound healing [145].

Nano-liposomes incorporated with royal jelly have been produced by the thin lipid-film hydration technique. The nano-liposomes, prepared from 10-hydroxy-2-decanoic fatty acid, significantly enhanced the royal jelly's transcutaneous absorption and antimicrobial activity [146]. Further examples of herbal-based vesicular delivery systems established for burn treatment are given in Table 10.

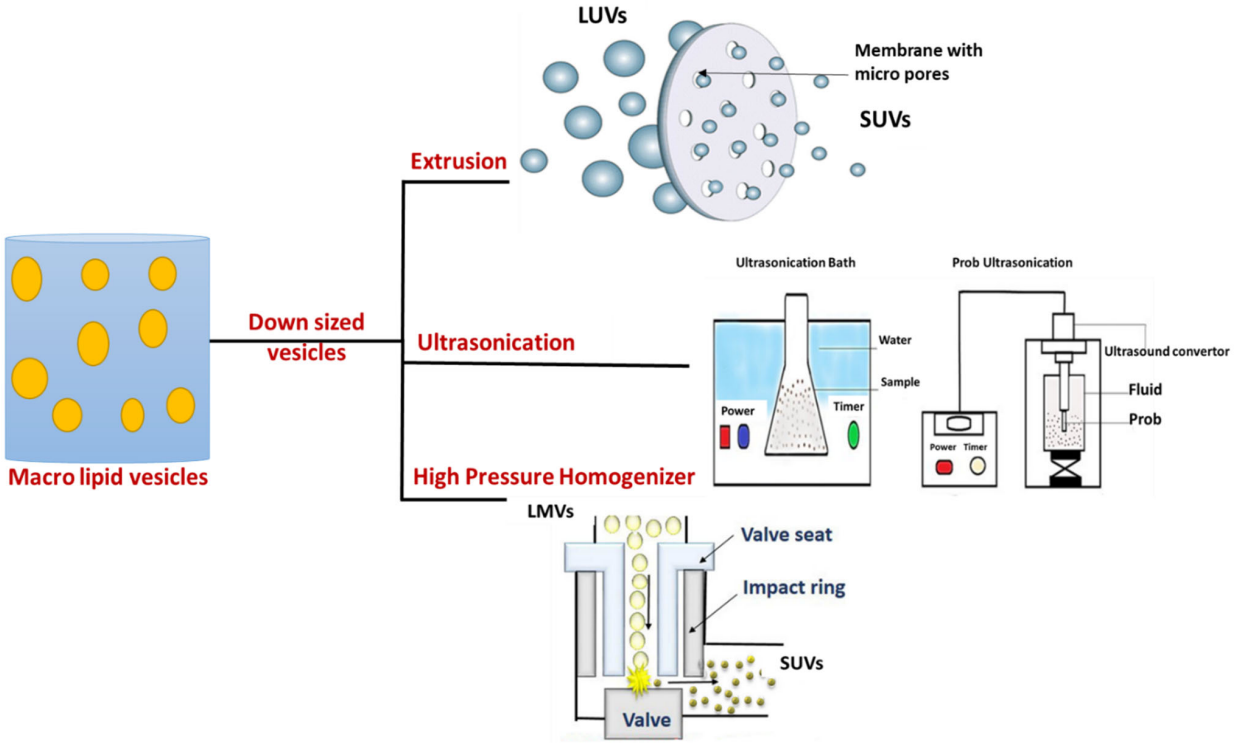

Figure 4. Techniques for the vesicle downsizing of nano/micro vesiculosomes.

Table 10. Herbal-loaded vesiculosomes for burn treatment.

Vesicular Carrier	Herb	Clinical Evidence	References
Liposomes	*Aloe vera*	Anti-inflammatory and antimicrobial activities.	[147–151]
	Hippophae rhamnoides	Anti-inflammatory/antioxidant properties.	
	Angelica Sinensis	Stimulates collagen production, and human skin fibroblast proliferation.	
	Catharanthus roseus (Vinca rosea)	Antimicrobial activity.	
	Calendula officinalis (marigold)	Antibacterial and anti-inflammatory properties.	
Noisomes	*Sesamum indicum*	Improves wound tensile strength, and wound contraction.	[152–154]
	Morinda citrifolia (Noni)	Improves the hydroxyproline content and decreases the wound.	
	Rosmarinus officinalis L. (Rosemary)	Reduces inflammation and enhances wound contraction, re-epithelialization, angiogenesis, and collagen deposition in diabetic mice with full-thickness wounds.	
Phytochromes	*Camellia sinensis*	Reduces the healing duration and wound length.	[155]

5. Current Status and Future Concepts

The application of vesicular DDSs alters the biodistribution and pharmacokinetics of drug molecules by reducing clearance, metabolism, and distribution volume. This can also be applied for the drug targeting of diseased tissues via increasing the capillary permeability. Liposomes, for example, may carry biological medications made of macromolecules, such as antisense oligonucleotides, cloned genes, recombinant proteins, etc. [156]. Classic liposomes, however, have diminutive value because they do not penetrate the skin deeply. On the other hand, specially designed and modified liposomes are capable of achieving enhanced drug delivery from different administration routes [157]. Despite this, the pharma market is not rich with these types of formulas; liposome-based products are few due to the obstacles associated with large-scale production. For instance, Liposomal Histx (Quali®-C) is a food supplement based on vitamin C and quercetin produced by Equisalud in the form of oral suspension [158]. Previous research has reported that vitamin C is an effective antioxidant candidate in burn conditions because it shows efficacy in decreasing fluid and ventilation requirements in the acute phase after the burn wound, as well as improving wound healing. Quercetin decreases apoptosis and increases autophagy, thereby improving tissue viability in the stasis area of burn wounds [159]. The main purpose behind using liposome lipid carriers is to improve these supplements' bioavailability and efficacy [160]. Another example of innovative nutrition with vitamin C is Nutricology®, Micro Liposomal C [161]. This product contains vitamin C-loaded sunflower phospholipid-based liposomes in the form of an oral liquid preparation.

On the other hand, liposome topical preparation has been produced and applied for the repair of damaged skin, such as burned skin. Decorté® Liposome Advanced Repair Serum is one of these products. The product is powered by Liposome Technology™ in the form of topical serum that offers sustained-release skin hydration and support [162]. Moreover, treatment with tretinoin significantly increases the skin's distensibility by lowering the skin's resistance and elastance; therefore, topical tretinoin has been suggested for post-burn scarred skin [163]. Furthermore, liposomes are an effective tool for retinol protection against oxidation by light due to the incorporation of sterols into the liposome components. Recently, it was reported that a dual-ointment formulation containing retinoic acid-loaded transfersomes and cationic deformable liposomes loaded with epidermal growth factor has been fabricated and examined for its skin permeation compared with a control. As a result, the deformable liposomes significantly enhanced drug penetration into the deep skin layers, and consequently, the formula was considered to be promising for the treatment of deep, partial-thickness burn wounds [164].

Finally, to obtain a complete perspective on the future application of vesicular DDSs in burn management, we used the Google Patents engine https://patents.google.com (accessed on 5 February 2022) and collected some relevant innovations that have been proposed for burn therapy, skin scarring reduction, and wound healing, as presented in Table 11.

Table 11. Examples of patent innovations for the application of vesiculosomes in burn therapies.

Patent Number	Source	Patent Title	Vesicles	Publication Date	Reference
CN102949341B	China	Tacrolimus transfersome solution and preparation method thereof	Transferosomes	9 April 2014	[165]
US7476400B2	United States	High-concentration lidocaine compositions and methods for their preparation	Liposomes	13 January 2009	[166]

Table 11. *Cont.*

Patent Number	Source	Patent Title	Vesicles	Publication Date	Reference
EP2915541B1	European Patent Office	Vesicles which include epidermal growth factors and compositions that contain the same	Liposomes	9 November 2016	[167]
US5716638A	United States	Composition for applying active substances to or through the skin	Ethosomes	10 February 1998	[168]
CA2117046C	Canada	Liposomal antibiotic formulation	Liposomes	3 October 2000	[169]
US20200276231A1	United States	Enhanced antivirulent for antibiotic-resistant bacteria	Liposomes	3 September 2020	[170]
WO2012153075A2	WIPO	Topical cosmetic composition containing an improved pro-penetrating system		15 November 2012	[171]
US9468599B2	United States	Composition and method for compounded therapy	Transferosomes	18 October 2016	[172]
JP2018009026A	Japan	Transdermal delivery	Transferosomes	18 January 2018	[173]
WO2019004563A1	WIPO	Method of preparing bioactive substance-encapsulated ethosome, ethosome composition, and cosmetic composition including ethosome composition	Ethosomes Liposomes	3 January 2019	[174]
KR100446832B1	South Korea	Liquid droplets for the manufacture of preparation for the non-invasive application or the non-invasive transport of active ingredients through barriers	Liposomes	4 September 2004	[175]

Indeed, although vesiculosomes have tremendous potential for human research, these systems have also been hampered by the lack of international standards and assessment methods regarding their biocompatibility, safety, and targeting efficiencies. They are also limited in their industrial production due to complex fabrication and assessment processes, as well as their undeniable drawbacks. Despite these technical difficulties, the trend towards utilizing these systems to their fullest potential is unavoidable and unstoppable, since vesiculosomes certainly comprise the most promising and cost-effective treatments to promote burn wound healing and skin regeneration.

6. Discussion and Expert Opinion

As discussed earlier, there are three different stages of burns: first, second, and third, which are different in terms of extent, depth of the burned skin, and symptoms. Burn injuries are also treated differently according to the extent and the area of the body affected. Consequently, burn therapy can range from skin cooling and simple topical antimicrobial therapy to skin grafting and surgical intervention. A burn of the third degree is considered the severest burn injury which can cause a wide range of health problems. Preparations

such as skin grafting and biological and synthetic substituents for treating third-degree burns are expensive and hard to come by. Additionally, third-degree burns can result in systemic infections such as bloodstream infections and pneumonia, and eventually death in many cases [176]. However, superficial burn wounds can heal quickly, without problems, and with less probability of scar formation, especially when treated with proper wound dressings and other topical preparations.

Currently, most commercially available burn treatments are conventional and topically applied. These topical preparations are available in different pharmaceutical dosage forms such as ointments, creams, gels, and dressings, and are commonly used for the therapy of mild-to-moderate burn stages.

As a matter of fact, the topical route has drawn considerable attention due to its advantages over other routes of administration. This is because topical dosage forms are non-invasive and show good patient compliance, since they are easily applied and removed by the patient. Moreover, a variety of skin diseases can be treated using topical drug administration, including psoriasis, microbial infections, and acne. Additionally, topical treatment allows the drug to be deposited directly onto the affected area, increasing the therapeutic efficiency and reducing undesirable adverse effects. However, drug penetration to deep skin layers remains the main obstacle with topical treatment. In addition, most of these therapies are ointment-based, exposing wounds to cross-contamination when they come into touch with dust, dirt, moisture, water, liquids, particles, and so on [177]. Topical solutions of sodium hypochlorite, iodine, H_2O_2, and other drugs are utilized to treat burn wound infections, though multiple dosing frequency is required.

Many techniques and formulation aspects have been suggested to improve the transcutaneous absorption of these products, for example, drug loading to lipid-based vesiculosomes is one of these attempts. Previous research has proven that loading medications into these lipid carriers could significantly improve their diffusion and absorption deeply into the skin, leading to better skin healing activity. Moreover, treating burn injuries with vesiculosome-based medications via different routes of administration, such as oral, is rare, and the most valuable products for burn treatments are those that may be used topically.

On the other hand, systemic antibiotics may be used in burn therapy and may be needed in large doses, which can lead to antibiotic resistance. Topical antibiotics or antiseptics are effective but have several side effects, even though they do not cause resistance [178]. Only a few FDA-approved medicines can effectively cure second- and third-degree burn wounds. The constant growth of antibiotic-resistant pathogen strains, frequently with multiple drug resistance, and the discovery of novel antibiotics and formulation development have demanded extensive research and the discovery of superior alternative treatments. For example, the incorporation of antibiotics (e.g., silver sulfadiazine and bacitracin) into lipid vesiculosomes has resulted in two achievements, including dramatic improvement in antimicrobial activity and a significant reduction in bacterial resistance due to increasing drug bioavailability and targeting.

Several advantages have been obtained beyond drug loading with these lipid carriers; however, a limited number of vesiculosome-based commercial products are currently produced and marketed because of the high cost of the ingredients and the complexity of manufacturing.

We believe that our review article, based on the information we have, may assist people in improving their knowledge about advanced burn treatment. In recent years, the expansion of nano/micro-medicine has brought new insight into skin regeneration and burn management. Thus, the current study provides a good review of the literature on advanced burn therapies loaded with lipid-based vesicular drug delivery systems, and their multiple advantages as well as limitations. Moreover, readers will obtain a greater understanding about the stages of burns, and how to treat each of them. The potential use of herbal and natural products loaded with vesiculosomes has also been discussed.

Therefore, we have provided a thorough review of potential improvements for topical formulations/treatments for burn management.

7. Conclusions

Burn injuries can negatively impact people's quality of life, as they are detrimental to their physical and mental health. There are also several challenges related to burn treatment, especially for burn wounds and scarring from second- and third-degree burns, which require extensive treatment from a surgical standpoint and reconstruction using tissue and cell cultures.

Moreover, current treatments for simple burn wounds have also failed to deliver favorable results. In recent years, nanomedicine has developed, resulting in new approaches to skin regeneration and burn healing, such as lipid-based nanovesicles, which are favored over traditional dosage forms due to their ability to control drug release, increase the solubility of poorly soluble drugs, improve drug stability, provide better efficacy and minimal side effects, and increase patient compliance.

On the other hand, the formulation design of such systems requires a detailed understanding of the physical and chemical properties of the active ingredients, excipients, and production techniques, as well as drug bioavailability. Furthermore, these systems have a greater ability to load both hydrophilic as well as hydrophobic drugs, and provide multiple methods of administration. Consequently, it is inevitable that researchers will continue exploring the potential of these lipid vesicular carriers, overcome the technical challenges, and develop effective burn treatment systems using these systems.

Our review refers to these lipid vesicles (liposomes, niosomes, ethosomes, transfersomes cubosomes, and phytosomes) as vesiculosomes. These vesiculosomes could enhance drug concentration in the deep layers of the skin and consequently enhance the effectiveness of wound-healing therapies in the treated burn areas. Most of the vesiculosome-loaded drugs presented in this article demonstrated an enhancement in wound-healing rate. In addition, different designs of assessment models for burn/wound therapy were tabulated in this article. However, in many of the reviewed articles, only in vitro studies were used to assess drug efficacy. Therefore, efforts should be made to continue studying vesiculosomes clinically to improve skin permeability and increase drug bioavailability to be able to offer patients more effective forms of burn management.

Author Contributions: Resources, writing—original draft preparation, preparation of figures and video abstract, N.A.M., N.A., F.A., A.S.B.S.; conceptualization, supervision, writing—review and editing, B.K.A.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The APC was funded by the authors.

Institutional Review Board Statement: This work was approved by the Research Unit of Dubai Pharmacy College of Girls (Reference No. REC/UG/2021/01, dated 14 October 2021).

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors acknowledge the assistance of Noor Al Mahri, General Civil Aviation Authority of the United Arab Emirates in the technical aspects of the article.

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

References

1. Jeschke, M.G.; van Baar, M.E.; Choudhry, M.A.; Chung, K.K.; Gibran, N.S.; Logsetty, S. Burn injury. *Nat. Rev. Dis. Prim.* **2020**, *6*, 1–25. [CrossRef] [PubMed]
2. Hao, D.; Qu, M.; Nourbakhsh, M. Experimental study of burn damage progression in a human composite tissue model. *Biology* **2021**, *10*, 40. [CrossRef]
3. Neha Pathak, M. Treating Pain Caused by Burn: 1st, 2nd, and 3rd Degree. WebMed. Published. 2020. Available online: https://www.webmd.com/pain-management/guide/pain-caused-by-burn (accessed on 1 June 2022).
4. Halim, A.S.; Khoo, T.L.; Mohd Yussof, S.J. Biologic and synthetic skin substitutes: An overview. *Indian J. Plast. Surg.* **2010**, *43*, S23–S28. [CrossRef] [PubMed]
5. Ogundipe, K.O.; Adigun, I.A.; Solagberu, B.A. Economic burden of drug use in patients with acute burns: Experience in a developing country. *J. Trop. Med.* **2009**, *2009*, 734712. [CrossRef] [PubMed]

6. Leppert, W.; Malec-Milewska, M.; Zajaczkowska, R.; Wordliczek, J. Transdermal and topical drug administration in the treatment f pain. *Molecules* **2018**, *17*, 681. [CrossRef]
7. Norman, G.; Christie, J.; Liu, Z.; Westby, M.J.; Jefferies, J.M.; Hudson, T.; Edwards, J.; Mohapatra, D.P.; Hassan, I.A.; Dumville, J.C. Antiseptics for burns. *Cochrane Database Syst. Rev.* **2017**, *12*, CD011821. [CrossRef]
8. Cancio, L.C. Topical antimicrobial agents for burn wound care: History and current status. *Surg. Infect.* **2021**, *22*, 3–11. [CrossRef]
9. Abdul Rasool, B.K.; Hussain, F.N.; Bahrainwala, I.M.; Akbar, N.; Umar, S.; Kalady, S.P.; Shamsheer, Z. Advances in vaccine delivery strategies to promote effective immunization. *J. Appl. Pharm. Sci.* **2022**, *12*, 001–026. [CrossRef]
10. Agarwal, S.; Muniyandi, P.; Maekawa, T.; Kumar, D.S. Vesicular systems employing natural substances as promising drug candidates for MMP inhibition in glioblastoma: A nanotechnological approach. *Int. J. Pharm.* **2018**, *551*, 339–361. [CrossRef]
11. Rommasi, F.; Esfandiari, N. Liposomal Nanomedicine: Applications for drug delivery in cancer therapy. *Nanoscale Res. Lett.* **2021**, *16*, 95. [CrossRef]
12. Lamichhane, N.; Udayakumar, T.S.; D'Souza, W.D.; Simone, C.B., 2nd; Raghavan, S.R.; Polf, J.; Mahmood, J. Liposomes: Clinical Applications and Potential for Image-Guided Drug Delivery. *Molecules* **2018**, *23*, 288. [CrossRef] [PubMed]
13. He, H.; Lu, Y.; Qi, J.; Zhu, Q.; Chen, Z.; Wu, W. Adapting liposomes for oral drug delivery. *Acta Pharm. Sin. B* **2019**, *9*, 36–48. [CrossRef] [PubMed]
14. Dubald, M.; Bourgeois, S.; Andrieu, V.; Fessi, H. Ophthalmic drug delivery systems for antibiotherapy—A review. *Pharmaceutics* **2018**, *13*, 10. [CrossRef] [PubMed]
15. Hong, S.S.; Oh, K.T.; Choi, H.G.; Lim, S.J. Liposomal formulations for nose-to-brain delivery: Recent advances and future perspectives. *Pharmaceutics* **2019**, *17*, 540. [CrossRef]
16. Dai, T.; Huang, Y.Y.; Sharma, S.K.; Hashmi, J.T.; Kurup, D.B.; Hamblin, M.R. Topical antimicrobials for burn wound infections. *Recent Pat. Antiinfect. Drug Discov.* **2010**, *5*, 124–151. [CrossRef]
17. Matei, A.-M.; Caruntu, C.; Tampa, M.; Georgescu, S.R.; Matei, C.; Constantin, M.M.; Constantin, T.V.; Calina, D.; Ciubotaru, D.A.; Badarau, I.A.; et al. Applications of nanosized-lipid-based drug delivery systems in wound care. *Appl. Sci.* **2021**, *11*, 4915. [CrossRef]
18. Ghasemiyeh, P.; Mohammadi-Samani, S. Potential of nanoparticles as permeation enhancers and targeted delivery options for skin: Advantages and disadvantages. *Drug Des. Devel. Ther.* **2020**, *14*, 3271–3289. [CrossRef]
19. Lin, D.M.; Koskella, B.; Lin, H.C. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World J. Gastrointest. Pharm. Ther.* **2017**, *8*, 162–173. [CrossRef]
20. Duplessis, C.A.; Biswas, B. A review of topical phage therapy for chronically infected wounds and preparations for a randomized adaptive clinical trial evaluating topical phage therapy in chronically infected diabetic foot ulcers. *Antibiotics* **2020**, *9*, 377. [CrossRef]
21. Chhibber, S.; Kaur, J.; Kaur, S. Liposome entrapment of bacteriophages improves wound healing in a diabetic mouse MRSA infection. *Front. Microbiol.* **2018**, *9*, 561. [CrossRef]
22. Chadha, P.; Katare, O.P.; Chhibber, S. Liposome loaded phage cocktail: Enhanced therapeutic potential in resolving Klebsiella Pneumoniae mediated burn wound infections. *Burn* **2017**, *43*, 1532–1543. [CrossRef] [PubMed]
23. Li, Z.; Liu, M.; Wang, H.; Du, S. Increased cutaneous wound healing effect of biodegradable liposomes containing madecassoside: Preparation optimization, in vitro dermal permeation, and in vivo bioevaluation. *Int. J. Nanomed.* **2016**, *11*, 2995–3007. [CrossRef] [PubMed]
24. Parchen, G.P.; Jacumazo, J.; Koop, H.S.; Biscaia, S.M.P.; Trindade, E.S.; Silveira, J.L.M.; de Freitas, R.A. Modulation of epidermal growth factor release by biopolymer-coated liposomes. *J. Pharm. Sci.* **2020**, *109*, 2294–2301. [CrossRef]
25. Choi, J.U.; Lee, S.W.; Pangeni, R.; Byun, Y.; Yoon, I.S.; Park, J.W. Preparation and in vivo evaluation of cationic elastic liposomes comprising highly skin-permeable growth factors combined with hyaluronic acid for enhanced diabetic wound-healing therapy. *Acta Biomater.* **2017**, *57*, 197–215. [CrossRef] [PubMed]
26. Hurler, J.; Berg, O.A.; Skar, M.; Conradi, A.H.; Johnsen, P.J.; Skalko-Basnet, N. Improved burn therapy: Liposomes-in-hydrogel delivery system for mupirocin. *J. Pharm. Sci.* **2012**, *101*, 3906–3915. [CrossRef]
27. Wadhwa, S.; Singh, B.; Sharma, G.; Raza, K.; Katare, O.P. Liposomal fusidic acid as a potential delivery system: A new paradigm in the treatment of chronic plaque psoriasis. *Drug Deliv.* **2016**, *23*, 1204–1213. [CrossRef]
28. Nicolosi, D.; Cupri, S.; Genovese, C.; Tempera, G.; Mattina, R.; Pignatello, R. Nanotechnology approaches for antibacterial drug delivery: Preparation and microbiological evaluation of fusogenic liposomes carrying fusidic acid. *Int. J. Antimicrob. Agents* **2015**, *45*, 622–626. [CrossRef]
29. Lichtenstein, A.; Margalit, R. Liposome-encapsulated silver sulfadiazine (SSD) for the topical treatment of infected burn: Thermodynamics of drug encapsulation and kinetics of drug release. *J. Inorg. Biochem.* **1995**, *60*, 187–198. [CrossRef]
30. Patel, D.; Patel, N. Fabrication and characterization of sterically stabilized liposomes of topotecan. *Futur J. Pharm. Sci.* **2020**, *6*, 1–18. [CrossRef]
31. Guan, J.; Shen, Q.; Zhang, Z.; Jiang, Z.Y.M.; Qian, J.; Lu, W.; Zhan, C. Enhanced immunocompatibility of ligand-targeted liposomes by attenuating natural IgM absorption. *Nat. Commun.* **2018**, *9*, 1–11. [CrossRef]
32. Homann, H.H.; Rosbach, O.; Moll, W.; Vogt, P.M.; Germann, G.; Hopp, M.; Langer-Brauburger, B.; Reimer, K.; Steinau, H.U. A liposome hydrogel with polyvinylpyrrolidone iodine in the local treatment of partial-thickness burn wounds. *Ann. Plast. Surg.* **2007**, *59*, 423–427. [CrossRef] [PubMed]

33. Peng, S.; Zou, L.; Liu, W.; Li, Z.; Liu, W.; Hu, X.; Chen, X.; Liu, C. Hybrid liposomes composed of amphiphilic chitosan and phospholipid: Preparation, stability and bioavailability as a carrier for curcumin. *Carbohydr. Polym.* **2017**, *156*, 322–332. [CrossRef] [PubMed]
34. Liu, W.; Liu, J.; Liu, W.; Li, T.; Liu, C. Improved physical and in vitro digestion stability of a polyelectrolyte delivery system based on layer-by-layer self-assembly alginate-chitosan-coated nanoliposomes. *J. Agric. Food Chem.* **2013**, *61*, 4133–4144. [CrossRef] [PubMed]
35. Kozhikhova, K.V.; Ivantsova, M.N.; Tokareva, M.I.; Shulepov, I.D.; Tretiyakov, A.V.; Shaidarov, L.V.; Rusinov, V.L.; Mironov, M.A. Preparation of chitosan-coated liposomes as a novel carrier system for the antiviral drug Triazavirin. *Pharm. Dev. Technol.* **2018**, *23*, 334–342. [CrossRef]
36. Abdul Rasool, B.K.; Shehab, N.G.; Khan, S.A.; Bayoumi, F.A. A new natural gel of Fagonia indica Burm f. extract for the treatment of burn on rats. *Pak. J. Pharm. Sci.* **2014**, *27*, 73–81.
37. Zadeh, B.S.M.; Zamin, B.K. The effect of chitosan coating on mafenide acetate-loaded liposome characterization and delivery through burned rat skin. *Asian J. Pharm. Clin. Res.* **2019**, *12*, 212–217. [CrossRef]
38. Hao, J.; Guo, B.; Yu, S.; Zhang, W.; Zhang, D.; Wang, J.; Wang, Y. Encapsulation of the flavonoid quercetin with chitosan-coated nano-liposomes. *Food Sci. Technol.* **2017**, *85*, 37–44. [CrossRef]
39. Price, C.I.; Horton, J.W.; Baxter, C.R. Topical liposomal delivery of antibiotics in soft tissue infection. *J. Surg. Res.* **1990**, *49*, 174–178. [CrossRef]
40. Nunes, P.S.; Rabelo, A.S.; Souza, J.C.; Santana, B.V.; da Silva, T.M.; Serafini, M.R.; Dos Passos Menezes, P.; Dos Santos Lima, B.; Cardoso, J.C.; Alves, J.C.; et al. Gelatin-based membrane containing usnic acid-loaded liposome improves dermal burn healing in a porcine model. *Int. J. Pharm.* **2016**, *513*, 473–482. [CrossRef]
41. Laurent, A.; Pantet, O.; Laurent, L.; Laurent, L.; Hirt-Burri, N.; Roessingh, A.B.; Raffoul, W.; Laurent, P.; Monod, M.; Applegate, L.A. Potency and stability of liposomal Amphotericin B formulated for topical management of Aspergillus spp. infections in burn patients. *Burn Open* **2020**, *4*, 110–116. [CrossRef]
42. Değim, Z.; Çelebi, N.; Alemdaroğlu, C.; Deveci, M.; Öztürk, S.; Özoğul, C. Evaluation of chitosan gel containing liposome-loaded epidermal growth factor on burn wound healing. *Int. Wound J.* **2011**, *8*, 343–354. [CrossRef] [PubMed]
43. Boyd, A.N.; Blair, M.E.; Degenkolb, K.E.; Foster, D.R.; Hartman, B.C.; Sood, R.; Walroth, T.A. A prospective analysis describing the innovative use of liposomal bupivacaine in burn patients. *Burn* **2020**, *46*, 370–376. [CrossRef] [PubMed]
44. Karami, Z.; Hamidi, M. Cubosomes: Remarkable drug delivery potential. *Drug. Discov. Today* **2016**, *21*, 789–801. [CrossRef]
45. Rarokar, N.R.; Khedekar, P.B. Cubosomes: A vehicle for delivery of various therapeutic agents. *MOJ Toxicol.* **2018**, *4*, 19–21. [CrossRef]
46. Garg, G.; Saraf, S.; Saraf, S. Cubosomes: An overview. *Biol Pharm. Bull.* **2007**, *30*, 350–353. [CrossRef] [PubMed]
47. Yang, Z.; Tan, Y.; Chen, M.; Dian, L.; Shan, Z.; Peng, X.; Wu, C. Development of amphotericin B-loaded cubosomes through the SolEmuls technology for enhancing the oral bioavailability. *AAPS PharmSciTech* **2012**, *13*, 1483–1491. [CrossRef]
48. Yang, Z.; Peng, X.; Tan, Y.; Chen, M.; Zhu, X.; Feng, M.; Xu, Y.; Wu, C. optimization of the preparation process for an oral phytantriol-based Amphotericin B cubosomes. *J. Nanomater.* **2011**, *2011*, 308016. [CrossRef]
49. Nasr, M.; Younes, H.; Abdel-Rashid, R.S. Formulation and evaluation of cubosomes containing colchicine for transdermal delivery. *Drug Deliv. Transl. Res.* **2020**, *10*, 1302–1313. [CrossRef]
50. Han, S.; Shen Jq Gan, Y.; Geng, H.; Zhang, X.; Zhu, C.; Gan, L. Novel vehicle based on cubosomes for ophthalmic delivery of flurbiprofen with low irritancy and high bioavailability. *Acta Pharm. Sin.* **2010**, *31*, 990–998. [CrossRef]
51. Cytryniak, A.; Nazaruk, E.; Bilewicz, R.; Górzyńska, E.; Żelechowska-Matysiak, K.; Walczak, R.; Mames, A.; Bilewicz, A.; Majkowska-Pilip, A. Lipidic cubic-phase nanoparticles (cubosomes) loaded with doxorubicin and labeled with 177Lu as a potential tool for combined chemo and internal radiotherapy for cancers. *Nanomaterials* **2020**, *10*, 2272. [CrossRef]
52. Beena, P.; Varghese, S.A.; Alexander, J.A.; Raju, S.P.; Koshy, S.; Mathew, F.E.; Abraham, E. Formulation and evaluation of cubosomal gel of an anti-inflammatory agent. *Res. J. Pharm. Tech.* **2021**, *14*, 857–862. [CrossRef]
53. Morsi, N.M.; Abdelbary, G.A.; Ahmed, M.A. Silver sulfadiazine-based cubosome hydrogels for topical treatment of burn: Development and in vitro/in vivo characterization. *Eur. J. Pharm. Biopharm.* **2014**, *86*, 178–189. [CrossRef] [PubMed]
54. Mahlapuu, M.; Björn, C.; Ekblom, J. Antimicrobial peptides as therapeutic agents: Opportunities and challenges. *Crit. Rev. Biotechnol.* **2020**, *40*, 978–992. [CrossRef] [PubMed]
55. Boge, L.; Browning, K.L.; Nordström, R.; Campana, M.; Damgaard, L.S.E.; Seth Caous, J.; Hellsing, M.; Ringstad, L.; Andersson, M. Peptide-loaded cubosomes functioning as an antimicrobial unit against Escherichia coli. *ACS Appl. Mater. Interfaces* **2019**, *11*, 21314–21322. [CrossRef] [PubMed]
56. Boge, L.; Umerska, A.; Matougui, N.; Bysell, H.; Ringstad, L.; Davoudi, M.; Eriksson, J.; Edwards, K.; Andersson, M. Cubosomes post-loaded with antimicrobial peptides: Characterization, bactericidal effect and proteolytic stability. *Int. J. Pharm.* **2017**, *526*, 400–412. [CrossRef]
57. Boge, L.; Hallstensson, K.; Ringstad, L.; Johansson, J.; Andersson, T.; Davoudi, M.; Larsson, P.T.; Mahlapuu, M.; Håkansson, J.; Andersson, M. Cubosomes for topical delivery of the antimicrobial peptide LL-37. *Eur. J. Pharm. Biopharm.* **2019**, *134*, 60–67. [CrossRef]
58. Rahman, H.S.; Othman, H.H.; Hammadi, N.I.; Yeap, S.K.; Amin, K.M.; Abdul Samad, N.; Alitheen, N.B. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. *Int. J. Nanomed.* **2020**, *15*, 2439–2483. [CrossRef]

59. Khalifa, A.M.; Abdul Rasool, B.K. Optimized mucoadhesive coated niosomes as a sustained oral delivery system of famotidine. *AAPS PharmSciTech* **2017**, *18*, 3064–3075. [CrossRef]
60. Aparajay, P.; Dev, A. Functionalized niosomes as a smart delivery device in cancer and fungal infection. *Eur. J. Pharm. Sci.* **2022**, *168*, 106052. [CrossRef]
61. Abdul Rasool, B.K.; Azeez, O.S.; Lootah, H.A.; Abusharbain, I.M.; Abu-Alhaj, H.A.; Nessa, F. Extended-release niosomal hydrogel for ocular targeting of piroxicam: In vitro and ex vivo evaluation. *Br. J. Pharm. Res.* **2014**, *4*, 2494–2510. [CrossRef]
62. Durga, B.G.; Veera, L.P. Recent advances of nonionic surfactant-based nano-vesicles (niosomes and proniosomes): A brief review of these in enhancing transdermal delivery of drug. *Future J. Pharm. Sci.* **2020**, *6*, 100. [CrossRef]
63. Muzzalupo, R.; Tavano, L. Niosomal drug delivery for transdermal targeting: Recent advances. *Res. Rep. Transdermal. Drug Deliv.* **2015**, *4*, 23–33. [CrossRef]
64. Drugbank Online. Silver Sulfadiazine. Available online: https://go.drugbank.com/drugs/DB05245 (accessed on 18 October 2021).
65. Dharashivkar, S.S.; Sahasrabuddhe, S.H.; Saoji, A.N. Niosomally encapsulated silver sulfadiazine gel for burn treatment. *J. Microencapsul.* **2015**, *32*, 137–142. [CrossRef] [PubMed]
66. Sohrabi, S.; Haeri, A.; Mahboubi, A.; Mortazavi, A.; Dadashzadeh, S. Chitosan gel-embedded moxifloxacin niosomes: An efficient antimicrobial hybrid system for burn infection. *Int. J. Biol. Macromol.* **2016**, *85*, 625–633. [CrossRef]
67. Yilmaz Atay, H. Antibacterial Activity of Chitosan-Based Systems. *Funct. Chitosan* **2020**, *6*, 457–489. [CrossRef]
68. Farmoudeh, A.; Akbari, J.; Saeedi, M.; Ghasemi, M.; Asemi, N.; Nokhodchi, A. Methylene blue-loaded niosome: Preparation, physicochemical characterization, and in vivo wound healing assessment. *Drug Deliv. Transl. Res.* **2020**, *10*, 1428–1441. [CrossRef]
69. Yucel, B.; Coruh, A.; Deniz, K. Salvaging the zone of stasis in burn by pentoxifylline: An experimental study in rats. *J. Burn Care Res.* **2019**, *40*, 211–219. [CrossRef]
70. Aghajani, A.; Kazemi, T.; Enayatifard, R.; Amiri, F.T.; Narenji, M. Investigating the skin penetration and wound healing properties of niosomal pentoxifylline cream. *Eur. J. Pharm. Sci.* **2020**, *151*, 105434. [CrossRef]
71. Muzzalupo, R.; Tavano, L.; Lai, F.; Picci, N. Niosomes containing hydroxyl additives as percutaneous penetration enhancers: Effect on the transdermal delivery of sulfadiazine sodium salt. *Colloids Surf. B Biointerfaces* **2014**, *123*, 207–212. [CrossRef]
72. Nur Un, R.; Barlas, B.F.; Yavuz, M.; Seleci, D.A.; Seleci, M.; Gumus, Z.P.; Guler, E.; Demir, B.; Can, M.; Coskunol, H.; et al. Phyto-niosomes: In vitro assessment of the novel nanovesicles containing marigold extract. *Int. J. Polym. Mater. Polym. Biomater.* **2015**, *64*, 927–937. [CrossRef]
73. Dharashivkar, S.; Sahasrabuddhe, S.; Saoji, A.N. Silver sulfadiazine niosomes: A novel sustained-release once-a-day formulation for burn treatment. *Int. J. Pharm. Pharm. Sci.* **2014**, *6*, 611–616.
74. Bolatchiev, A.; Baturin, V.; Bazikov, I.; Maltsev, A.; Kunitsina, E. Effect of antimicrobial peptides HNP-1 and hBD-1 on Staphylococcus aureus strains in vitro and in vivo. *Fundam Clin. Pharmacol.* **2020**, *34*, 102–108. [CrossRef]
75. Heidari, F.; Akbarzadeh, I.; Nourouzian, D.; Mirzaie, A.; Bakhshandeh, H. Optimization and characterization of tannic acid-loaded niosomes for enhanced antibacterial and anti-biofilm activities. *Adv. Powder Technol.* **2020**, *31*, 4768–4781. [CrossRef]
76. Ali, A.; Sarhan, H.A.; Magdy, T. Preparation and characterization of phenytoin sodium niosomes for enhanced closure of skin injuries. *Int. J. Pharm. Pharm. Sci.* **2014**, *6*, 5426.
77. Ali, M.; Abdel Motaal, A.; Ahmed, M.A.; Alsayari, A.; El-Gazayerly, O.N. An in vivo study of Hypericum perforatum in a niosomal topical drug delivery system. *Drug Deliv.* **2018**, *25*, 417–425. [CrossRef]
78. Hallan, S.S.; Sguizzato, M.; Mariani, P.; Cortesi, R.; Huang, N.; Simelière, F.; Marchetti, N.; Drechsler, M.; Ruzgas, T.; Esposito, E. Design and characterization of ethosomes for transdermal delivery of caffeic acid. *Pharmaceutics* **2020**, *12*, 740. [CrossRef]
79. Ascenso, A.; Raposo, S.; Batista, C.; Cardoso, P.; Mendes, T.; Praça, F.G.; Bentley, M.V.; Simões, S. Development, characterization, and skin delivery studies of related ultradeformable vesicles: Transfersomes, ethosomes, and transethosomes. *Int. J. Nanomed.* **2015**, *10*, 5837–5851. [CrossRef]
80. Razavi, S.; Partoazar, A.; Takzaree, N.; Fasihi-Ramandi, M.; Bahador, A.; Darvishi, M.H. Silver sulfadiazine nanoethogel for burn healing: Characterization and investigation of its in vivo effects. *Nanomedicine* **2018**, *13*, 1319–1331. [CrossRef]
81. Kumar, L.; Verma, S.; Singh, M.; Chalotra, T.; Utreja, P. Advanced drug delivery systems for transdermal delivery of nonsteroidal anti-inflammatory drugs: A review. *Curr. Drug Deliv.* **2018**, *15*, 1087–1099. [CrossRef]
82. Paliwal, S.; Tilak, A.; Sharma, J.; Dave, V.; Sharma, S.; Yadav, R.; Patel, S.; Verma, K.; Tak, K. Flurbiprofen loaded ethosomes—Transdermal delivery of anti-inflammatory effect in rat model. *Lipids Heal. Dis.* **2019**, *18*, 1–15. [CrossRef]
83. Anjum, F.; Zakir, F.; Verma, D.; Aqil, M.; Singh, M.; Jain, P.; Mirza, M.A.; Anwer, M.K.; Iqbal, Z. Exploration of nanoethosomal transgel of naproxen sodium for the treatment of arthritis. *Curr. Drug Deliv.* **2020**, *17*, 885–897. [CrossRef]
84. Ghanbarzadeh, S.; Arami, S. Enhanced transdermal delivery of diclofenac sodium via conventional liposomes, ethosomes, and transfersomes. *BioMed Res. Int.* **2013**, *2013*, 616810. [CrossRef]
85. Chourasia, M.K.; Kang, L.; Chan, S.Y. Nanosized ethosomes bearing ketoprofen for improved transdermal delivery. *Results Pharma Sci.* **2011**, *1*, 60–67. [CrossRef]
86. Barupal, A.K.; Gupta, V.; Ramteke, S. Preparation and characterization of ethosomes for topical delivery of aceclofenac. *Indian J. Pharm. Sci.* **2010**, *72*, 582–586. [CrossRef]
87. Qadir, A.; Ahmad, U.; Ali, A.; Shahid, A.; Aqil, M.; Khan, N.; Ali, A.; Almalki, W.H.; Alghamdi, S.; Abul Barkat, M.; et al. *Lipid Engineered Nanoparticle Therapy for Burn Wound Treatment*; Bentham Science Publishers: Sharjah, United Arab Emirates, 2021. [CrossRef]

88. Fu, X.; Shi, Y.; Wang, H.; Zhao, X.; Sun, Q.; Huang, Y.; Qi, T.; Lin, G. Ethosomal gel for improving transdermal delivery of Thymosin β-4. *Int. J. Nanomed.* **2019**, *14*, 9275–9284. [CrossRef]
89. Sarwa, K.K.; Suresh, P.K.; Rudrapal, M.; Verma, V.K. Penetration of tamoxifen citrate loaded ethosomes and liposomes across human skin: A comparative study with confocal laser scanning microscopy. *Curr. Drug Deliv.* **2014**, *11*, 332–337. [CrossRef]
90. Kehinde, E.O.; Akrutiben, S.; Patel, J. Revolutionary approach towards transdermal drug delivery: Ethosomal gels. *J. Pharm. Res. Int.* **2021**, *33*, 35–43. [CrossRef]
91. Rai, S.; Pandey, V.; Rai, G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: The state of the art. *Nano Rev. Exp.* **2017**, *8*, 1325708. [CrossRef]
92. Opatha, S.A.T.; Titapiwatanakun, V.; Chutoprapat, R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. *Pharmaceutics* **2020**, *12*, 855. [CrossRef]
93. Shamshiri, M.K.; Momtazi-Borojeni, A.A.; Shahraky, M.K.; Rahimi, F. Lecithin soybean phospholipid nano-transfersomes as potential carriers for transdermal delivery of the human growth hormone. *J. Cell. Biochem.* **2019**, *120*, 9023–9033. [CrossRef]
94. Al Shuwaili, A.H.; Rasool, B.K.; Abdulrasool, A.A. Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline. *Eur. J. Pharm. Biopharm.* **2016**, *102*, 101–114. [CrossRef]
95. Omar, M.M.; Hasan, O.A.; Sisi, A.M.E.l. Preparation and optimization of lidocaine transferosomal gel containing permeation enhancers: A promising approach for enhancement of skin permeation. *Int. J. Nanomed.* **2019**, *14*, 1551. [CrossRef]
96. Chaudhari, Y.; Dharashivkar, S.S.; Palkar, P.; Chaudhari, M.A.; Ruhatiya, G.; Patil, M.; Gaikwad, M. Formulation and evaluation of transfersomal cream of acriflavine. *Int. Res. J. Pharm.* **2016**, *7*, 75–78. [CrossRef]
97. Caddeo, C.; Manca, M.L.; Peris, J.E.; Usach, I.; Sales, O.D.; Matos, M.; Busquets, X.F.; Fadda, A.M.; Manconi, M. Tocopherol-loaded transfersomes: In vitro antioxidant activity and efficacy in skin regeneration. *Int. J. Pharm.* **2018**, *551*, 34–41. [CrossRef]
98. Di Lonardo, A.; De Rosa, M.; Graziano, A.; Pascone, C.; Lucattelli, E. Effectiveness of topical α-Tocopherol Acetate in burn infection treatment. *Ann. Burn Fire Disasters* **2019**, *32*, 282.
99. Leonyza, A.; Surini, S. Optimization of sodium deoxycholate-based transfersomes for percutaneous delivery of peptides and proteins. *Int. J. Appl. Pharm.* **2019**, *11*, 329–332. [CrossRef]
100. Allaw, M.; Pleguezuelos-Villa, M.; Manca, M.L.; Caddeo, C.; Aroffu, M.; Nacher, A.; Diez-Sales, O.; Saurí, A.R.; Ferrer, E.E.; Fadda, A.M.; et al. Innovative strategies to treat skin wounds with mangiferin: Fabrication of transfersomes modified with glycols and mucin. *Nanomedicine* **2020**, *15*, 1671–1685. [CrossRef]
101. Lu, M.; Qiu, Q.; Luo, X.; Liu, X.; Sun, J.; Wang, C.; Lin, X.; Deng, Y.; Song, Y. Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. *Asian J. Pharm. Sci.* **2019**, *14*, 265–274. [CrossRef]
102. Alharbi, W.S.; Almughem, F.A.; Almehmady, A.M.; Jarallah, S.J.; Alsharif, W.K.; Alzahrani, N.M.; Alshehri, A.A. Phytosomes as an emerging nanotechnology platform for the topical delivery of bioactive phytochemicals. *Pharmaceutics* **2021**, *13*, 1475. [CrossRef]
103. Kumar, A.B.; Habbu, P.; Thimmasetty, L.; Hullatti, P.; Kumar, S.R. Phytosomes as novel drug delivery system for herbal medicine—A review. *Syst. Rev. Pharm.* **2016**, *8*, 5–7. [CrossRef]
104. Barani, M.; Sangiovanni, E.; Angarano, M.; Rajizadeh, M.A.; Mehrabani, M.; Piazza, S.; Gangadharappa, H.V.; Pardakhty, A.; Mehrbani, M.; Dell'Agli, M.; et al. Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. *Int. J. Nanomed.* **2021**, *16*, 6983–7022. [CrossRef] [PubMed]
105. Rafiee, M.H.; Abdul Rasool, B.K. An overview of microparticulate drug delivery system and its extensive therapeutic applications in diabetes. *Adv. Pharm. Bull.* **2022**. [CrossRef]
106. Sravanthi, M.; Krishna, J.S. Phytosomes: A novel drug delivery for herbal extracts. *Int. J. Pharm. Sci. Res.* **2017**, *4*, 949–959. [CrossRef]
107. Singh, D.; Upadhyay, P.; Upadhyay, S. Phytosomes: An advanced drug delivery system for herbal drug. *Glob. J. Pharmaceu. Sci.* **2018**, *6*, 1. [CrossRef]
108. Safta, D.A.; Bogdan, C.; Moldovan, M.L. Vesicular nanocarriers for phytocompounds in wound care: Preparation and characterization. *Pharmaceutics* **2022**, *14*, 991. [CrossRef]
109. Shahzad, M.N.; Ahmed, N. Effectiveness of Aloe Vera gel compared with 1% silver sulphadiazine cream as burns wound dressing in second-degree burns. *J. Pak. Med. Assoc.* **2013**, *63*, 225–230.
110. Jain, P.; Taleuzzaman, M.; Kala, C.; Kumar Gupta, D.; Ali, A.; Aslam, M. Quality by design (Qbd) assisted development of phytosomal gel of aloe vera extract for topical delivery. *J. Liposome Res.* **2021**, *31*, 381–388. [CrossRef]
111. Darvishi, B.; Dinarvand, R.; Mohammadpour, H.; Kamarul, T.; Sharifi, A.M. Dual l-Carnosine/Aloe vera Nanophytosomes with Synergistically Enhanced Protective Effects against Methylglyoxal-Induced Angiogenesis Impairment. *Mol. Pharm.* **2021**, *18*, 3302–3325. [CrossRef]
112. Mazumder, A.; Dwivedi, A.; Fox, L.T.; Brümmer, A.; du Preez, J.L.; Gerber, M.; du Plessis, J. In vitro skin permeation of sinigrin from its phytosome complex. *J. Pharm. Pharmacol.* **2016**, *68*, 1577–1583. [CrossRef]
113. Agrawal, S.; Yallatikar, T.; Gurjar, P. Reversed-phase high-performance liquid chromatographic method development and validation for allyl isothiocyanate estimation in phytosomes of Brassica nigra extract. *J. Adv. Pharm. Technol. Res.* **2019**, *10*, 126. [CrossRef]
114. Allawi, H.M.; Al-bayati, M. Formulation of Camellia sinensis phytosome encapsulated diclofenac and effect on analgesia and inflammation in mice. *Cancer Nanotechnol.* **2020**, *24*, 175–190.

115. Demir, B.; Barlas, F.B.; Guler, E.; Gumus, P.Z.; Can, M.; Yavuz, M.; Coskunol, H.; Timur, S. Gold nanoparticle loaded phytosomal systems: Synthesis, characterization and in vitro investigations. *RSC Adv.* **2014**, *4*, 34687–34695. [CrossRef]
116. Lim, A.W.; Ng, P.Y.; Chieng, N.; Ng, S.F. Moringa oleifera leaf extract–loaded phytophospholipid complex for potential application as wound dressing. *J. Drug. Deliv. Sci. Technol.* **2019**, *54*, 101329. [CrossRef]
117. Varadkar, M.; Gadgoli, C. Preparation and evaluation of wound healing activity of phytosomes of crocetin from Nyctanthes arbor-tristis in rats. *J. Tradit. Complement. Med.* **2021**, *12*, 354–360. [CrossRef]
118. Pananchery, J.; Gadgoli, C. Phytosomes of naphthoquinone enriched extract of root bark of Onosma echioides exhibit wound healing activity in rats. *Indones. J. Pharm.* **2021**, *32*, 474–483. [CrossRef]
119. Rajashekar, K.; Sundari, P.J.; Srinivas, P.; Venkateshwara, S. Development of a topical phytosomal gel of Woodford fruticosa. *WJPPS* **2015**, *4*, 919–932.
120. Sarheed, O.; Rasool, B.K.; Abu-Gharbieh, E.; Aziz, U.S. An investigation and characterization of alginate hydrogel dressing loaded with metronidazole prepared by combined inotropic gelation and freeze-thawing cycles for controlled release. *AAPS PharmSciTech* **2015**, *16*, 601–609. [CrossRef]
121. Sofowora, A.; Ogunbodede, E.; Onayade, A. The role and place of medicinal plants in the strategies for disease prevention. *Afr. J. Tradit. Complement. Altern. Med.* **2013**, *10*, 210–229. [CrossRef]
122. Liang, J.; Cui, L.; Li, J.; Guan, S.; Zhang, K.; Li, J. Aloe vera: A Medicinal Plant Used in Skin Wound Healing. *Tissue Eng. Part B Rev.* **2021**, *27*, 455–474. [CrossRef]
123. Miastkowska, M.; Kulawik-Pióro, A.; Szczurek, M. Nanoemulsion Gel Formulation Optimization for Burn Wounds: Analysis of Rheological and Sensory Properties. *Processes* **2020**, *8*, 1416. [CrossRef]
124. Hekmatpou, D.; Mehrabi, F.; Rahzani, K.; Aminiyan, A. The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review. *Iran. J. Med. Sci.* **2019**, *44*, 1. [PubMed]
125. Rösch, D.; Krumbein, A.; Mügge, C.; Kroh, L.W. Structural investigations of flavonol glycosides from sea buckthorn (Hippophaë rhamnoides) pomace by NMR spectroscopy and HPLC-ESI-MS n. *J. Agric. Food Chem.* **2004**, *52*, 4039–4046. [CrossRef] [PubMed]
126. Sadowska, B.; Budzyńska, A.; Stochmal, A.; Żuchowski, J.; Różalska, B. Novel properties of Hippophae rhamnoides L. twig and leaf extracts—Anti-virulence action and synergy with antifungals studied in vitro on Candida spp. model. *Microb. Pathog.* **2017**, *107*, 372–379. [CrossRef] [PubMed]
127. Xiang, L.; Wang, J.; Zhang, G.; Rong, L.; Wu, H.; Sun, S.; Guo, Y.; Yang, Y.; Lu, L.; Qu, L. Analysis and identification of two similar traditional Chinese medicines by using a three-stage infrared spectroscopy: Ligusticum chuanxiong, Angelica sinensis and their different extracts. *J. Mol. Struct.* **2016**, *1124*, 164–172. [CrossRef]
128. Zhong, L.J.; Hua, Y.L.; Ji, P.; Yao, W.L.; Zhang, W.Q.; Li, J.; Wei, Y.M. Evaluation of the anti-inflammatory effects of volatile oils from processed products of Angelica sinensis radix by GC–MS-based metabolomics. *J. Ethnopharmacol.* **2016**, *191*, 195–205. [CrossRef]
129. Kulkarni, R.N.; Baskaran, K.; Jhang, T. Breeding medicinal plant, periwinkle [*Catharanthus roseus* (L) G. Don]: A review. *Plant. Genet. Resour. Characterisation Util.* **2016**, *14*, 283–302. [CrossRef]
130. Das, S.; Krishi Viswavidyalaya, C.; Sharangi, A.B. Madagascar periwinkle (*Catharanthus roseus* L.): Diverse medicinal and therapeutic benefits to humankind. *J. Pharm. Phytochem.* **2017**, *6*, 1695–1701.
131. Givol, O.; Kornhaber, R.; Visentin, D.; Cleary, M.; Haik, J.; Harats, M. A systematic review of Calendula officinalis extract for wound healing. *Wound Repair Regen.* **2019**, *27*, 548–561. [CrossRef]
132. Nicolaus, C.; Junghanns, S.; Hartmann, A.; Murillo, R.; Ganzera, M.; Merfort, I. In vitro studies to evaluate the wound healing properties of Calendula officinalis extracts. *J. Ethnopharmacol.* **2017**, *196*, 94–103. [CrossRef]
133. Thakur, V.; Vishwavidyalya, R.D.; Paroha, S. Climatic impact on physical properties, oil and protein content of two sesame (*Sesamum indicum* L.) varieties. *Int. J. Chem. Stud.* **2018**, *6*, 2098–2104.
134. Afroz, M.; Zihad, S.M.N.K.; Uddin, S.J.; Rouf, R.; Rahman, M.S.; Islam, M.T.; Khan, I.N.; Ali, E.S.; Aziz, S.; Shilpi, J.A.; et al. A systematic review on antioxidant and antiinflammatory activity of sesame (*Sesamum indicum* L.) oil and further confirmation of antiinflammatory activity by chemical profiling and molecular docking. *Phyther. Res.* **2019**, *33*, 2585–2608. [CrossRef]
135. Almeida, É.S.; de Oliveira, D.; Hotza, D. Properties and Applications of Morinda citrifolia (Noni): A Review. *Compr. Rev. Food Sci. Food Saf.* **2019**, *18*, 883–909. [CrossRef]
136. Jin, M.; Wang, Y.; Yang, X.; Yin, H.; Nie, S.; Wu, X. Structure characterization of a polysaccharide extracted from noni (*Morinda citrifolia* L.) and its protective effect against DSS-induced bowel disease in mice. *Food Hydrocoll.* **2019**, *90*, 189–197. [CrossRef]
137. Ramadon, D.; Anwar, E.; Diazputri Utami, T. Transfersomal gel containing green tea (Camellia sinensis L. kuntze) leaves extract: Increasing in vitro penetration. *Artic Asian J. Pharm. Clin. Res.* **2017**, *10*, 294–298. [CrossRef]
138. Farooqui, A.; Khan, A.; Borghetto, I.; Kazmi, S.U.; Rubino, S.; Paglietti, B. Synergistic antimicrobial activity of Camellia sinensis and Juglans regia against multidrug-resistant bacteria. *PLoS ONE* **2015**, *10*, e0118431. [CrossRef]
139. Nutrizio, M.; Gajdoš Kljusurić, J.; Marijanović, Z.; Dubrović, I.; Viskić, M.; Mikolaj, E.; Chemat, F.; Režek Jambrak, A. The potential of high voltage discharges for green solvent extraction of bioactive compounds and aromas from rosemary (*Rosmarinus officinalis* L.)—Computational simulation and experimental methods. *Molecules* **2020**, *25*, 3711. [CrossRef]
140. Andrade, J.M.; Faustino, C.; Garcia, C.; Ladeiras, D.; Reis, C.P.; Rijo, P. Rosmarinus officinalis L.: An update review of its phytochemistry and biological activity. *Future Sci. OA* **2018**, *4*, FSO283. [CrossRef]

141. Borges, R.S.; Ortiz, B.L.S.; Pereira, A.C.M.; Keita, H.; Carvalho, J.C.T. Rosmarinus officinalis essential oil: A review of its phytochemistry, anti-inflammatory activity, and mechanisms of action involved. *J. Ethnopharmacol.* **2019**, *229*, 29–45. [CrossRef]
142. Hızır-Kadı, İ.; Gültekin-Özgüven, M.; Altin, G.; Demircan, E.; Özçelik, B. Liposomal nanodelivery systems generated from proliposomes for pollen extract with improved solubility and in vitro bioaccessibility. *Heliyon* **2020**, *6*, e05030. [CrossRef]
143. Raemdonck, K.; Braeckmans, K.; Demeester, J.; De Smedt, S.C. Merging the best of both worlds: Hybrid lipid-enveloped matrix nanocomposites in drug delivery. *Chem. Soc. Rev.* **2014**, *43*, 444–472. [CrossRef]
144. Aytekin, A.A.; Tuncay Tanrıverdi, S.; Aydın Köse, F.; Kart, D.; Eroğlu, İ.; Özer, Ö. Propolis-loaded liposomes: Evaluation of antimicrobial and antioxidant activities. *J. Liposome Res.* **2020**, *30*, 107–116. [CrossRef]
145. El-Kased, R.F.; Amer, R.I.; Attia, D.; Elmazar, M.M. Honey-based hydrogel: In vitro and comparative In vivo evaluation for burn wound healing. *Sci. Rep.* **2017**, *7*, 9692. [CrossRef]
146. Perminaite, K.; Maria, F.A.; Sinico, C.; Ramanauskiene, K. Formulation of liposomes containing royal jelly and their quality assessment. *J. Nanosci. Nanotechnol.* **2021**, *21*, 2841–2846. [CrossRef]
147. Sogut, O.; Aydemir, S.U.; Sezer, S. Liposomal delivery systems for herbal extracts. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102147. [CrossRef]
148. Ghatnur, S.M.; Sonale, R.S.; Balaraman, M.; Kadimi, U.S. Engineering liposomes of leaf extract of seabuckthorn (SBT) by supercritical carbon dioxide (SCCO2)-mediated process. *J. Liposome Res.* **2012**, *22*, 215–223. [CrossRef]
149. Arora, D.; Rani, A.; Sharma, A. A review on phytochemistry and ethnopharmacological aspects of genus Calendula. *Pharmacogn. Rev.* **2013**, *7*, 179–187. [CrossRef]
150. Dosio, F.; Milla, P. EC-145, a folate-targeted Vinca alkaloid conjugate for the potential treatment of folate receptor-expressing cancers drug profile. *Curr. Opin. Investig. Drugs* **2010**, *11*, 1424–1433.
151. Cui, M.; Di Pan, Z.H.; Pan, L.Q. Danggui Buxue extract-loaded liposomes in thermosensitive gel enhance in vivo dermal wound healing via activation of the VEGF/PI3K/Akt and TGF-β/Smads signaling pathway. *Evid.-Based Complement. Altern. Med.* **2017**, *2017*, 8407249. [CrossRef]
152. Abdelfattah, S.; Nasr, M.; Ali, A.; Genedy, A.S. Vesicular systems used for wound healing. *Arch. Pharm. Sci. Ain. Shams. Univ.* **2021**, *5*, 184–203. [CrossRef]
153. Rohilla, S.; Bhatt, D.C.; Gupta, A. Therapeutic potential of phytomedicines and novel polymeric strategies for significant management of candidiasis. *Curr. Pharm. Des.* **2018**, *24*, 1748–1765. [CrossRef]
154. García-Díaz, M.; Patiño, B.; Vázquez, C.; Gil-Serna, J. A novel niosome-encapsulated essential oil formulation to prevent aspergillus flavus growth and aflatoxin contamination of maize grains during storage. *Toxins* **2019**, *11*, 646. [CrossRef]
155. Liu, F.; Wang, Y.; Ding, Z.; Zhao, L.; Xiao, J.; Wang, L.; Ding, S. Transcriptomic analysis of flower development in tea (*Camellia sinensis* L.). *Gene* **2017**, *631*, 39–51. [CrossRef]
156. Filipczak, N.; Pan, J.; Yalamarty, S.S.K.; Torchilin, V.P. Recent advancements in liposome technology. *Adv. Drug Deliv. Rev.* **2020**, *156*, 4–22. [CrossRef]
157. Ferrari, G.; Pang, L.Y.; De Moliner, F.; Vendrell, M.; Reardon, R.J.M.; Higgins, A.J.; Chopra, S.; Argyle, D.J. Effective penetration of a liposomal formulation of bleomycin through ex-vivo skin explants from two different species. *Cancers* **2022**, *14*, 1083. [CrossRef]
158. HISTX—Liposomal Vitamin C and Quercetin—LipoLife. Lipolife. Available online: https://www.lipolife.co.za/histx-liposomal-vitamin-c-quercetin/ (accessed on 12 March 2022).
159. Mi, Y.; Zhong, L.; Lu, S.; Hu, P.; Pan, Y.; Ma, X.; Yan, B.; Wei, Z.; Yang, G. Quercetin promotes cutaneous wound healing in mice through Wnt/β-catenin signaling pathway. *J. Ethnopharmacol.* **2022**, *290*, 115066. [CrossRef]
160. Khalili, A.; Alipour, S.; Fathalipour, M.; Purkhosrow, A.; Mashghoolozekr, E.; Bayat, G.; Nekooeian, A.A. Liposomal and Non-Liposomal Formulations of Vitamin C: Comparison of the Antihypertensive and Vascular Modifying Activity in Renovascular Hypertensive Rats. *Iran. J. Med. Sci.* **2020**, *45*, 41–49. [CrossRef]
161. What Is Liposomal Vitamin C? Health Benefits, Usage & Dosage. Available online: https://vitaminc.co.uk/what-is-liposomal-vitamin-c-health-benefits-usage-and-dosage/ (accessed on 14 March 2022).
162. Concept Crucial Values for The Brand. Decorté. Available online: https://www.decortecosmetics.com/ourstory/my/crucialvalues.html (accessed on 14 March 2022).
163. Dematte, M.F.; Gemperli, R.; Salles, A.G.; Dolhnikoff, M.; Lanças, T.; Saldiva, P.H.; Ferreira, M.C. Mechanical evaluation of the resistance and elastance of post-burn scars after topical treatment with tretinoin. *Clinics* **2011**, *66*, 1949–1954. [CrossRef]
164. Lu, K.J.; Wang, W.; Xu, X.L.; Jin, F.Y.; Qi, J.; Wang, X.J.; Kang, X.Q.; Zhu, M.L.; Huang, Q.L.; Yu, C.H.; et al. A dual deformable liposomal ointment functionalized with retinoic acid and epidermal growth factor for enhanced burn wound healing therapy. *Biomater. Sci.* **2019**, *7*, 2372–2382. [CrossRef]
165. Huaqing, L.; Chuqin, Y.; Wei, L.; Taxi, L. Tacrolimus Transfersome Solution and Preparation Method Thereof. CN102949341B, 4 April 2014. Available online: https://patents.google.com/patent/CN102949341B/en?oq=CN102949341B (accessed on 5 February 2022).
166. Patel, P.M. High-Concentration Lidocaine Compositions and Methods for Their Preparation. US7476400B2, 13 January 2009. Available online: https://patents.google.com/patent/US7476400B2/en?oq=US7476400B2 (accessed on 5 February 2022).
167. Milián, H.J.S.; Rull, L.V.; Díaz, E.M.; Acosta, J.A.B.; Puig, I.C.; Miró, J.V. Vesicles Which Include Epidermal Growth Factor and Compositions that Contain Same. EP2915541B1, 9 November 2016. Available online: https://patents.google.com/patent/EP2915541B1/en?oq=EP2915541B1 (accessed on 5 February 2022).

168. Touitou, E. Composition for Applying Active Substances to or through the Skin. US5716638A, 10 February 1998. Available online: https://patents.google.com/patent/US5716638A/en?oq=US5716638 (accessed on 5 February 2022).
169. Pang, N.S.; Bohnen, M.A. Liposomal Antibiotic Formulation. CA2117046C, 3 October 2000. Available online: https://patents.google.com/patent/CA2117046C/en?oq=CA2117046C (accessed on 5 February 2022).
170. Alexander, L.; Wu, H.G. Enhanced Antivirulent for Antibiotic-Resistant Bacteria. US20200276231A1, 3 September 2020. Available online: https://patents.google.com/patent/US20200276231A1/en?oq=US20200276231A1 (accessed on 5 February 2022).
171. Thorel, G.N. Topical Cosmetic Composition Containing an Improved Pro-Penetrating System. WO2012153075A2, 24 January 2013. Available online: https://patents.google.com/patent/WO2012153075A2/en?oq=wo2012153075A2 (accessed on 5 February 2022).
172. Ray, J.R.; Hodge, C.D. Composition and Method for Compounded Therapy. US9468599B2, 18 October 2016. Available online: https://patents.google.com/patent/US9468599B2/en?oq=US9468599B2 (accessed on 5 February 2022).
173. Edelson, J.; Timothy, K.; Zhang, B. Transdermal Delivery. JP2018009026A, 18 January 2018. Available online: https://patents.google.com/patent/JP2018009026A/en?oq=JP2018009026A (accessed on 6 February 2022).
174. Kim, Y.M.; Jang, G.H.; Park, Y.J.; Oh, G.H. Method of Preparing Bioactive Substance-Encapsulated Ethosome, Ethosome Composition, and Cosmetic Composition Including Ethosome Composition. WO2019004563A1, 3 January 2019. Available online: https://patents.google.com/patent/WO2019004563A1/en?oq=WO2019004563A1 (accessed on 6 February 2022).
175. Chegregor, C. Liquid Droplets for the Manufacture of a Preparation for the Non-Invasive Application or for the Non-Invasive Transport of Active Ingredients through Barriers. KR100446832B1, 4 September 2004. Available online: https://patents.google.com/patent/KR100446832B1/en?oq=KR100446832B1 (accessed on 6 February 2022).
176. Azevedo, M.M.; Pina-Vaz, C.; Rodrigues, A.G. The Role of Phage Therapy in Burn Wound Infections Management: Advantages and Pitfalls. *J. Burn Care Res.* **2022**, *43*, 336–342. [CrossRef]
177. PlumX- Novel Microbe-Resistant Clay Dressing for Healing Burn Wounds. Available online: https://plu.mx/plum/a/?repo_url=https://stars.library.ucf.edu/honorstheses/1193&theme=plum-bigben-theme (accessed on 19 June 2022).
178. Khan, A.D.; Rastogi, V.; Lavhale, P.M.; Jain, J. Novel approaches for herbal drug delivery in wound healing: A review. *Indian J. Pharm. Sci.* **2022**, *84*, 247–260. [CrossRef]