RSC Pharmaceutics

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Pharm.*, 2024, **1**, 9

Nanotechnology-driven wound healing potential of asiaticoside: a comprehensive review

Mohit Kumar, [a] Devesh Kumar,[a] Syed Mahmood,[b] Varinder Singh,[a] Shruti Chopra,[a] Ayah R. Hilles[c] and Amit Bhatia *[a]

Asiaticoside (AC) is a naturally occurring phytoconstituent that aids in wound healing by stimulating collagen biosynthesis. However, the physical properties of AC, such as its high molecular weight (959.12 g mol^{-1}), poor water solubility, and low permeability, restrict its therapeutic benefits. Additionally, the management of inflammation and angiogenesis in wound healing using AC-loaded wound dressings can be challenging in terms of its delivery across the skin layers. These challenges can be rectified by utilizing nanotechnology. The concept of nanotechnology is widely utilized in dermatology to boost the therapeutic efficacy of the entrapped drug. The AC-loaded nano-carriers deliver the drug at their target site in order to increase their efficacy, stability, and safety. These carriers efficiently distribute the loaded drug to the different skin layers. The current review focuses on the limitations associated with the topical administration of asiaticoside and the many initiatives made so far for effective and safe topical delivery using innovative constituents and techniques, along with other potential benefits of AC in wound healing, diabetes, inflammation, and depression.

Received 23rd October 2023,
Accepted 12th February 2024

DOI: 10.1039/d3pm00024a

rsc.li/RSCPharma

1. Introduction

A wound refers to a physical trauma or harm to the body that disrupts the structure of the skin or underlying tissues. Injuries may arise from several factors, such as accidents, trauma, surgeries, or underlying medical disorders.[1] They manifest in different forms, such as incisions resulting from sharp objects, lacerations with jagged edges caused by blunt force, abrasions from friction against rough surfaces, contusions or bruises. These result in damaged blood vessels, punctures from pointed objects, avulsions where a portion of skin or tissue is forcefully torn away, and gunshot wounds inflicted by projectiles fired from firearms.[2,3] The degree of a wound may range from superficial lacerations and abrasions that can be treated with simple first aid whereas more intricate injuries require expert medical intervention. Appropriate wound management is crucial for preventing infections, promoting healing, and minimising the risk of complications.[4] Despite advancements in wound dressing and healthcare, wounds continue to be a global concern. The global prevalence and incidence of wounds are detailed in Table 1.

1.1 Wound classification

Wounds can be classified as either acute or chronic, depending on how long they take to heal.[16] Acute wounds are caused by various factors such as surgical procedures, mechanical trauma, or burns, and they follow a predictable healing process.[17] Chronic wounds occur when there is a failure in the processes involved in tissue repair.[18] Certain medical conditions can hinder the healing process and lead to persistent wounds, such as infections caused by microorganisms,[19] venous or arterial disorders,[20] and diabetes.[21] The characteristics of acute and chronic wounds are shown in Table 2.

Wounds, which are frequently caused by tissue injury, recover through a series of intricate processes involving the interplay between growth factors and cytokines. These processes replace the injured cells and restore the organ's integrity.[33–35] The intricate wound healing system has been divided into four stages: inflammation, proliferation and re-epithelialization, and tissue remodelling. Although these mechanisms try to replace damaged tissue at the wound site, they often result in scarring (particularly in adults). Scars are one of the leading causes of physical, psychological, and physiological illness.[36,37] While the process of wound healing and scar formation, as well as how to avoid them, are not entirely understood, advances in the underlying mechanism have resulted in successful therapies. The major cause of dermal injuries associated with burns, surgery,

[a]*Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University (MRSPTU), Bathinda, 151001 Punjab, India. E-mail: dramitbhatia04@gmail.com*
[b]*Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, 50603 Kuala Lumpur, Malaysia*
[c]*INHART, International Islamic University Malaysia, Jalan Gombak, 53100 Selangor, Malaysia*

Table 1 Global prevalence and incidence of wounds

Type of wound	Population demographics	Incidence rate	Prevalence rate (globally)	Risk factors	Geographic distribution	Ref.
Venous leg ulcers	Adult population aged >65 years	0.17% overall	3%–4%	Family history, obesity, deep venous thrombosis, and increasing age	England, Western countries	5 and 6
Diabetic foot ulcers	Adult population aged 45 years and above	2–5% annually	6.3%	Poor glycemic control, calluses, foot deformities, improper foot care, ill-fitting footwear, underlying peripheral neuropathy and poor circulation, dry skin	Highest in North America, Belgium, Canada and the USA Lowest in Asia, Europe, Africa and Oceania	5 and 7
Pressure ulcers	Senior population aged above 70 years	Ranged 4.5%–78.4%	5.2%–12.3% at admission and at discharge respectively	Immobility, incontinence, lack of sensory perception, poor nutrition and hydration, and medical conditions affecting blood flow	Highest in US as compared to 195 other low, middle, and high sociodemographic index countries	5, 8 and 9
Surgical wound infection	Adult population aged >50	2.5%	0.5–3%	Patient-related factors include existing infection, low serum albumin concentration, older age, obesity, smoking, diabetes mellitus, and ischemia secondary to vascular disease or irradiation	Africa and US	10 and 11
Burn wound infections	All ages (mostly adults injured with flame burns and young children with scald burns)	26.93%	11 million annually	Nosocomial infection, immunocompromised patients (burn injury, cutaneous and respiratory tract injury, long Intensive Care Unit (ICU) stays)	Africa, Australia & New Zealand, Asia, Europe, Middle and South America, North America	12 and 13
Arterial ulcers	Geriatric population	12–14%	0.4% to 0.8%	Atherosclerosis, hypertension, diabetes, and atrial fibrillation, all of which are more prevalent in the geriatric population	USA	14 and 15

and trauma frequently results in scar development during the healing process, which reduces the functionality of normal skin and causes aesthetic and psychological damage.[38,39] Numerous therapeutic interventions and non-surgical methods, such as silicon dressings, radiation, laser therapy, and radiotherapy, have been used for scarless repair.[40–44]

Mohit Kumar

Mohit Kumar is a PhD scholar and research assistant in the Indian Council of Medical Research-sponsored project at the Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, India. With a remarkable four years of research background in pharmaceutical sciences and drug delivery, Mohit has dedicated his expertise to addressing the global concern of burn-related wound infections, affecting approximately 11 million people globally every year. His prolific academic journey includes the authorship of 8 book chapters and 39 publications, published in high-impact science journals. His outstanding contributions have earned him prestigious accolades such as the Young Researcher Award at an international conference in Pondicherry (India 2023) and the Best Paper Award at ICONICA 2020 India. He has been recognized by the Central Library of Medicine Foundation of Argentina for groundbreaking research focused on perfumes.

Devesh Kumar

Devesh Kumar is an M. Pharmacy Research Scholar in the Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, India. His academic journey includes the authorship of 1 book chapters and 7 publications published in high-impact science journals. His research interests are focused on the design of multifunctional peptides and nanomaterials in biomedicine.

Table 2 The characteristics of chronic and acute wounds

Characteristics	Acute wound	Chronic wound	Ref.
Onset	Usually short, it goes through every stage that regular wound healing goes through	Prolonged treatment, may cause a delay in one or more healing stages, leaving a permanent disorder	22 and 23
The stages of infection	Normally there are 4 stages – haemostasis, inflammation, proliferation, and remodelling	There is prolonged inflammation, and inadequate proliferation and remodelling phase	24
Inflammatory response	Generally, heals quickly as a part of the healing process	It is normal for chronic inflammation to persist and obstruct recovery	25 and 26
Appearance of the wounds	Typically, there is little tissue loss, and the outer edges are clean	Irregular wound edges, often accompanied by venous tracts, undermining, or tissue necrosis	27 and 28
Duration of wound healing	Three months in cases of acute wound	Three months or longer, and up to seven months	29
Skin pathology related to the epidermis	The epithelial layer in cases of acute wound remains normal	Hyperkeratotic (in which the outer layer becomes thicker) or parakeratotic (anucleate keratinocytes)	30
Granulation tissue	Normal production	Hypoxia of the tissue due to low oxygen levels, fibroblasts, and neoangiogenesis Tissue hypoxia: insufficient granulation tissue formation	31
Immunology	Normal	Immunology is not normal	4
Clinical examples	Abrasions, surgical wounds superficial burns	Cardiovascular lower-limb ulcers, diabetes wounds, heterogeneous aetiology ulcers, ulcers caused by pressure, infections in wounds	32

Wound healing is a dynamic and complicated process that involves a balance of different cells, cytokines, growth factors, pathways, and extracellular matrix (ECM) formation.[45] The pro-inflammatory cytokines interleukin-6 (IL-6) and IL-8 promote scarring, whereas the anti-inflammatory cytokine IL-10 has the opposite effect.[46–48] Less scar tissue has developed as a result of the simultaneous addition of several growth factors,[49–51] cytokines, and cells to wound matrices, but the problem of scarless outcomes has not yet been resolved.[52] As the healing process progresses through remodeling phases, inflammatory responses and angiogenesis undergo dynamic alterations at various stages to affect the development of the extracellular matrix (ECM) and, eventually, scar formation.[53,54] The complex variables (growth factors, cytokines, cells, and ECM) control angiogenesis and inflammation at different phases of the healing process to determine the outcomes of scars.[55,56] To promote the healing of scarless wounds, a variety of biomaterials, together with cell-laden matrices, have been developed to actively control angiogenesis

Syed Mahmood

Dr Syed Mahmood completed a Bachelor's in Pharmacy in 2011 and a Master's in Pharmacy (Pharmaceutics) in 2013. He also holds a post-graduate diploma in Pharmaceutical Drug Regulatory Affairs. In 2014 he started his PhD and completed it in 2017. His PhD research was on drug delivery and technologies. After his PhD, he worked at University Malaysia Pahang, as a senior lecturer teaching in the pharmaceutical engineering department. His specialization is in the field of pharmaceutical technology and engineering areas which include drug delivery animal models, analytical chemistry (LC-MS, HPLC), wound healing studies (hydrogel and nanofibers) and system validation and qualification. Currently he is working at Universiti Malaya in the pharmacy faculty attached to the pharmaceutical technology department.

Varinder Singh

Dr Varinder Singh is working as Assistant Professor at the Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, Punjab. He obtained his Ph.D. (Pharmaceutical Sciences) from Punjabi University, Patiala, Punjab, India. His research interests primarily lie in the discovery and development of natural products for therapeutic use. He is well-versed in the fields of natural product chemistry (isolation, and characterization of bioactive natural compounds), drug discovery, and pharmacology. He has a strong record of publications in high-impact peer-reviewed journals (40 peer-reviewed publications), with many of his papers cited extensively in the field of natural products. He has 1 patent granted. He has been awarded numerous travel grants by government and non-government organisations including Alzheimer's Association International, DST, ICMR and IBRO.

and inflammation. These matrices typically generate suitable microenvironments for wound healing.[55]

Recently, there has been an increase in interest in and demand for herbal medicines due to several reasons. These include claims about their effectiveness, a change in patients' preferences towards natural remedies, the expensive and adverse effects of modern medicines, and the progress made in herbal medicines through scientific research and technological advancements.[57] The diverse range of chemicals found in phytochemicals and organically produced compounds provide notable benefits in facilitating the process of wound healing. These compounds contribute to the recovery process through a variety of mechanisms, making them advantageous for promoting overall healing and tissue repair.[33,58] For example, in one study, Khan *et al.* investigated the wound-healing potential of *Berberis lycium* extract. The authors revealed that the prepared polyvinyl alcohol nanofibers loaded with *Berberis lycium* possess excellent wound healing and antibacterial activity.[59] In another study, Manconi and colleagues investigated the use of baicalin for the treatment of wounds.[60] The same research discovered that baicalin had skin-restorative capabilities utilizing the nanohydrogel platform.[61] Medicinal plants used to treat wounds have been demonstrated to be effective in combating infection and accelerating wound healing.[62,63] Among the commonly accessible therapeutic herbs, it has been claimed that extracts of *Centella asiatica* (L.) (CA) Urban, also known as Asiatic Penny-wort,[64,65] belonging to the Apiaceae family, have qualities capable of curing specific ailments, such as ulcerous skin abnormalities,[66] burns-related wounds,[67] duodenal and stomach ulcers.[68] These effects of *Centella asiatica* (L.) have been attributed to the presence of AC, an important compound. AC is a triterpene glycoside compound found in various plant species, most notably in *Centella asiatica* (L)., commonly known as gotu kola. Gotu kola is a small herbaceous plant that has been traditionally used in traditional medicine systems in Asia for its potential health benefits.[69] The biological activities of AC are diverse and include anti-inflammatory,[70] antioxidant action,[71] stimulation of collagen,[72] and angiogenesis production.[73] AC has been utilized therapeutically to promote the healing of wounds and lessen the development of scar tissue. However, the therapeutic use of AC as a topical medication or as a bioactive ingredient in wound matrices and dressings is restricted by its insolubility in water.[74] In addition, various studies have revealed that AC loaded into wound dressings and in liposomal carriers improved wound healing processes; however, these face challenges in managing inflammation and angiogenesis during wound healing.[75,76] This could be due to poor penetration of AC across the skin. Improving the loading and release management of AC would lead to better results for scarless wound healing. One solution to this problem is to use nanotechnology, which can improve the delivery of drug to the target site, and increase its efficacy, stability, and safety.[77] Nanocarriers play an important role in enhancing drug penetration through the *stratum corneum*, the skin's outermost layer.[78] The *stratum corneum* is a major barrier, limiting the passage of drugs. Nanocarriers circumvent this difficulty by using their distinct characteristics and interactions with the skin.[79] Nanocarriers interact more favourably with the *stratum corneum* due to their smaller particle size, which allows deeper penetration.[80] Furthermore, the lipid-based composition of many nanocarriers allows them to fuse with the lipids in the

Shruti Chopra

Dr Shruti Chopra is working as Assistant Professor with the Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, Punjab. Her area of expertise is pharmaceutical analysis, particularly analytical method development & validation, liquid chromatography and mass spectroscopy (LC-MS). She is a recipient of the Startup Young Scientist project by the Science and Engineering Research Board (SERB), Government of India. She is guiding three doctorate scholars and has guided 1 PhD and 10 M. Pharm. theses. Dr Chopra has 5 patents and 37 publications in reputed international as well as national journals with an equal number of presentations and invited lectures to her credit. She is member of editorial and reviewers' boards of various prestigious journals.

Amit Bhatia

Dr Amit Bhatia is working as a Professor at the Department of Pharmaceutical Sciences & Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda, Punjab. Dr Bhatia has been working in the area of drug delivery, formulation development and strategies. He has gained vast and varied exposure through country-wide interaction with regulatory and research experts while leading initiatives contributing to strategic inputs and operational oversight in formulation development. He has transferred 3 technologies to industry and has 7 patents granted to him. He has guided 3 PhD and 23 PG students. He has published 70 research and review articles, in prestigious journals. He is on the board of the reviewers' panel for various international journals of high repute. He has delivered various invited lectures on research and academics at different institutions.

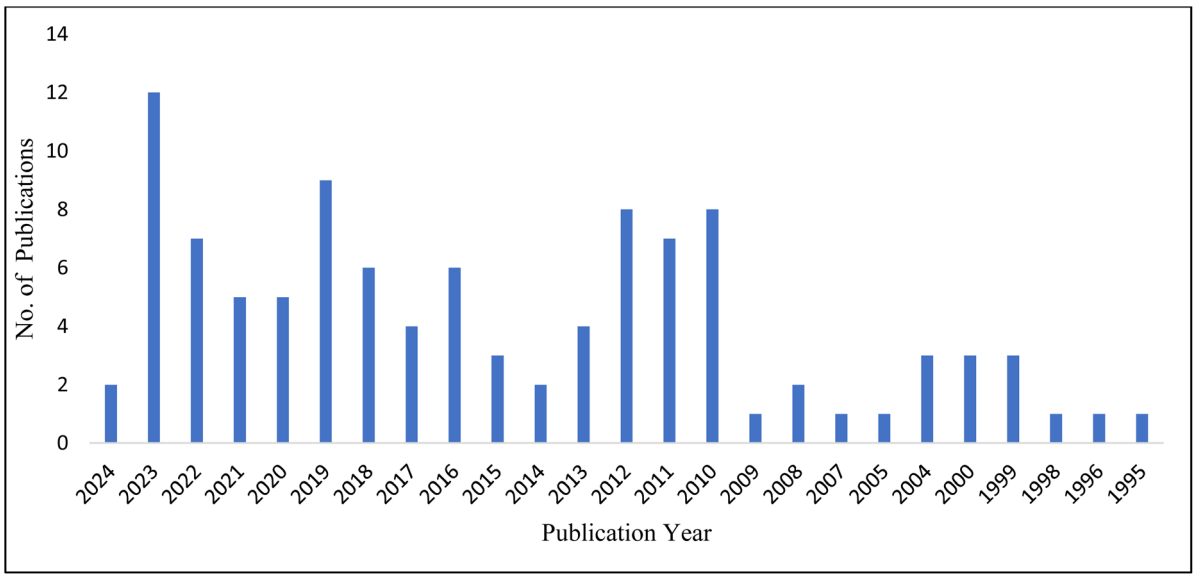

Fig. 1 PubMed search engine result demonstrating research publications published w.r.t. years starting from 1995 to 2024.

stratum corneum, increasing drug diffusion through intercellular gaps.[81] Some nanocarriers can also encapsulate both hydrophilic and hydrophobic drugs, making them suitable for a wider spectrum of therapeutic agents. Furthermore, surface changes to nanocarriers may be designed to improve adhesion and contact with the skin, hence enhancing drug retention and penetration.[82] Nanocarriers control the release of loaded drug which also helps to ensure long-term drug delivery and therapeutic benefits.[83] Overall, nanocarriers provide a viable pathway for improving drug absorption across the *stratum corneum*, furthering the science of transdermal drug administration with potential uses in dermatology.[84] In this review, the authors discussed the limitations of the topical administration of AC and highlighted various initiatives for effective and safe topical delivery using novel techniques, along with other potential benefits of AC in managing diabetes, inflammation, and depression. The authors gathered information about AC from articles published up to 2024 and listed in PubMed, Web of Science, Elsevier, Google Scholar and similar databases. The keywords used in our search included "asiaticoside", "*Centella asiatica*", "wound healing", "anti-inflammatory", "neuroprotective", "skin", *etc*. By carefully analyzing the research on asiaticoside, it was found that there is an increase in AC-based research, which can be demonstrated by contemplating the PubMed search engine results using asiaticoside in wound healing as a keyword (Fig. 1).

2. Phases of wound healing

2.1 Phase 1: haemostasis phase

Haemostasis is a vital physiological response triggered when blood is present outside the body or escapes from the blood vessels, serving as the body's innate mechanism to stop bleeding and prevent excessive blood loss.[39,85] This complex process unfolds in three rapid and sequential steps. The initial response involves a vascular spasm, where blood vessels constrict to minimize blood loss. Following this, the second step, platelet plug formation, occurs as platelets adhere together to create a temporary seal, covering the breach in the vessel wall.[85] Platelet plug formation is a crucial step in the haemostatic process, activated by the presence of von Willebrand factor (vWF), a glycoprotein found in plasma. Platelets play a pivotal role in haemostasis, undergoing significant changes when encountering injured endothelial cells.[86] Upon activation, platelets change shape, release granules, and acquire a "sticky" quality. Platelets express receptors, including glycoprotein receptors, facilitating their adhesion to collagen. Activated platelets, in turn, express glycoprotein receptors that enable interactions with other platelets, leading to aggregation and adhesion,[87] and release cytoplasmic granules, such as adenosine diphosphate (ADP), serotonin, and thromboxane A2. ADP attracts more platelets to the affected area, serotonin acts as a vasoconstrictor, and thromboxane A2 assists in platelet aggregation, vasoconstriction, and degranulation.[22,88,89] This release of chemicals creates a positive feedback loop, as more platelets are attracted to the site, adhere, and release their chemicals, reinforcing the platelet plug. This intricate process highlights the dynamic and coordinated role of platelets in ensuring effective haemostasis and preventing excessive bleeding.[90] The third and final step, known as coagulation or blood clotting, reinforces the platelet plug by introducing fibrin threads that act as a molecular glue to solidify the clot.[91] Within seconds of vessel wall disruption, platelets adhere to the sub-endothelial surface, and within minutes, fibrin strands intersperse among the wound, completing the formation of the platelet plug.[92] This orchestrated sequence ensures effective haemostasis, safeguarding the body against

excessive bleeding and contributing to the overall maintenance of vascular integrity.[93]

2.2 Phase 2: inflammatory phase

The inflammatory phase is a critical component of the body's response to injury, infection, or tissue damage, and is responsible for initiating the healing process. This dynamic phase is distinguished by a series of processes coordinated by the immune system.[85] Blood arteries dilate when injured, resulting in increased blood flow to the damaged region. This vasodilation is accompanied by increased permeability, which allows immune cells like neutrophils and macrophages to move to the area of damage.[94] These immune cells are essential for removing debris, infections, and injured tissue. Chemical mediators such as cytokines and prostaglandins help to attract and activate immune cells, which amplifies the inflammatory response.[95] While inflammation is a defensive process that helps to eliminate risks and initiate healing, a too lengthy or severe inflammatory response may contribute to chronic diseases. The inflammatory phase prepares the groundwork for subsequent stages of tissue repair by stimulating the elimination of injured cells and providing an environment favourable to tissue regeneration and healing. Balancing the inflammatory response is critical for effective wound healing and avoiding challenges caused by chronic inflammation.[96]

2.3 Phase 3: proliferative phase

The proliferative phase, which occurs after the inflammatory phase, is characterised by the active repair and regeneration of injured tissue. Several cellular activities take place during this period to aid in tissue healing.[97] Fibroblasts, which are specialised cells responsible for collagen production, move to the wound site and form a new extracellular matrix, providing structural support to the healing tissue.[98] Angiogenesis, or the development of new blood vessels, occurs to restore the vascular network required for nutrition delivery to the healing region.[99] Furthermore, epithelial cells within the wound boundaries multiply and move to cover the wound surface, providing a protective layer. The granulation tissue, which is rich in blood vessels and fibroblasts, covers the wound gap and acts as a temporary scaffold for tissue repair.[100] The proliferative phase is distinguished by an integrated approach of cellular activity, extracellular matrix synthesis, and angiogenesis to restore and reinforce the injured tissue. This phase provides the groundwork for the ensuing remodelling phase, which ensures the restoration of tissue integrity and function.[101] Proper synchronisation of these processes is required for effective wound healing and to avoid excessive scarring.[102]

2.4 Phase 4: maturation phase

The maturation phase, also known as the remodelling phase, is the final step of wound healing, after the inflammatory and proliferative stages.[103] It entails gradually reshaping and refining the newly developed tissue in order to improve its strength and effectiveness. During maturation, collagen fibres undergo reorganisation and cross-linking, which increases the tensile strength and endurance of the repaired tissue.[104] This phase is distinguished by the elimination of superfluous or excess collagen and cells by apoptosis, a programmed cell death process. The tissue is constantly altered to better tolerate mechanical forces and recover its original structure. While the maturation phase can take weeks, months, or even years, the ultimate aim is to have repaired tissue that nearly mimics its original, uninjured shape.[105] The maturation phase is critical for improving the quality of tissue healing and reducing scar formation, assuring the regenerated tissue's long-term functioning and durability. Proper wound care and support during this phase help to achieve the ideal balance of tissue strength and flexibility in the ultimate healed result.[1,106] The schematic diagram of wound healing phases is depicted in Fig. 2.

3. Method of extracting asiaticoside

Extraction is the process of carefully and deliberately extracting certain components or substances from a larger entity, such as a natural resource, combination, or chemical. In general, plant material is extracted by washing the analyte from the matrix into the solvent and diffusion through the cell wall.[107] Many methods are adopted for the extraction of AC.

3.1 Maceration

Maceration is a technique used in a variety of areas, most notably culinary arts, pharmacy, and herbal medicine. This method involves the soaking of an item, usually plant material, in a liquid to soften and break down its cellular structure, enabling the extraction of flavours, fragrances, or active molecules.[108] Maceration is a popular procedure used in pharmaceutical and herbal applications to extract therapeutic components from plants using solvents such as alcohol or oil. This gentle but efficient method allows for the absorption of beneficial elements, making maceration a flexible and commonly used treatment in both ancient and contemporary settings.[109] Organic solvents such as methanol, ethanol, or a mixture of water and alcohol are employed when dealing with CA. Typically, aqueous extracts produced *via* this method exhibit cytotoxic and antioxidant properties. The cosmetics industry has also implemented maceration, using propylene glycol and water as solvents for extracting the leaves and stalks of CA over the course of several days.[110] In one study, Pittella *et al.* isolated flavonoid and phenolic components from CA. Additionally, CA can be macerated to extract a wide range of compounds, including carotenoids, flavonoids, phenolics, saponins, alkaloids, and tannins, depending on the solvents employed and the duration of the extraction process.[111]

3.2 Distillation

Distillation is a prevalent separation technique that separates components of a mixture or purifies liquids by utilising differences in boiling points. It involves heating a liquid to produce vapour and then cooling that vapour to condense it back into a liquid state.[112] Prior to the vaporisation of components with

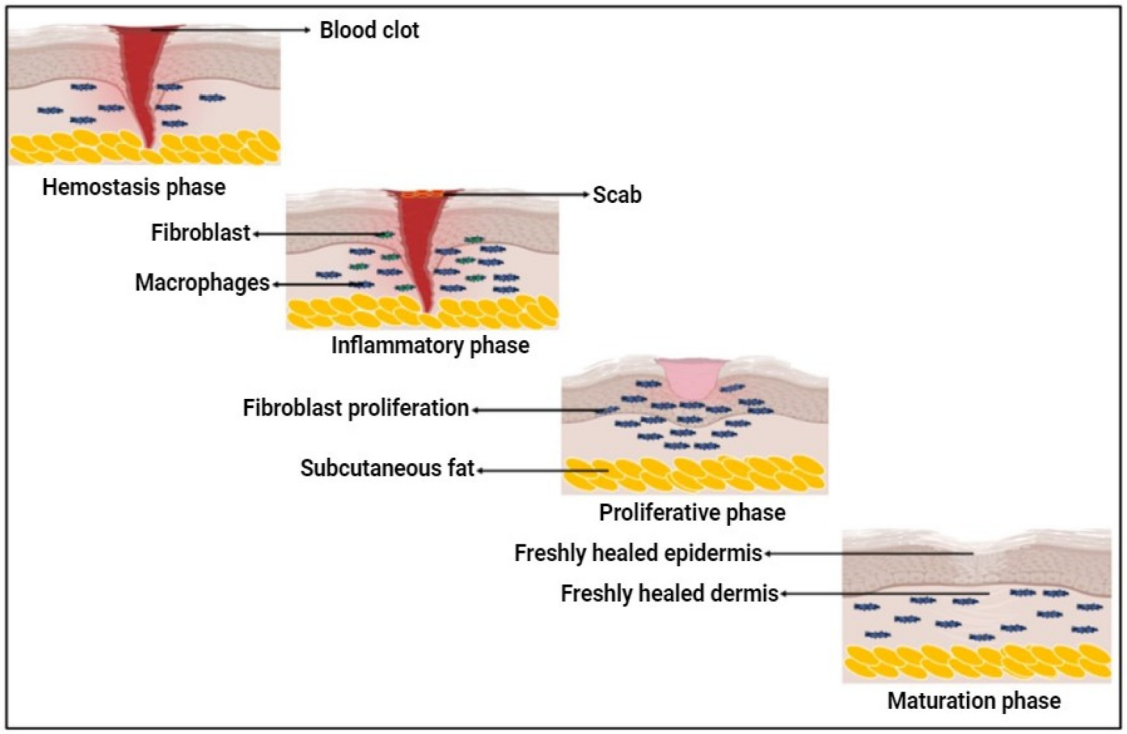

Fig. 2 Phases of wound healing.

higher boiling points, those with lower boiling points persist in the liquid phase. The aforementioned method is frequently implemented in the manufacturing of compounds, intoxicating beverages, and essential oils. As a crucial method for extracting purified substances from complex mixtures, distillation is utilised in laboratories and across a variety of industries.[113] In one study, dry and fresh leaves of CA were extracted by steam distillation with distilled water and vinegar. Using fresh leaves instead of dried ones during the extraction process facilitates the identification of numerous compounds. Steam distillation is an effective method for producing the highest-grade oil.[114] In one study, authors extracted 47 components using distillation extraction.[115]

3.3 Soxhlet extraction

Soxhlet extraction is a widely utilised method for extracting compounds from solid materials. The process involves placing the solid sample in a thimble and repeatedly passing a solvent, typically an organic one such as hexane or ethanol, through the sample.[116] The solvent evaporates, ascends through a vertical condenser, and then returns to the sample chamber. This continuous cycle enables efficient extraction of the desired compounds.[117] Soxhlet extraction is particularly advantageous for extracting compounds that are not easily vaporised and are sensitive to heat. It is commonly employed in various fields, including chemistry, pharmaceuticals, and food analysis, to separate and concentrate specific components from solid matrices.[118] In one study, Thamarai Selvi *et al.* discovered that by subjecting 500 g of powdered CA to Soxhlet extraction for 8 hours, using an ethanol-to-solid ratio of 1 : 4, they obtained extracts that included saponins, terpenoids, alkaloids, and phenols. However, these extracts did not contain steroids, flavonoids, tannins, proteins, carbohydrates, or glycosides.[119] Rahman *et al.* conducted another study where they utilised 100% ethanol, 50% ethanol, and water as solvents for Soxhlet extraction in order to acquire total polyphenols, flavonoids, β-carotene, tannins, and vitamin C from CA. The research demonstrated that the 50% ethanol extract of CA exhibited a markedly elevated concentration of polyphenols and flavonoids, whilst the 100% ethanol extract yielded the greatest levels of β-carotene and tannins. In contrast, the water extract of CA exhibited a higher concentration of vitamin C compared with the 50% and 100% ethanol extracts.[120]

3.4 Ultrasonic extraction

Ultrasonic extraction is a contemporary and effective method used to extract chemicals from diverse materials, including plants, herbs, and seeds. This technique involves the application of ultrasonic waves to a liquid medium that contains the sample, resulting in the development and subsequent collapse of small bubbles, a phenomenon known as cavitation.[121] Cavitation induces fast changes in pressure and temperature, generating microjets and shockwaves that aid in the liberation of bioactive substances from the solid matrix into the solvent. Ultrasonic extraction is renowned for its capacity to augment extraction rates and boost yields in comparison with conventional approaches. This procedure is extensively used in sectors such as food, pharmaceuticals, and cosmetics to get

superior extracts while minimising the time and amount of solvents used in the process.[122] In one study, Shen *et al.* utilised ultrasonic extraction for the extraction of asiaticoside. For ultrasonic extraction, 2.0 g of dried, finely powdered sample was mixed with 50 mL of a 9 : 1 mixture of methanol and water in a flask. The flask was then put in an ultrasonic bath for 1 hour. The extraction was done twice, and then the extracts were mixed. The combined extract was put through a filter, and the filtrate was evaporated using a rotary evaporator at 50 °C until it was dry. The residue was then mixed with 9 parts methanol and 1 part water to make 10 mL. Before analysis, the extract was filtered through a 0.45 μm nylon filter membrane.[123]

3.5 Microwave extraction

Microwave extraction (MAE) is a fast and efficient technique used to extract chemicals from diverse materials, including plants, seeds, and other organic components. During this procedure, the sample is exposed to microwave radiation in the presence of a suitable solvent.[123] The microwaves generate thermal energy in the sample, resulting in expedited extraction operations. The approach is renowned for its capacity to substantially decrease extraction durations, boost product quantities, and optimise the overall efficacy of the extraction procedure.[124] Microwave extraction is a widely used method in labs and enterprises due to its rapidity, accuracy, and efficiency in extracting desired chemicals from various sources.[125] The powder sample (1.0 g) was transferred to the microwave extraction containers and suspended in 25 mL of a 9 : 1 methanol–water mixture. According to a pre-designed scientific trial, the temperature rises to 70 °C in 0–5 minutes, and then remains steady at 70 °C for 15 minutes. The required solvent quantities were introduced to the vessels and tested under MAE for 20 minutes. Following extraction, the containers were chilled to room temperature before being opened. The residue was then mixed with 9 parts methanol and 1 part water to make 10 mL. Before analysis, the extract was filtered through a 0.45 μm nylon filter membrane.[123]

3.5 Multi-step extraction method

Method-1. Step-I: Dry Centella is mixed with ethanol in the concentration of 50%–90% v/v. The solution is filtered, then ethanol is removed *via* reduced pressure concentration, the ethanol-free concentrated liquid is diluted with water, and finally, the Centella total saponin water solution is obtained *via* centrifugal filtration. To obtain Centella total saponin water solution, the dry powder of Centella is mixed with ethanol in the concentration of 50–90% v/v, and then heat extracted 3 times, each for 180 minutes, and the united extraction liquid is evaporated to density 1.01–1.15 g mL^{-1}, then diluted with water, and centrifuging obtains Centella total saponin water solution.

Step-II: Total saponin water solution is entered into the macroporous resin column (model AB-8, HPD100, fraction size – 0.3–1.2 mm), and the washed resin was colourless, indicating that the effluent liquid is free from any significant impurities. A 15–30% ethanol (v/v) and 50–80% ethanol (v/v) solution were used to wash post more respectively, and a 50–80% ethanol (v/v) elutriant was collected, pooled and concentrated to density 1.01–1.05 g ml^{-1}; 3–5% activated carbon was added, and filtering while hot obtained the eluant in fractions (pressure 73.8 bar, temp. 70 °C).

Step-III: Take a 50%–80% (v/v) ethanol eluant, add activated carbon, and perform a decolourisation to obtain a column-loading liquid, filter the column-loading liquid, add the filtered liquid to a preparative chromatography column, with a filler of C18 bonded silica gel filler (preparative chromatography is used to purify sufficient quantities of a substance for further use, rather than analysis), and collect a fraction of the eluant containing madecassoside and asiaticoside using methanol/water as the moving phase; concentrating and drying then gives the resulting product. In this step, the consumption of 40–70% methanol (v/v) is 3–5 times the column volume. There are two sections of collection: the first is the asiaticoside component, and the second is the CA glucoside (madecassoside and asiaticoside) component; correspondingly, concentrate drying yields the product.[126,127]

4. Challenges associated with topical delivery of asiaticoside

The skin is the body's primary protective barrier, consisting of three major layers: the epidermis, dermis, and subcutaneous tissue. Each layer has unique structural properties that contribute to its barrier function.[128,129] The epidermis, or outermost layer, is made up of densely packed cells known as keratinocytes, which provide mechanical strength and waterproofing. The *stratum corneum*, a specialised layer of the epidermis, is essential for restricting substance penetration. The dermis contains blood arteries, nerves, and connective tissue, while the subcutaneous tissue provides insulation.[130,131]

Skin barrier properties play an important role in controlling drug penetration. Because of its compact, lipid-rich composition, the *stratum corneum* serves as an effective barrier, preventing most substances from entering.[132,133] Certain substances, however, can get inside the skin *via* a variety of pathways, including intercellular, transcellular, and appendageal. Intercellular permeation occurs between keratinocytes *via* the lipid matrix, while transcellular permeation occurs through the cells themselves.[134,135] Appendageal channels, such as hair follicles and sweat glands, provide alternate penetration routes.[136] Factors such as molecular size, lipophilicity, and charge impact compounds' ability to cross the skin barrier, making knowing these routes critical for drug delivery and skincare applications.[137]

The major challenges associated with the topical delivery of AC are its insolubility and bioavailability.[138] AC is a pentacyclic triterpene with a high molecular weight of 959.12 g mol^{-1} and is difficult to ionise; its maximum solubility in water is 307.347 pg mL^{-1} and it has a short plasma half-life. The equi-

librium oil–water partition coefficient is 2.24.[139] Poor solubility in aqueous and oil media reduces dose-dependent effects and absorption, severely limiting its applicability and mechanistic investigation. The low water solubility of drugs has always posed a significant challenge to the development of drug delivery devices. Poor solubility may restrict drug dissolution *in vivo*, resulting in limited absorption, which can pharmacologically impair the therapeutic effectiveness of the medicine.[140] The drug's physicochemical characteristics, such as pKa, solubility, log *P* and molecular mass, are also significant when choosing the components for the topical delivery vehicle.[141,142] Many chemicals lack the physical parameters [such as low molecular weight, appropriate lipophilicity [log *P* (o/w = 1–3)], and low melting point] to passively penetrate the skin at therapeutic levels, restricting the topical delivery of drugs.[143] The development of technologies to enhance delivery into the skin has been a major research focus for over half a century. 'Passive' technologies involve the use of formulation excipients, chemical penetration enhancers, and various types of micro and nano-delivery system.[144] When choosing an excipient for a topical vehicle for acidic and unstable drugs, special care must be taken to ensure that it will not only mask the drug's acidic group's potential for irritation but also offer the environment for efficient topical delivery and the preservation of chemical integrity.[145,146] The many difficulties presented by AC while creating the optimal topical formulations are shown in Fig. 3.

5. Wound healing potential of asiaticoside

AC is well-known for its anti-keloid and anti-hypertrophic scar properties.[150] Many researchers discovered that AC improved initial skin cell adhesion and increased the quantity of normal human dermal fibroblasts.[151,152] Initial cell adhesion is the process by which cells interact and attach to neighbouring cells through specialized molecules (cadherins, integrins and selectins) of the cell surface such as cell junctions, or through indirect interaction, where cells attach to the surrounding extracellular matrix, a gel-like structure containing molecules released by the cells into the spaces between them.[153,154] AC increases the skin cell activity involved in wound healing and may have therapeutic benefits.[155] Shukla *et al.* reported the wound-healing activity of AC. AC (0.2%, topical) application to rats (excision-type wound) resulted in improved enzymatic and non-enzymatic antioxidants which ultimately help in healing.[156] Ruszymah *et al.*[157] investigated the effects of CA on the proliferation and migration of rabbit corneal epithelial (RCE) cells. The CA was utilised in different concentrations such as 7.8, 15.6, 31.2, 62.5, 125, 250, 500, and 1000 ppm (ppm – part pers million). The study revealed that the proliferation of RCE cells was not substantially impacted by CA supplementation at concentrations up to 500 ppm. However, the proliferation of rabbit corneal epithelial (RCE) cells was signifi-

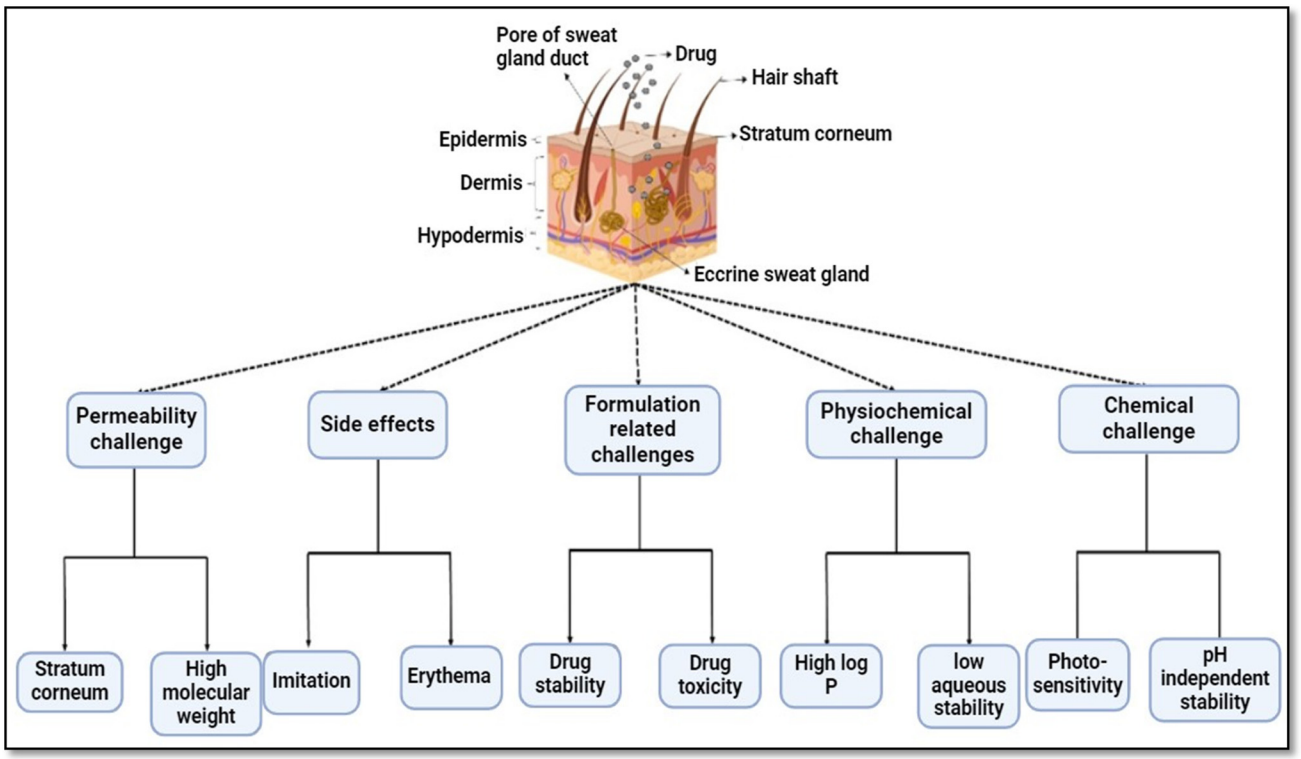

Fig. 3 Challenges associated with the topical delivery of asiaticoside.[147–149]

cantly inhibited at a concentration of 1000 ppm. Nevertheless, when exposed to concentrations as high as 62.5 ppm, the migration rate of RCE cells significantly increases in comparison with the control group.[157] Shetty *et al.*[158] investigated the influence of CA on dexamethasone-suppressed and normal wound healing in a rat model. The 4 g kg^{-1} dose of CA was used in wound healing. The author observed a significant increase in wound-breaking strength in the extract-treated group.[158] Ahmed *et al.* investigated the wound healing activity of the AC-rich fraction on a rabbit model.[159] The authors demonstrated that there is a reduction in wound size, and epithelialization, in the AC-treated group.[159] Sung *et al.* reported the wound-healing activity of CA-loaded hydrocolloid wound dressing (HCD) on Sprague–Dawley rats. After one month of study, the authors reported that there is a decrease in the excision wound size. The developed HCD exhibited outstanding swelling, drug release, and mechanical characteristics. In comparison with the commercial product, it increased the curative effect on excision, infection, and abrasion wounds in rats. Therefore, this hydrogel containing CA has the potential to be considered a viable option for treating different types of wound.[160] Azis *et al.* studied the wound-healing activity of the methanolic fraction of AC in New-Zealand white albino rabbits. The AC was utilized in the concentration of 119.89 μg mL^{-1},[161] which accomplished wound healing.[161] The authors used this concentration of asiaticoside because prior studies conducted by Lee *et al.* and colleagues[151] showed that, at this concentration, the number of treated fibroblast cells started increasing consistently. AC had no effect on the keratinocyte development rate, according to the same study by Lee *et al.*[151] Because of this, the present investigation just used asiaticoside in its human dermal fibroblast (HDF) scratch assay. Ahmed *et al.*[162] developed asiaticoside-loaded cross-linked polyvinyl alcohol/polyethylene glycol (PVA/PEG) hydrogel film. The prepared formulation is able to release 90% of the drug within 12 hours. The cytotoxicity investigations show that the developed formulation is compatible with cells and does not exhibit toxicity. Additionally, the microbiological limit tests revealed the absence of any microbial growth in any of the samples. The PVA/PEG hydrogel, developed by the freeze-thaw process, exhibited excellent fluid absorption capacity, elasticity, and safety. Consequently, it has significant promise as a material for wound dressing. Nevertheless, it is advisable to do further study on the formulation's *in vivo* effectiveness and long-term storage stability.[162] A study by Chatterjee and co-workers was conducted to examine the wound healing effects of AC on Wistar albino rats (either sex). The authors revealed that there was a reduction in the wound area when the asiaticoside-rich cream was applied to the rats.[163] In another study,[164] the authors investigated the wound healing activity of asiaticoside. Topical administrations of asiaticoside (0.2%) solution to guinea pig punch wounds resulted in an increase in tensile strength, rise in hydroxyproline, higher collagen content, and improved epithelialization. In streptozotocin-diabetic rats, where healing is tardy, a 0.4% solution of asiaticoside, applied topically to punch wound epithelization, enhanced the collagen content, hydroxyproline content and tensile strength.[164] A study by Liu *et al.* investigated the wound-healing potential of AC in diabetic rats/patients. The authors revealed that there was an increase in the expression of miRNA-21-5p among individuals with diabetic wounds (DW) and defined its function in signalling pathways associated with the process of chronic ulcer wound healing. The proliferation of cells was notably enhanced by LV-miRNA-21-5p overexpression, whereas the application of AC-Medium dose (AC-M) and AC-Low dose (AC-L) in combination with nitroprusside (SNP) augmented migration and proliferation. Additional examination unveiled potential targets of miRNA-21-5p, including TGF-β1, SMAD7, and TIMP3. The confirmation of their interaction with miRNA-21-5p was achieved *via* dual luciferase assays. This study revealed that the anti-DW drugs increased the expression of TGF-1 and SMAD7 while inhibiting the expression of TIMP3 in a high-glucose environment.[165] Paocharoen *et al.* investigated the different extracts of AC for the wound healing activity. In this study, male Sprague-Dawley rats, weighing between 250–300 g, were randomly allocated into incision and burn wound groups. Each group was further divided into seven subgroups for treatment: (1) untreated; (2) normal saline; (3) Tween 20®- (vehicle control); (4) hexane extract-; (5) ethyl acetate extract-; (6) methanol extract-; and (7) aqueous extract-treated groups. Topical application of the respective test substances was conducted once daily. For the incision wound group, the tensile strength of the wound was assessed on the seventh day post-wounding. In the burn wound group, the overall appearance and progress of wound healing were evaluated on days 3, 7, 10, and 14 following the burn injury, prior to histopathological examination. The various extracts derived from CA demonstrated positive effects in promoting the wound healing process for both incision and burn wounds. Notably, the ethyl acetate extract, containing asiatic acid, exhibited the highest efficacy among the components studied, suggesting that asiatic acid plays a crucial role in facilitating wound healing.[166] In one randomized controlled study involving 200 diabetic patients, the application of CA extract was found to accelerate the wound healing process. The participants were administered two capsules of CA extract, each containing 50 mg of AC, three times a day. The outcomes revealed improved wound contraction compared with the placebo group. Additionally, the CA extract demonstrated the ability to inhibit the formation of scar tissue. This suggests that the use of CA extract may be a beneficial intervention in promoting efficient wound healing and minimizing scar formation in diabetic patients.[167]

6. Mechanism of asiaticoside

6.1. Wound healing activity

AC affects many metabolic processes that are critical to human tissue, which ultimately results in collective tissue healing. During the process of healing, AC induces exposed tissue to produce and secrete antioxidants, which is important element

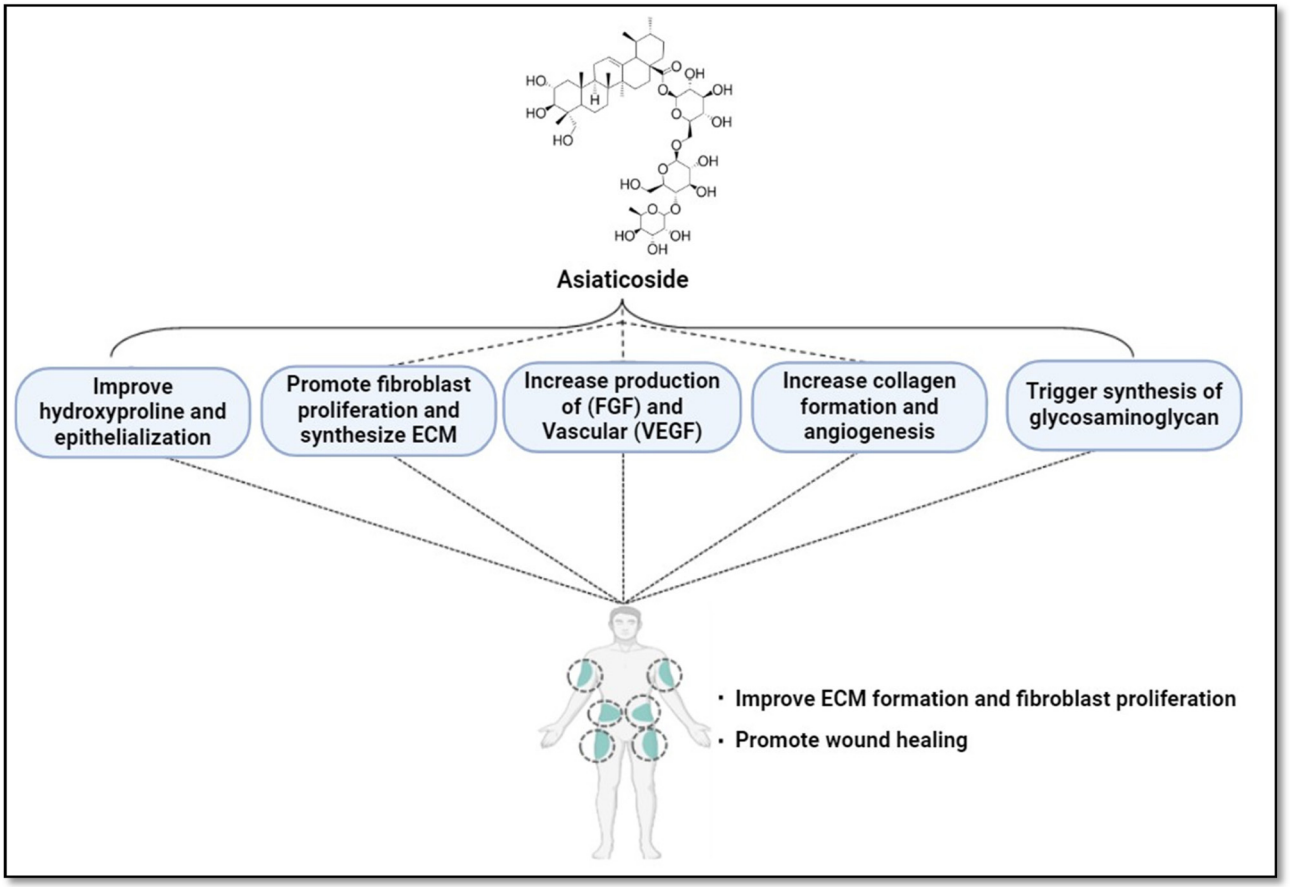

Fig. 4 Mechanism of action of asiaticoside.

for wound healing.[156] CA may aid wound healing due to enhanced angiogenesis. This might be the result of its action on collagen I, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) synthesis.[168,169] FGF increases the proliferation of endothelial cells in early angiogenesis. VEGF similarly promotes the development of new capillaries by regulating cell proliferation, differentiation, and migration.[170] In a tilt wound model, AC isolated from CA improves hydroxyproline and collagen levels, as well as tensile strength and the rate of epithelialization. Additionally, AC plays a role in the process of wound healing by contributing to the proliferation of fibroblasts and the synthesis of extracellular matrix (ECM).[171] Lu *et al.*[172] reported that cell cycle progression, collagen production, and cell proliferation were seen in human dermal fibroblast cells in response to AC.[172] According to Lu *et al.*, asiaticoside can boost extracellular matrix (ECM) formation and fibroblast proliferation, both of which are known to be crucial for wound healing.[173,174] The diagrammatic representation of the mechanism of AC is depicted in Fig. 4.

6.2 Anti-inflammatory, antipyretic, and antioxidant activity and neuroprotective activity

Glutamate is crucial in the process of transmitting signals between neurons, as well as synaptic plasticity. Glutamate attaches to ionotropic receptors such as *N*-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors.[175] During pathological situations such as stroke, traumatic injury, and inflammation, a significant accumulation of cytoplasmic calcium influx *via* NMDA receptors leads to excitotoxicity and neuronal destruction. The research found that AC inhibits the increase in Ca^{2+} levels caused by NMDA, indicating that AC partially contributes to neuroprotection by inhibiting the entry of calcium *via* NMDA receptors.[176,177] In one study, the authors found that administering AC can change depressive-like behaviour, raise monoamine neurotransmitter levels, lower inflammation in the hippocampus, and improve pNF-κBp65 and NLRP3 inflammasome levels in the chronic unpredictable mild stress (CMS) mouse model. It was additionally believed that AC might have an antidepressant-like effect by changing the cAMP/PKA/NF-κB/NLRP3/CREB/BDNF signalling system.[178]

Some studies showed that inflammatory cytokines play a crucial role in the development of depression in both humans and animals. It has also been shown that suppressing inflammatory processes could help people with depression.[179–181] In particular, inflammation factors have been shown to have an impact on the breakdown pathways of monoamine neurotransmitter precursors. This may cause the levels of these neu-

rotransmitters to rise.[182] Another study found that AC had a strong anti-inflammatory effect in animal models of brain damage, spinal cord injury, and ischemia-reperfusion injury.[183–185] A study demonstrated that CMS raised IL-1β, IL-6, and TNF-α levels in the hippocampus, which were lowered through the administration of asiaticoside. This suggests that AC has an antidepressant effect which may be due to its anti-inflammatory potential.[178]

7. Novel drug delivery systems

Novel drug delivery systems (NDDS) seem to be a better option than developing a new drug as they are associated with many benefits like less expenditure, being less time-consuming, and more profit for small companies who cannot afford huge costs to develop new drugs.[39,186,187] NDDS are used to improve the activity of the drug and to reduce the side effects as shown in Table 3.

The Nobel Prize winner Sir Paul Ehlrich, who imagined drug molecules as "magic bullets" that could only reach the intended place to demonstrate their action, is credited with the idea of NDDS (in 1905). The idea of "magic bullets" changed into "magic guns", or NDDS.[212] Fig. 5 illustrates how these carriers interact with skin elements to efficiently distribute the loaded medicine to the different skin layers.[145,213] These carriers can carry the drug to different skin layers through one or many mechanisms, as shown in Fig. 5, depending on their compositional characteristics.[214,215] (1) Biocompatible and biosimilar excipient carriers, such as liposomes and microemulsions, can integrate with the lipids of biological membranes. (2) Smaller carriers, such as lipid nanoparticles (SLNs/NLCs), micro and nanoemulsions, and flexible carriers, such as ethosomes and flexible membrane vesicles (FMVs), can transfer drugs *via* the intercellular gaps of skin cells. (3) The osmoregulated delivery of elastic vesicles such as FMVs and ethosomes can be triggered by the moisture cloud beneath the SC. (4) Small lipid-based carriers, such as SLNs/NLCs, also infiltrate the skin *via* a transcellular channel, namely keratinocytes. (5) A significant number of colloidal carriers are adsorbed to the SC and release the medication *via* diffusion. (6) The transappendageal pathway, which involves passing *via* hair follicles and sweat and sebaceous glands, is currently recognised as one of the key routes of drug delivery by NDDS.[216,217] The NDDS are utilized as carriers to deliver the drugs at their target site in order to increase their efficacy, stability and safety. For example, niosomes are used as a delivery carrier for many drugs like gliclazide,[205] ketoconazole,[218] transdermal formulations,[219] timolol maleate,[220] folic acid[221] *etc*. Nowadays liposomes are utilized to deliver many drugs such as paclitaxel,[222] cyclosporine,[223] cefepime,[224] cabazitaxel,[225] glycyrrhetinic acid,[226] curcumin,[227] ibuprofen,[228] tedizolid phosphate[229] *etc*. in order to improve their efficacy and stability. Similarly, ethosomes may impair drug molecules with various physicochemical characteristics, including hydrophilic,[230] lipophilic and amphiphilic.[231] Many drugs such as aceclofenac,[232] diclofenac diethylamine,[233] mycophenolic acid,[234] *etc*. have been delivered by ethosomes. In order to increase the therapeutic efficacy of drugs phytosomes are utilised to supply numerous medicines including mitomycin C,[235] *Boswellia serrata* extract,[236] curcumin,[237] quercetin[238] *etc*. For instance, several drug carriers, such as Lipusu (liposomal paclitaxel), Ambisome (liposomal amphotericin B), Psorisome (liposomal dithranol), and Fungisome (liposomal amphotericin B), are successful examples of NDDS systems.[239–242]

8. Advantages of nanocarriers

Nanocarriers offer a breakthrough paradigm in topical drug delivery, offering several benefits that boost pharmaceutical innovation to new heights.[243] These tiny carriers, often on the nanoscale scale, have revolutionary potential for overcoming the limits of traditional formulations.[244] One of their foremost advantages lies in their ability to enhance the bioavailability of drugs by facilitating efficient penetration through the intricate layers of the skin.[245] The nanoscale dimensions confer an increased surface area and an augmented drug payload, ensuring a profound and targeted therapeutic impact.[246] Furthermore, nanocarriers have an excellent ability to encapsulate both hydrophobic and hydrophilic drug moieties, increasing the range of pharmacological agents suitable for topical administration.[247] This flexibility extends beyond traditional limitations, providing a complete answer to the issues faced by various drug physicochemical features.[248] Nanocarriers' regulated and sustained release kinetics provides unparalleled precision to formulations, carefully influencing the temporal components of drug delivery for optimal therapeutic effects.[249] Additionally, the inherent potential of nanocarriers to circumvent biological barriers and reach the targeted skin layers with clinical accuracy is illustrative of their ability to overcome obstacles that are associated with traditional drug delivery.[250]

9. Topical delivery of asiaticoside-employing NDDS

NDDS are currently widely utilized in order to deliver the drug topically. These systems enhance drug stability, bioavailability and efficacy.[251,252] The carriers that are used in the topical delivery of AC are shown in Fig. 6.

9.1 Liposomes

A liposome combines the Greek terms lipo, which means fat, and somes, which means body. Alec D. Bangham created the first liposomes in England in 1961. Liposomes are tiny, spherical synthetic vesicles composed of phospholipids (non-poisonous) and cholesterol.[253,254] Due to their small sizes and hydrophilic and hydrophobic characteristics, liposomes can be used as medication delivery vehicles. Their characteristics are dependent on the lipid content, surface charge, size, and production technique.[255] Liposomes are spherical-shaped micro-

Table 3 Various drug delivery carriers studied as a part of NDDS for topical drug delivery

Carrier system		Composition	Size	Special comments	Ref.
Micellar carrier	Polymeric micelles	Polystyrene, poly(ethylene glycol)–poly(ε-caprolactone) and poloxamers	30–100 nm	Micellar carriers are essential for improving the delivery of drugs to the skin, as they employ different mechanisms to enhance drug solubility, skin penetration, and overall effectiveness. When it comes to topical drug delivery, surfactants or amphiphilic polymers are frequently utilised to form these micelles. The main process involves enclosing hydrophobic drug molecules within the core of the micelles, which enhances their solubility in the aqueous vehicle of the topical formulation. This solubilization helps to keep the drug in a stable and evenly distributed state, preventing any unwanted precipitation or clustering. In addition, micellar carriers have the ability to interact with the skin's lipids, which helps the loaded drug penetrate through the stratum corneum, the outermost layer of the skin. Micelles have the unique ability to interact with both the water-loving and oil-loving parts of the skin, facilitating the effective delivery of drugs through the skin	188 and 189
	Mixed micelles	Ionic surfactants, polymers and co-polymers	10–100 nm		190 and 191
	Phospholipid-based micelles	Phosphatidylcholine, sugars, glycolipids, and triglycerides	5–20 nm		192
Particulate carriers	Solid lipid nanoparticles	Cholesterol, triglycerides, fatty acids and waxes	50–1000 nm	Particulate carriers, including nanoparticles, microparticles, and nanocarriers, are used in the topical administration of drugs to improve the effectiveness and regulated release of the drugs. These carriers enable the transportation of pharmaceutical substances *via* several processes. Nanoparticles possess a diminutive size that facilitates their interaction with the skin at a tiny scale, hence facilitating effective permeation through the stratum corneum, which is the outermost layer of the skin. Moreover, the particulate carriers possess a favourable ratio of surface area to volume, which effectively increases the interaction between the carrier and the skin. This interaction promotes attachment and facilitates the release of drugs	193 and 194
	Nanostructured lipid carriers	Lipids, surfactants and co-surfactants	10–1000 nm		195 and 196
	Polymeric nanoparticles	Polysaccharides and proteins	1–1000 nm		197 and 198
Emulsified carriers	Microemulsion	Water, oil, a surfactant, and a cosurfactant	10–300 nm	Emulsions are colloidal dispersions of two immiscible liquids, usually oil and water, stabilised by surfactants. In the context of topical drug administration, the emulsified carrier acts as a vehicle for incorporating lipophilic and hydrophilic drugs, enabling a broader spectrum of therapeutic agents to be developed. The emulsion structure ensures that the drugs are distributed evenly and precisely, improving skin contact and boosting drug absorption. Furthermore, the emulsified carrier may function as a reservoir mechanism, slowly releasing the drug into the skin over time. The emulsion's composition and surfactant characteristics also influence skin penetration by modifying the stratum corneum's barrier function. Furthermore, emulsified carriers may increase the stability of certain drugs, preventing deterioration and preserving effectiveness during storage. Overall, emulsified carriers provide a diverse platform for topical drug administration by resolving solubility issues, optimising drug release kinetics, and increasing the overall performance of pharmaceutical formulations applied to the skin	199 and 200
	Nano-emulsion	Oil, water, surfactant	10–1000 nm		201 and 202
	Lipid emulsion	Phospholipids, emulsifiers, oil and water	0.5–5 μm		203 and 204
Vesicular carriers	Liposomes	Phospholipid, cholesterol and API	0.025–2.5 μm	The primary functions of vesicular carriers, including liposomes, ethosomes, and niosomes, are to improve the stability of the encapsulated compounds, facilitate sustained release, and enhance drug permeation. An essential mechanism involves the potential of vesicles to alter the structure of the stratum corneum, which is the outermost layer of epidermis. Vesicles are capable of interacting with the lipid bilayers of the stratum corneum, thereby transiently creating pathways for drug penetration and temporarily disrupting its integrity. Furthermore, it is possible to engineer vesicles with a diminutive size that can traverse the intercellular spaces of the stratum corneum, thereby facilitating improved drug transportation to the dermal layer	205 and 206
	Niosomes	Non-ionic surfactants, hydration medium and cholesterol	0.025–0.1 μm		207
	Ethosomes	Phospholipid, alcohol, polyglycerol and water	100–1000 nm		208
	Transferosomes	Edge activators such as Span 80 and phospholipids	50–500 nm		209 and 210
	Phytosomes	Phospholipids, such as phosphatidylcholine, produce a lipid-compatible molecular complex with the herbal ingredients	100–1000 nm		211

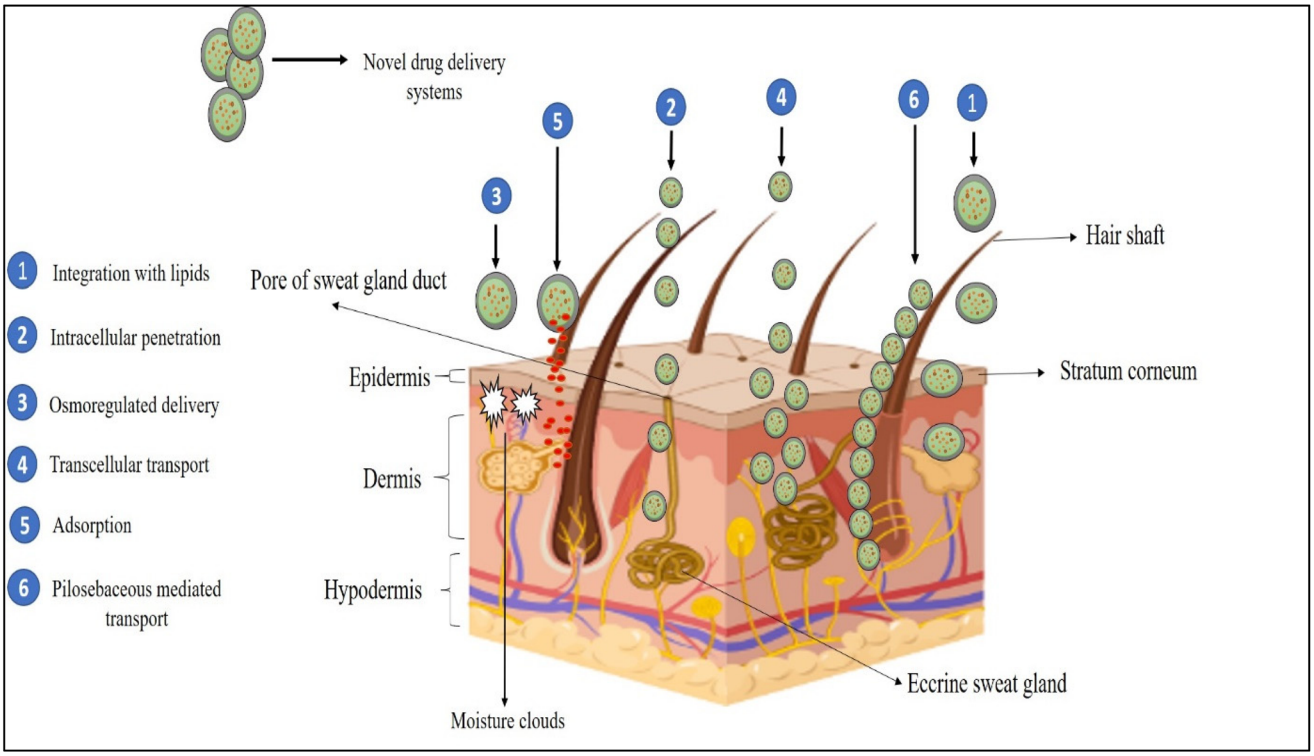

Fig. 5 The drug-loaded NDDS penetration across the skin through different mechanisms.

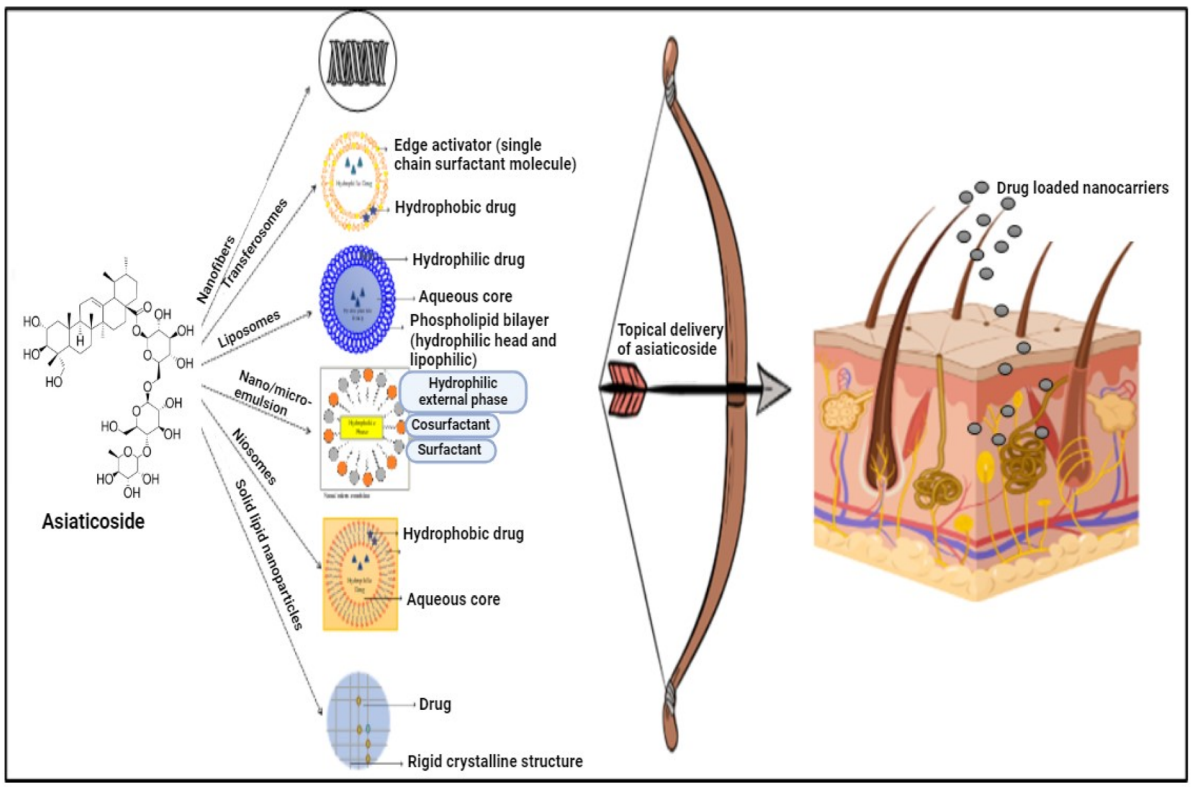

Fig. 6 Topical delivery of asiaticoside employing NDDS.

vesicles epitomizing the first generation of nanocarriers that have been fortunately expanding from the laboratory scale up to clinical applications.[256] These liposomal systems have been an entrenched drug delivery platform with a major influence on patient well-being.[257,258] Liposomes are composed of a bi-layer of natural or synthetic non-toxic phospholipids which instinctively form closed structures at the time of hydration. These kinds of vesicle have one or more bi-layer membranes known as lamellae.[259–262] However, the different structure of liposomes enables drug encapsulation with diverse lipophilicities.[263,264] A study reported by Paolino *et al.* on ultra-deformable liposomes provided the significantly enhanced *in vitro* skin penetration of AC showing a 10-fold increase with respect to the free drug solution and promoting *in vivo* collagen production. Liposome-based AC delivery through the topical route is a promising delivery system for effective wound healing.[265] Feng *et al.* prepared injectable hydrogel with AC-loaded liposomes for burn wound healing. *In vitro* studies have demonstrated that the hydrogels possess remarkable antibacterial efficacy against *Escherichia coli* and *Staphylococcus aureus*. The results of the *in vivo* study conducted on Sprague–Dawley rats using a burn-wound infection model indicate that the hydrogel demonstrated significant efficacy in promoting wound healing and exhibited superior wound healing properties.[266]

9.2 Microspheres

Microspheres are "monolithic spheres or therapeutic agents, distributed throughout the matrix either as a molecular dispersion of particles"[267] or as a structure composed of one or more miscible polymers in a continuous phase in which molecular or macroscopic droplet particles are distributed. They are tiny spherical particles with sizes in the micrometer range (usually 1–1000 micrometres). Starches, gums, proteins, fats, and waxes that are biodegradable man-made polymers and modified natural materials are used to prepare microspheres.[268] In one study, Sharma *et al.*[269] used these biodegradable polymers in order to prepare microspheres. Albumin and gelatin are natural polymers, while polyglycolic acid and polylactic acid are manufactured polymers. Albumin controls the release of drugs from microspheres[270] whereas polyglycolic acid and polylactic acid improve the stability of encapsulated drugs.[271] The solvents which are utilized to dissolve the polymeric materials are chosen based on the solubilities and stabilities of polymer and drug, as well as process safety and economic factors.[272,273] Zhang *et al.* studied AC-loaded microspheres for wound healing. They investigated the release kinetics and cellular uptake profiles of AC-microspheres, exploring their therapeutic impact on wound healing and skin appendage regeneration through both *in vitro* and *in vivo* assessments. The results revealed that the optimized AC-microspheres exhibited a spherical spongy structure with cylindrical holes. Efficient loading and sustained release of AC were achieved within the microspheres. Cellular uptake of AC from the microspheres was notably enhanced, being 9.1 times higher than that of the free solution. *In vitro* experiments demonstrated that AC-microspheres significantly promoted the proliferation and migration of keratinocytes, along with accelerated wound healing. Moreover, these microspheres exhibited marked effects on re-epithelization, collagen synthesis, and pro-angiogenesis during rat full-skin wound healing *in vivo.* The porous microsphere emerged as an innovative carrier for the sustained delivery of poorly soluble AC, leading to improved absorption and therapeutic outcomes. AC-microspheres, as a promising topical preparation, demonstrated excellent regenerative effects in wound therapy.[274]

9.3 Nano-emulsions

The nano-emulsion is either the oil-in-water (O/W) or water-in-oil (W/O) type, which primarily depends on the method of preparation. The water acts as a continuous phase whereas oil is the dispersed phase in the O/W type of emulsion,[202,275] whereas the inversed condition results in a W/O emulsion. Nano-emulsions (NEs) have tiny droplet sizes which enable a uniform diffusion of active ingredients throughout the skin.[276] The nano-emulsion has a low surface tension and wide surface area, and due to this only 3 to 10% of surfactants are required during nano-emulsion preparation.[277,278] Huimin *et al.* developed AC-loaded NEs and nano-emulsion-based gel (NBGs) for the topical delivery of AC. The *ex vivo* permeation study revealed that the permeation rate of AC-NEs is very high. According to Huimin *et al.*, the *ex vivo* skin permeation of AC from prepared NEs was 13.65 times more than that of ordinary gel when determined by using Franz diffusion. The prepared AC-NBGs also showed good penetrability when compared with the enhancer group. The pharmacokinetic study showed that the prepared AC-NEs when applied to the mouse model achieved the peak level of the drug (C_{max}/μg g^{-1} – 656.28 ± 19.42) in the skin very quickly (t_{max}/h-6), retained the drug mass concentration in the subcutaneous tissue and maintained the plasma drug concentration for a long time with high bioavailability. Additionally, the mechanism of AC-NEs and AC-NBGs was studied by HE (hematoxylin and eosin) staining and CLSM (confocal laser scanning microscopy).[279] In a similar study, Muthia and team prepared AC-NE lotion. The prepared NEs exhibited a mean particle size of 19.88 ± 2.3 nm, while the size in the lotion formulation was 198.4 ± 11.52 nm. The polydispersity index indicated good uniformity (0.329 ± 0.065), and the zeta potential was −30.9 mV, suggesting stability. Stability tests over 8 weeks at varying temperatures (4 ± 2 °C, 28 ± 2 °C, 40 ± 2 °C) confirmed the resilience of the NE lotion, with no notable changes in physical properties or pH values observed. The cumulative amount of AC penetration was significantly higher for the NE lotion (1558.65 ± 66.93 μg cm^{-2}) compared with the lotion alone (1260.364 ± 71.42 μg cm^{-2}). The flux of the NE lotions (2.1255 ± 0.31 μg cm^{-2} h^{-1}) surpassed that of the lotion (1.4506 ± 0.49 μg cm^{-2} h^{-1}). These findings underscore the enhanced penetration and stability of the NE lotion, suggesting its potential as an effective carrier for AC in topical applications.[280]

9.4 Nanoparticles

Nanoparticles are novel drug carriers with diameters of 1 to 100 nm. The nanoparticles are the carrier systems in which the drug dissolves, encapsulates or binds to the polymeric matrix.[281] The nano-capsule or nanosphere formation is based on the method of preparation. Nano-spheres are matrix systems in which the drug is physically and evenly distributed, while nano-capsules are systems in which the drug is contained in a cavity surrounded by a unique polymer membrane.[282–285] A study conducted by Rocha *et al.* developed AC-loaded nanoparticles for topical delivery with both dried (D) and glycolic (G) extracts encapsulated in nanostructured lipid carriers (NLC). They formulated two different forms, NLC-D and NLC-G, respectively, for effective skin delivery. The investigation involved *in vitro* release and skin permeation studies. Additionally, electron paramagnetic resonance (EPR) analysis was conducted to elucidate the lipid dynamics within the NLC matrices and the impact on *stratum corneum* (SC) membrane fluidity. The release of AC from NLC-D was approximately 23.7%, while NLC-G demonstrated a notable 2-fold increase in AC release over the same period. EPR data revealed that NLC effectively enhanced SC membrane fluidity, with NLC-G exhibiting a more pronounced effect. Furthermore, NLC-G facilitated the penetration of AC into deeper skin layers, with quantifiable amounts detected in the epidermis/dermis (9.14 ± 0.54 μg cm^{-2}) within 24 h. In contrast, similar AC permeation from NLC-D was achieved only after 48 h (10.42 ± 1.41 μg cm^{-2}). The accelerated release of AC from NLC-G contributed to enhanced skin permeation, and the augmented SC fluidity induced by NLC-G appeared to further increase AC penetration into deeper skin layers. As a result, nanoparticles appear to have a potential for topical delivery.[286] In another research study Kwon *et al.* investigated the wound healing and skin protective property of CA (includes AC, madecassoside, asiatic acid, and madecassic acid) loaded nanoparticles. An approx. 67% drug was encapsulated into the prepared nanoparticles and showed negligible cytotoxicity in human skin fibroblast cells. The prepared nanoparticles have the ability to decrease the expression of matrix metalloproteinase (MMP-1). The developed nanoparticles when tested on mouse skin showed high flux and were retained in the skin with a large concentration of drug.[287] Liu *et al.* developed bioactive composite hydrogels by incorporating decellularized extracellular matrix (ECM), GelMA, and AC-loaded polydopamine nanoparticles (AC@PDA). These hydrogels were designed as wound dressings with the potential to enhance the healing process. *In vitro* cytotoxicity assessments conducted on human skin and fibroblasts demonstrated favourable biocompatibility for all hydrogels. To evaluate the *in vivo* wound healing efficacy, tests were performed using a full-thickness excisional wound model in mice. Notably, the AC@PDA/ECM-G hydrogel exhibited fast wound closure without scarring, and showcased the highest formation of hair follicles. The superior performance of the AC@PDA/ECM-G hydrogel in promoting wound healing indicates its potential utility as a promising wound dressing.[288] Similarly, Narisepalli *et al.* developed AC-loaded polymeric nanoparticles for diabetic wound healing. The presence of AC in the formulation was found to induce a notable proliferation and migration of fibroblasts in *in vitro* cell culture studies. Furthermore, the administration of AC-loaded polymeric nanoparticles to diabetic rats for the treatment of the wounds of diabetic rats resulted in enhanced wound healing efficacy, as evidenced by increased collagen biosynthesis, upregulated levels of COL-1 protein, and enhanced expression of α-SMA in comparison with the control groups.[289]

9.5 Niosomes

Niosomes are vesicular nanocarriers that self-assemble after being hydrated with synthetic surfactants and sufficient concentrations of cholesterol or other amphiphilic compounds. Handjani-Vila *et al.* describe for the first time this kind of vesicle.[290] Niosomes are vesicular structures similar to liposomes and have the capability to transport both lipophilic and hydrophilic medicines. The reason for making niosomes is that surfactants are thought to have greater chemical stability than phospholipids, which are utilised to make liposomes. Phospholipids are quickly hydrolysed due to the presence of an ester bond.[291] Because of the unreliable reproducibility caused by the use of lecithins in liposomes, scientists are looking for vesicles made from alternative materials, such as non-ionic surfactants. Niosomes are a potential drug delivery vehicle, and because they are less toxic, they are non-ionic and increase the therapeutic index of drugs by limiting their action to the target cells. They are small laminary structures that are also called non-ionic surfactant vesicles, formed in combination with cholesterol and hydrated by aquatic media.[292] Wichayapreechar *et al.*[293] created CA extract-loaded niosomes (CAE-Nio) and niosomes with hyaluronic acid surface modifications (CAE-Nio-HA). The niosomes had high drug loading capacity (% DL) and encapsulation efficiency (% EE), which were respectively 3–7% and 71–77%. When HA was added to niosomes, % DL reduced, zeta-potential elevated, particle size increased in a dose-dependent manner, and % EE was unaltered. The sustained-release profile of CAE-loaded niosomes was controlled by a diffusion-based mechanism. In comparison with CAE-Nio and CAE solution, asiaticoside, a moderately polar molecule from CAE-Nio-HA, was better able to enter the stratum corneum and dermis. For periods longer than four months, CAE-Nio-HA formulations demonstrated better stability at low temperatures (4 °C and 25 °C). The created Nio-HA is a potential AC delivery method that can increase dermal absorption, permeability, and accumulation in healthy epidermis and dermis layers.[293] Kim *et al.*[294] investigated the wound-healing activity of AC-loaded niosomes. The study revealed that prepared niosomes showed better penetration of the drug and the wound healing activity was 3.2 times more than the control group when tested on a full-thickness rat model.[294]

9.6 Nanofibers

Nanofibers have outstanding qualities that promote wound healing.[295] The nanofibers' high surface area to volume ratio,

coupled with their microporous structure, promotes cell adhesion, proliferation, migration, and differentiation, which are all very desirable qualities for tissue engineering applications.[296–298] At the same time, the high permeability and absorption rate may absorb the exudate that has accumulated on the wound surface and keep the environment moist so that it is conducive to the healing process. Additionally, the large surface area makes it easier to load and transport bioactive components like medicines and growth hormones.[299,300] Nanofibers have been proposed as topical drug delivery systems for natural substances.[301,302] Due to increased water retention, weight loss, and a large surface area of the nanofiber mat, the AC was added to ultrafine cellulose acetate electrospun nanofibers, which demonstrated enhanced skin permeability of the drug.[302] Similarly, compared with as-cast films, an ultra-fine cellulose acetate nanofiber mat containing asiaticoside or curcumin demonstrated improved drug release.[303] Zhu *et al.* prepared AC-loaded coaxial electrospun nanofibers for the treatment of profound partial-thickness burn injuries. Vascular endothelial growth factor, proliferating cell nuclear antigen and tumour necrosis factor were upregulated, and interleukin 6 and tumour necrosis factor-alpha were downregulated, in order to improve wound healing *in vivo.*[304] Anand *et al.* prepared AC-loaded nanofibers. In this study, the authors develop and assess a multifunctional nanofibrous scaffold comprising polyvinyl alcohol (PVA), sodium alginate (SA), and silk fibroin (SF), loaded with AC for application in diabetic rats. Scanning electron microscopy (SEM) analysis revealed fibre diameters ranging from 100 to 200 nm and tensile strengths between 12.41 and 16.80 MPa. The cross-linked nanofibers exhibited a sustained release of AC over an extended period. Evaluation on HaCaT cells through MTT and scratch assays confirmed minimal cytotoxicity and significant cell migration, respectively. Antimicrobial testing demonstrated the scaffold's excellent efficacy against *P. aeruginosa* and *S. aureus* bacteria. *In vivo* studies further showcased enhanced wound healing in diabetic rats, and histopathological examinations highlighted the scaffold's ability to restore a normal skin structure. Overall, these findings underscore the potential of the PVA-SA-SF-based nanofibrous scaffold loaded with AC as a multifunctional and effective approach for wound healing in diabetic conditions.[305] Lie *et al.* prepared AC-loaded nanofibers for wound healing. A straightforward blending–centrifugation transport method was utilized to efficiently load hydrophobic AC. The polymer and active ingredients are dissolved in an appropriate solvent throughout the preparation procedure. The drug-soluble solvent was added to the polymer-dissolving solvent in order to dissolve the drug and polymer simultaneously. AC accelerated skin regeneration and reduced scar formation by modulating inflammatory reactions and angiogenesis. The *in vivo* experiments revealed that these AC-laden silk hydrogels have intriguing applications in scarless tissue regeneration.[306]

Due to its extensive therapeutic characteristics, CA has substantial commercial potential. More in-depth study of this plant is clearly required to fully realize its medicinal potential. AC is sold under the brand name of TECA™. TECA™ is CA extract.[307] It contains AC, asiatic acid, and madecassic acid. It improves wound healing, collagen formation, microcirculation, and stretch marks. The therapeutic efficacy of AC is shown in Table 4.

10. Other potential benefits of asiaticoside

AC has numerous therapeutic effects. Apart, from wound healing AC showed antidepressant,[319] anti-diabetic,[320] anti-inflammatory and anti-pyretic activity[321] The versatile therapeutic benefits of AC are discussed below:

10.1 Anti-depressant activity

AC showed excellent anti-depressant-like activity. Liang *et al.* reported the anti-depressant activity of AC. AC was administered to mice in order to observe whether it had any anti-depressant effects using three different tests: a splash test in a chronic mild stress (CMS) model, a tail suspension test (TST), and a forced swimming test (FST). Stressed mice exhibited considerably more grooming activity when AC was administered (10 mg kg^{-1}). AC (10, 20 mg kg^{-1}, P.O) substantially reduced immobility time in the tail suspension test. These findings point to the possibility that AC acts similarly to antidepressants.[322] Luo *et al.* determined whether AC induces an antidepressant-like effect by way of BDNF (brain-derived neurotrophic factor) signalling activation under chronic unpredictable moderate stress (CUMS). The findings demonstrated that the reduced sucrose preference and increased immobility time exhibited in CUMS mice may be corrected by administering asiaticoside to the animals for four weeks. Furthermore, authors discovered that in both non-stressed and CUMS animals, AC up-regulated BDNF, PSD-95, and synapsing-I expression only in the hippocampus. The antidepressant-like effects of AC, however, were entirely nullified by the addition of K252a, an inhibitor of the BDNF receptor tropomyosin-related kinase receptor B (TrkB). The results suggested that the AC may stimulate BDNF signalling in the hippocampus to produce its antidepressant-like effect.[323] Verma *et al.* analyzed the oral administration of AC and its effects on AC distribution in the AC-borneol formula (FAB). AC was detected using HPLC.[324] The effectiveness of FAB and AC as antidepressants was analysed. Behavioural depression paradigms and the chronic unpredictable stress model (CUS) were utilized on rats that had been given the drugs either acutely or chronically. Pathological alterations were revealed by H&E staining, and levels of 5-HT, norephedrine (NE), BDNF, and TNF- were measured in the hippocampus. The injection of FAB, but not AC alone, resulted in the detection of AC in brain tissues from the rats, suggesting that borneol (BOR) facilitated the dispersion of AC in the brain.[325] Wang *et al.* explored the antidepressant-like activity of AC. Authors observed that AC increased the monoamine neurotransmitter levels and counteracted the rise in inflammatory cytokines caused by CMS. Additionally, AC antidepressant and anti-inflammatory effects

Table 4 Nanocarrier mediated delivery of asiaticoside

S. no.	Nanocarrier formulation	Size	*In vitro*/*in vivo* model	Application	Special outcomes	Ref.
1	Nanofiber	—	Sprague–Dawley (SD) rats	Burn wound healing	Nanofiber dressing also showed excellent wound-healing properties in the SD rat burn model	308
2	Nanoparticle	100.2 nm size	Sprague–Dawley rats	Neuroprotective activity	The prepared nanoparticles have the potential to function as a platform technology for neurodegenerative disease treatments	309
3	Lipid nanocarrier (liposome and niosomes)	Liposomes (42.33 ± 0.47 nm) and niosomes (55.73 ± 2.52 nm)	*In vitro* study	Antioxidant activity	Liposome and noisome formulations show promise as transdermal delivery systems for CA extract to enhance antioxidant activity	310
4	Hydrogels		*In vitro* study	Wound healing potential and anti-bacterial activity	The chitosan-based hydrogel preparation was optimized to provide the essential rheological characteristics for the release of the bioactive from the chitosan delivery system. Additionally, it showed adequate antibacterial activity	311
5	Polymeric colloidal	210 nm	*In vitro*	Dermatological and cosmetic applications	The author demonstrated that polymeric colloidal nanocarriers CA are proven to be safe, noncytotoxic, and do not cause cell transformation	312
6	Microneedle	200 μm × 200 μm × 500 μm ($W \times L \times H$)	Diabetic mice	Diabetic foot ulcer	The author concluded that the efficacy of microneedles made of γ-PGA hydrogel combined with AC in promoting the healing process of diabetic foot ulcers, thus providing support for the application of these microneedles in the treatment of chronic wounds	313
7	Transferosomes	27.15 ± 0.95 to 63.54 ± 2.51 nm	*In vitro* study	Hypertrophic scars	These pilot study outcomes support the effectiveness of the asiatic acid-entrapped transferosomal gel	314
8	Micro- and nanoparticles	Nanoparticles (200 ± 5.09 nm) and microparticle (8.79 ± 3.51 μm)	*In vitro* study	Anti-inflammatory	The epigallo-catechin-3-gallate-loaded microscale particles are biocompatible and have a long-lasting anti-inflammatory effect	315
9	Nanostructured lipid carriers	Asiatic acid nanostructured lipid carriers (AA-NLC) (139.30 ± 1.68 nm) and PEGylated asiatic acid nanostructured lipid carriers (P-AA-NLC) (160.50 ± 4.16 nm)	*In vitro* and *in vivo* study	Anti-fibrosis effects	P-AA-NLC may improve asiatic acid's anti-liver fibrosis effects in SD rats and increase AA's gastrointestinal absorption	316
10	Polyurethane foam	228–262 μm	New Zealand white albino rabbit	Partial thickness wound	The prepared polyurethane foam dressing promotes wound healing in rabbits	317
11	Alginate chitosan nanoparticles	486.2 nm	Mouse	Anti-excitotoxicity and neuroprotective action	Biological assessment studies demonstrated that ACNPs exhibit non-toxic effects on mouse neural stem cells (mNSCs). Moreover, these nanoparticles exhibited improved permeability across the blood–brain barrier, leading to a reduction in seizure activity	318

may be mediated *via* modulation of the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signalling pathway.[326] These findings have the potential for advancing AC development as an innovative therapy for the management of depression. However, further research is needed to regulate the therapeutic efficacy of AC in individuals with depression or

related diseases and to determine the mechanism by which it activates PKA signalling in depression.

10.2 Antidiabetic activity

AC also has antidiabetic activity. Fitrianda *et al.* reported the anti-diabetic action of AC in a mouse model. The saponin-rich-fraction, ethanolic extract of AC showed anti-diabetic activity in alloxan-induced diabetic mice. The AC inhibited glucose uptake by healthy cells in the pancreas.[327] In one study, the authors investigated the anti-diabetic activity of AC and *Andrographis paniculata* (AP) in the rat model. AC and AP used in a 30 : 70 ratio, when tested on rat model, exhibit excellent anti-diabetic activity. The combination also showed synergistic HDL-increasing and cholesterol-lowering activity.[328]

10.3 Anti-inflammatory and anti-pyretic activity

Researchers studied how AC affected the activity and expression of nitric oxide synthase in gastric ulcers, finding that it decreased ulcer size in a dose-dependent fashion. Additionally, it suppressed the activity and protein expression of inducible nitric oxide synthase, indicating its anti-inflammatory effect.[329] In a study where the authors compared the anti-inflammatory effects of AC-G and other pure phytoconstituents in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells, it was shown that AC-G greatly suppressed the production of nitric oxide and tumour necrosis factor-alpha.[330] In a dose-dependent way, AC was shown to boost fibronectin mRNA and protein expression in human periodontal ligament cells, while also increasing proliferation and protein synthesis. Matrix metalloproteinase-1 mRNA expression was suppressed by AC, although tissue inhibitor of metalloproteinase-1 mRNA expression was boosted.[331] The anti-inflammatory and anti-pyretic effects of AC were studied, and the results showed that the compound reduced the fever and inflammatory response brought on by LPS in a dose-dependent manner.[332] Analysis of the effects of AC on typical human skin cell activities associated with healing was performed. AC improved initial cell adhesion and migration in skin cells. Even more so, AC induced a proliferation boost in healthy human dermal fibroblasts in cell proliferation assays.[333] In a recent study, AC was investigated for its potential as an anti-inflammatory and immunomodulatory agent during the *in vivo* implantation of electro-spun polylactic-*co*-glycolic acid (PLGA) fibrous scaffolds. These scaffolds are widely used in tissue engineering for various applications, including bone, cartilage, skin, and neural regeneration, as well as drug delivery systems. However, the accumulation of degradation products from the implanted scaffolds triggers a host inflammatory response mediated by innate immune cells, such as dendritic cells, mast cells, granulocytes, and macrophages, hindering the desired tissue regeneration. The study revealed that AC effectively suppressed the expression of M1 (inflammatory) macrophages and inhibited the production of pro-inflammatory cytokines. Simultaneously, it promoted the expression of M2 macrophages, known for releasing anti-inflammatory cytokines. This dual action of AC is crucial in modulating macrophage polarization, which is reversible and holds therapeutic value, particularly in conditions where an imbalance between M1 and M2 macrophages contributes to pathogenesis. By blocking the host inflammatory response, AC demonstrated its potential as a favourable anti-inflammatory drug, offering promising outcomes for the successful implantation of PLGA fibrous scaffolds and, consequently, facilitating desirable tissue regeneration results.[334,335]

10.4 Antibacterial activity

CA shows antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. CA methanolic extract exhibited an inhibitory zone against *Vibrio alginolyticus*, *Vibrio vulnificus*, and *Streptococcus* sp.[336] Antibacterial activity against three *Vibrio* species (*V. harveyi*, *V. alginolyticus*, and *V. parahaemolyticus*) was found in a methanolic extract of CA reported by Sankar *et al.*[337] but not in an acetone, chloroform, or hexane extract.

10.5 Neuroprotective effect

According to research by Ramanathan *et al.*,[338] CA extract prevents the neurodegeneration caused by monosodium glutamate. CA water extract improved glutathione levels and antioxidant defences in brain areas in prepubescent mice exposed to oxidative stress caused by 3-nitropropionic acid.[339,340] A study investigated the *in vitro* performance of asiatic acid (AA) liposomes and surface-modified liposomes of AA, specifically chitosan-coated AA liposomes (CAAL) and stealth AA liposomes (SAAL), as potential therapeutic interventions for Alzheimer's disease. Utilizing Design-Expert software, an optimized formula was derived, and liposomes were prepared through the thin-film hydration method. The formulations were then comprehensively evaluated for various parameters, including compatibility, liposomal vesicle size, drug entrapment, drug content, dispersibility index, and surface morphology using transmission electron microscopy and atomic force microscopy. The release profiles demonstrated that both AA liposome (AAL) and SAAL exhibited sustained-release characteristics, releasing 97.00 ± 0.56% and 86.42 ± 0.38% of the drug over 18 hours, respectively. Notably, chitosan-coated AA liposomes (CAAL) demonstrated a comparable sustained release, with 85.45 ± 0.43% of the drug released within 24 hours. Moreover, the *ex vivo* permeation study indicated that CAAL exhibited superior permeation compared with the other two forms of liposomes.[341] A study conducted by Renju *et al.*, prepared AC-loaded alginate chitosan nanoparticles (ACNPs) for the management of antiproliferative activity in C6 glioma cells. The synthesized ACNPs, characterized by their spherical shape, particle size (200 nm), thermal stability, and acceptable polydispersity index, demonstrated promising properties for drug delivery. The encapsulation of AC within the ACNPs exhibited high efficiency, with 90% encapsulation, and controlled drug release, with only 10% released within 24 hours. The application of ACNPs showed positive outcomes in terms of cell viability and morphology in mouse primary brain astrocyte cells (mBA) cells. However, contrasting results

were observed in C6 glioma cells, where ACNP treatment led to dose-dependent cytotoxicity, late apoptosis, and necrosis. The results of this study indicate that ACNPs exhibit antiproliferative effects on C6 glioma cells by activating the intracellular reactive oxygen species (ROS) pathway, ultimately leading to apoptosis and necrosis. These findings shed light on the intricate mechanistic details involved in addressing brain disorders through the utilization of CA and its phytoconstituents.[342]

11. Future prospective

In the future, the combination of AC and nanotechnology is poised to revolutionize the field of wound care/[343,344] The synergistic potential of AC, a compound derived from CA with known wound healing properties, when harnessed alongside cutting-edge nanotechnological approaches, presents a groundbreaking avenue for transforming traditional wound care paradigms.[345] Further exploration into the optimization of nanocarriers and nano-formulations encapsulating AC could lead to enhanced targeted delivery, controlled release kinetics, and improved stability, increasing its therapeutic efficacy at wound sites.[346] Advanced nanotechnological approaches, such as stimulus-responsive or smart delivery systems, may enable the on-demand release of AC, responding to specific cues present in the wound microenvironment for precise and timely therapeutic interventions.[347] Moreover, the incorporation of innovative biomaterials and bioengineering techniques may facilitate the development of multifunctional scaffolds or dressings capable of simultaneously providing structural support, promoting tissue regeneration, and delivering AC in a controlled manner.[348] Additionally, combining AC with other bioactive agents or growth factors within nanocarriers could potentially create synergistic therapeutic effects, accelerating wound closure, reducing inflammation, and minimizing scar formation.[349] As research progresses, addressing challenges related to standardization, scalability, safety, and regulatory aspects will be pivotal in translating the AC-nanotechnology-driven approaches from bench to bedside. Collaborative efforts across multidisciplinary fields, including nanotechnology, pharmacology, biomaterials science, and clinical medicine, will be crucial in advancing these futuristic wound healing strategies and eventually offering more effective and personalized treatments for diverse wound types and patient populations.

12. Conclusion

The therapeutic potential of AC in wound healing is well-established, attributed to its ability to stimulate collagen biosynthesis. However, the inherent physical properties of AC, including its high molecular weight, poor water solubility, and low permeability, pose significant challenges to its effective topical administration. Nanotechnology emerges as a promising solution to overcome the hurdles associated with AC delivery. By encapsulating AC in nano-carriers, the drug's efficacy, stability, and safety can be significantly improved. These nano-carriers play a pivotal role in facilitating targeted delivery, ensuring efficient distribution of the loaded drug across various skin layers. The utilization of nanotechnology in dermatology represents a breakthrough in enhancing the therapeutic efficacy of AC, particularly in the context of wound healing. The integration of nanotechnology into the delivery of AC presents a transformative approach to unlocking its full therapeutic potential. As research and development in this field continue to advance, it is anticipated that innovative strategies will further enhance the topical delivery of AC, opening new avenues for its application in various medical conditions.

Abbreviations

AC	Asiaticoside
ECM	Extracellular matrix
FGF	Fibroblast growth factor
VEGF	Vascular endothelial growth factor
NDDS	Novel drug delivery systems
SC	Stratum corneum
MMP	Matrix metalloproteinase
AP	*Andrographis paniculata*
CA	*Centella asiatica*
LPS	Lipopolysaccharide
NBGs	Nano-emulsion-based gel

Author contributions

Mohit Kumar: writing – original draft preparation, collecting information, methodology. Devesh Kumar: collecting information, methodology. Syed Mahmood, Varinder Singh and Ayah R. Hilles: conceptualization, collecting information, revising draft. Shruti Chopra and Amit Bhatia: revising draft, and finalizing the manuscript.

Conflicts of interest

The author declares no conflict of interest, financial or otherwise.

Acknowledgements

Research grant (5/8-4/5/Env/2020-NCD-II Dated 22/12/2021) under Indian Council of Medical Research (ICMR), New Delhi, India. The authors would like to thank the Maharaja Ranjit Singh Punjab Technical University (MRSPTU) in Bathinda, India, for providing the research facilities. The authors would like to thank the Indian Council of Medical Research in New Delhi, India.

References

1 M. Kumar, D. Kumar, Y. Garg, S. Mahmood, S. Chopra and A. Bhatia, *Int. J. Biol. Macromol.*, 2023, 127331.
2 M. Kumari and D. K. Nanda, *Burns*, 2023, **49**, 1003–1016.
3 I. Kuchyn and V. Horoshko, *BMC Anesthesiol.*, 2023, **23**, 1–10.
4 K. Raziyeva, Y. Kim, Z. Zharkinbekov, K. Kassymbek, S. Jimi and A. Saparov, *Biomolecules*, 2021, **11**, 700.
5 N. Graves, C. J. Phillips and K. Harding, *Br. J. Dermatol.*, 2022, **187**, 141–148.
6 S. Probst, C. Saini, G. Gschwind, A. Stefanelli, P. Bobbink, M. Pugliese, S. Cekic, D. Pastor and G. Gethin, *Int. Wound J.*, 2021, **10**, 148.
7 K. McDermott, M. Fang, A. J. M. Boulton, E. Selvin and C. W. Hicks, *Diabetes Care*, 2023, **46**, 209–221.
8 P. M. G. Sardo, J. P. F. Teixeira, A. M. S. F. Machado, B. F. Oliveira and I. M. Alves, *J. Tissue Viability*, 2023, **32**, 179–187.
9 C. Siotos, A. M. Bonett, G. Damoulakis, A. Z. Becerra, G. Kokosis, K. Hood, A. H. Dorafshar and D. S. Shenaq, *ePlasty*, 2022, **22**, e19.
10 J. L. Seidelman, C. R. Mantyh and D. J. Anderson, *J. Am. Med. Assoc.*, 2023, **329**, 244–252.
11 D. A. Mengistu, A. Alemu, A. A. Abdukadir, A. Mohammed Husen, F. Ahmed and B. Mohammed, *Inq. J. Heal. Care Organ. Provision, Financ.*, 2023, **60**, 00469580231168746.
12 E. Opriessnig, H. Luze, C. Smolle, A. Draschl, R. Zrim, M. Giretzlehner, L.-P. Kamolz and S. P. Nischwitz, *Burns*, 2023, **49**, 1–14.
13 A. Markiewicz-Gospodarek, M. Kozioł, M. Tobiasz, J. Baj, E. Radzikowska-Büchner and A. Przekora, *Int. J. Environ. Res. Public Health*, 2022, **19**, 1338.
14 N. W. Shammas, *Vasc. Health Risk Manag.*, 2007, **3**, 229–234.
15 M. A. Allison, D. G. Armstrong, P. P. Goodney, N. M. Hamburg, L. Kirksey, K. J. Lancaster, C. I. Mena-Hurtado, S. Misra, D. J. Treat-Jacobson and K. T. White Solaru, *Circulation*, 2023, **148**, 286–296.
16 T. F. Herman and B. Bordoni.
17 L. Cañedo-Dorantes and M. Cañedo-Ayala, *Int. J. Inflammation*, 2019, 3706315.
18 V. Falanga, R. R. Isseroff, A. M. Soulika, M. Romanelli, D. Margolis, S. Kapp, M. Granick and K. Harding, *Nat. Rev. Dis. Primers*, 2022, **8**, 1–21.
19 L. Qiao, Y. Liang, J. Chen, Y. Huang, S. A. Alsareii, A. M. Alamri, F. A. Harraz and B. Guo, *Bioact. Mater.*, 2023, **30**, 129–141.
20 S.-Y. Ren, Y.-S. Liu, G.-J. Zhu, M. Liu, S.-H. Shi, X.-D. Ren, Y.-G. Hao and R.-D. Gao, *World J. Clin. Cases*, 2020, **8**, 5070.
21 S. Zhang, G. Ge, Y. Qin, W. Li, J. Dong, J. Mei, R. Ma, X. Zhang, J. Bai and C. Zhu, *Mater. Today Bio*, 2023, **18**, 100508.
22 S. al Guo and L. A. DiPietro, *J. Dent. Res.*, 2010, **89**, 219–229.
23 M. B. Dreifke, A. A. Jayasuriya and A. C. Jayasuriya, *Mater. Sci. Eng., C*, 2015, **48**, 651–662.
24 T. Maheswary, A. A. Nurul and M. B. Fauzi, *Pharmaceutics*, 2021, **13**, 981.
25 J. M. Reinke and H. Sorg, *Eur. Surg. Res.*, 2012, **49**, 35–43.
26 W. R. Perera, J. R. Hurst, T. M. A. Wilkinson, R. J. Sapsford, H. Müllerova, G. C. Donaldson and J. A. Wedzicha, *Eur. Respir. J.*, 2007, **29**, 527–534.
27 C. Politis, J. Schoenaers, R. Jacobs and J. O. Agbaje, *Front. Physiol.*, 2016, **7**, 507.
28 H. Kirwan and R. Pignataro, in *Patholology and Intervention in Musculoskeletal Rehabilitation*, Elsevier, Philadelphia, US, 2nd edn, 2016, ch. 2, pp. 25–62.
29 D. C. Bosanquet and K. G. Harding, *Wound Repair Regen.*, 2014, **22**, 143–150.
30 E. Lebrun, M. Tomic-Canic and R. S. Kirsner, *Wound Repair Regen.*, 2010, **18**, 433–438.
31 G. Petruk, J. Petrlova, F. Samsudin, R. Del Giudice, P. J. Bond and A. Schmidtchen, *Biomolecules*, 2020, **10**, 1572.
32 M. H. E. Hermans and T. Treadwell, *Microbiol. Wounds*, 2010, 83–134.
33 M. Kumar, P. Keshwania, S. Chopra, S. Mahmood and A. Bhatia, *AAPS PharmSciTech*, 2023, **24**, 1–26.
34 H. J. Lee and Y. J. Jang, *Int. J. Mol. Sci.*, 2018, **19**, 711.
35 S. R. Nussbaum, M. J. Carter, C. E. Fife, J. DaVanzo, R. Haught, M. Nusgart and D. Cartwright, *Value Heal.*, 2018, **21**, 27–32.
36 D. M. Bermudez, D. A. Canning and K. W. Liechty, *J. Pediatr. Urol.*, 2011, **7**, 324–331.
37 W. H. Peranteau, L. Zhang, N. Muvarak, A. T. Badillo, A. Radu, P. W. Zoltick and K. W. Liechty, *J. Invest. Dermatol.*, 2008, **128**, 1852–1860.
38 G. G. Gauglitz, H. C. Korting, T. Pavicic, T. Ruzicka and M. G. Jeschke, *Mol. Med.*, 2011, **17**, 113–125.
39 M. Kumar, S. Mahmood and U. K. Mandal, *Curr. Pharm. Des.*, 2022, **28**, 1480–1492.
40 D. Zhang, G. Cai, S. Mukherjee, Y. Sun, C. Wang, B. Mai, K. Liu, C. Yang and Y. Chen, *ACS Appl. Mater. Interfaces*, 2020, **12**, 5542–5556.
41 S. Guo, Q. Sun, Y. Zhou, S. Tong, X. Sun, K. Li and M. Lv, *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.*, 2020, **26**, e921263–e921261.
42 Y. Har-Shai and C. C. Zouboulis, *Plast. Reconstr. Surg.*, 2015, **136**, 397e–398e.
43 W.-R. Lee, S.-C. Shen, S. A. Al-Suwayeh, H.-H. Yang, C.-Y. Yuan and J.-Y. Fang, *J. Controlled Release*, 2011, **153**, 240–248.
44 Z. Zhang, J. Chen, J. Huang, Y. Wo, Y. Zhang and X. Chen, *Nanoscale Res. Lett.*, 2018, **13**, 1–12.
45 A. J. Singer and R. A. F. Clark, *N. Engl. J. Med.*, 1999, **341**, 738–746.
46 C. D. Marshall, M. S. Hu, T. Leavitt, L. A. Barnes, H. P. Lorenz and M. T. Longaker, *Adv. Wound Care*, 2018, **7**, 29–45.
47 C. Profyris, C. Tziotzios and I. Do Vale, *J. Am. Acad. Dermatol.*, 2012, **66**, 1–10.

48 L. Wang, J. Yang, B. Ran, X. Yang, W. Zheng, Y. Long and X. Jiang, *ACS Appl. Mater. Interfaces*, 2017, **9**, 32545–32553.
49 X. Wan, S. Liu, X. Xin, P. Li, J. Dou, X. Han, I.-K. Kang, J. Yuan, B. Chi and J. Shen, *Chem. Eng. J.*, 2020, **400**, 125964.
50 J. Li, C. Zhou, C. Luo, B. Qian, S. Liu, Y. Zeng, J. Hou, B. Deng, Y. Sun and J. Yang, *Theranostics*, 2019, **9**, 5839.
51 U. Park, M. S. Lee, J. Jeon, S. Lee, M. P. Hwang, Y. Wang, H. S. Yang and K. Kim, *Acta Biomater.*, 2019, **90**, 179–191.
52 M. Hesketh, K. B. Sahin, Z. E. West and R. Z. Murray, *Int. J. Mol. Sci.*, 2017, **18**, 1545.
53 H. D. Zomer, T. da Silva Jeremias, B. Ratner and A. G. Trentin, *Cytotherapy*, 2020, **22**, 247–260.
54 C. Kalirajan and T. Palanisamy, *Adv. Healthcare Mater.*, 2020, **9**, 2000247.
55 X. Zheng, Z. Ding, W. Cheng, Q. Lu, X. Kong, X. Zhou, G. Lu and D. L. Kaplan, *Adv. Healthcare Mater.*, 2020, **9**, 2000041.
56 J. Chen, H. Wang, L. Mei, B. Wang, Y. Huang, G. Quan, C. Lu, T. Peng, X. Pan and C. Wu, *J. Mater. Chem. B*, 2020, **8**, 2573–2588.
57 M. Ekor, *Front. Pharmacol.*, 2014, **4**, 177.
58 M. Sharma, S. Chopra and S. B. Prasad, *Int. J. Pharmacogn. Phytochem. Res.*, 2015, **7**, 197–200.
59 A. K. Khan, S. Kaleem, F. Pervaiz, T. A. Sherazi, S. A. Khan, F. A. Khan, T. Jamshaid, M. I. Umar, W. Hassan and M. Ijaz, *J. Drug Delivery Sci. Technol.*, 2023, **79**, 103987.
60 M. Manconi, M. L. Manca, C. Caddeo, D. Valenti, C. Cencetti, O. Diez-Sales, A. Nacher, S. Mir-Palomo, M. C. Terencio and D. Demurtas, *Nanomedicine*, 2018, **14**, 569–579.
61 M. Manconi, M. L. Manca, C. Caddeo, C. Cencetti, C. di Meo, N. Zoratto, A. Nacher, A. M. Fadda and P. Matricardi, *Eur. J. Pharm. Biopharm.*, 2018, **127**, 244–249.
62 G. Di Fabio, V. Romanucci, C. Di Marino, A. Pisanti and A. Zarrelli, *Curr. Pharm. Biotechnol.*, 2015, **16**, 506–516.
63 P. Monika, M. N. Chandraprabha, A. Rangarajan, P. V. Waiker and K. N. C. Murthy, *Front. Nutr.*, 2022, **127**, 104803.
64 P. S. Murphy and G. R. D. Evans, *Plast. Surg. Int.*, 2012, 190436.
65 T. Dongala, N. K. Katari, S. K. Ettaboina, A. Krishnan, M. M. Tambuwala and K. Dua, *Front. Mol. Biosci.*, 2021, 441.
66 T. Kartnig, *Herbs, Spices, Med. Plants Recent Adv. Bot. Hortic. Pharmacol.*, 2024, **10**, 86.
67 Q. Hou, M. Li, Y. Lu, D. Liu and C. Li, *Exp. Ther. Med.*, 2016, **12**, 1269–1274.
68 C. L. Cheng, J. S. Guo, J. Luk and M. W. L. Koo, *Life Sci.*, 2004, **74**, 2237–2249.
69 S. Bandopadhyay, S. Mandal, M. Ghorai, N. K. Jha, M. Kumar, D. Radha and A. Ghosh, *J. Cell. Mol. Med.*, 2023, **27**, 593–608.
70 Y. Zhou, S. Wang, J. Zhao and P. Fang, *Ann. Transl. Med.*, 2016, 761–769.
71 Z. He, Y. Hu, Z. Niu, K. Zhong, T. Liu, M. Yang, L. Ji and W. Hu, *J. Ethnopharmacol.*, 2023, **302**, 115865.
72 G. M. Seon, M. H. Lee, M.-A. Koo, S. H. Hong, Y. J. Park, H. K. Jeong, B.-J. Kwon, D. Kim and J.-C. Park, *Mater. Sci. Eng., C*, 2021, **121**, 111837.
73 Y. Zhang, Y. Han, J. Dong, F. Li and Y. Sun, *Balkan Med. J.*, 2024, **41**, 23.
74 S. Barge, D. Jade and N. C. Talukdar, in *Potent Anticancer Medicinal Plants*, Apple Academic Press, 2024, pp. 19–37.
75 T. Phaechamud, K. Yodkhum, J. Charoenteeraboon and Y. Tabata, *Mater. Sci. Eng., C*, 2015, **50**, 210–225.
76 N. Namviriyachote, P. Muangman, K. Chinaroonchai, C. Chuntrasakul and G. C. Ritthidej, *Int. J. Biol. Macromol.*, 2020, **143**, 510–520.
77 M. Kumar, R. Dogra and U. K. Mandal, *J. Drug Delivery Sci. Technol.*, 2022, 103533.
78 M. Kumar, U. K. Mandal and S. Mahmood, *Adv. Mod. Approaches Drug Delivery*, 2023, pp. 1–32.
79 R. Jain, I. Sarode, G. Singhvi and S. K. Dubey, *Curr. Pharm. Des.*, 2020, **26**, 4615–4623.
80 J. Prabha, M. Kumar, D. Kumar, S. Chopra and A. Bhatia, *Curr. Drug Delivery*, 2024, **21**, 1082–1105.
81 D. Patel, B. Patel and H. Thakkar, *Eur. J. Lipid Sci. Technol.*, 2021, **123**, 2000264.
82 D. Medina-Cruz, B. Saleh, A. Vernet-Crua, A. Ajo, A. K. Roy and T. J. Webster, in *Wound Healing, Tissue Repair, and Regeneration in Diabetes*, Elsevier, 2020, pp. 439–488.
83 M. R. Farahpour and H. Hamishehkar, *Colloids Surf., A*, 2021, **610**, 125748.
84 A. Barroso, H. Mestre, A. Ascenso, S. Simões and C. Reis, *Nano Sel.*, 2020, **1**, 443–460.
85 A. El Ayadi, J. W. Jay and A. Prasai, *Int. J. Mol. Sci.*, 2020, **21**, 1105.
86 C. Liu, M. H. Y. Teo, S. L. T. Pek, X. Wu, M. L. Leong, H. M. Tay, H. W. Hou, C. Ruedl, S. E. Moss and J. Greenwood, *Diabetes*, 2020, **69**, 2467–2480.
87 S. Wichaiyo, S. Lax, S. J. Montague, Z. Li, B. Grygielska, J. A. Pike, E. J. Haining, A. Brill, S. P. Watson and J. Rayes, *Haematologica*, 2019, **104**, 1648.
88 P. A. Borges, I. Waclawiak, J. L. Georgii, V. d. S. Fraga-Junior, J. F. Barros, F. S. Lemos, T. Russo-Abrahão, E. M. Saraiva, C. M. Takiya and R. Coutinho-Silva, *Front. Immunol.*, 2021, **12**, 651740.
89 R. J. Boucek, *Otolaryngol. Clin. North Am.*, 1984, **17**, 243–264.
90 N. Laurens, P. d Koolwijk and M. P. M. De Maat, *J. Thromb. Haemost.*, 2006, **4**, 932–939.
91 D. M. Monroe and M. Hoffman, *Haemophilia*, 2012, **18**, 11–16.
92 S. Singh, A. Young and C.-E. McNaught, *Surgery*, 2017, **35**, 473–477.
93 B. Guo, R. Dong, Y. Liang and M. Li, *Nat. Rev. Chem.*, 2021, **5**, 773–791.
94 S. Willenborg, L. Injarabian and S. A. Eming, *Cold Spring Harbor Perspect. Biol.*, 2022, **14**, a041216.
95 A. Nurkesh, A. Jaguparov, S. Jimi and A. Saparov, *Front. Cell Dev. Biol.*, 2020, **8**, 638.
96 Z. Xu, S. Han, Z. Gu and J. Wu, *Adv. Healthcare Mater.*, 2020, **9**, 1901502.

97 M. G. Visha and M. Karunagaran, *Int. J. Clin. Correl.*, 2019, **3**, 50–59.
98 M. G. El Baassiri, L. Dosh, H. Haidar, A. Gerges, S. Baassiri, A. Leone, F. Rappa and A. Jurjus, *Burns*, 2023, **49**, 989–1002.
99 E. Grambow, H. Sorg, C. G. G. Sorg and D. Strüder, *Med. Sci.*, 2021, **9**, 55.
100 P. Wei, C. Zhong, X. Yang, F. Shu, S. Xiao, T. Gong, P. Luo, L. Li, Z. Chen and Y. Zheng, *Burns Trauma*, 2020, **8**, tkaa020.
101 S. R. Goldberg and R. F. Diegelmann, *Crit. Limb Ischemia Acute Chronic*, 2017, pp. 131–136.
102 A. W. Jatoi, H. Ogasawara, I. S. Kim and Q.-Q. Ni, *Mater. Lett.*, 2019, **241**, 168–171.
103 H. Ren, F. Zhao, Q. Zhang, X. Huang and Z. Wang, *Burns Trauma*, 2022, **10**, tkac003.
104 J. M. Baron, M. Glatz and E. Proksch, *Dermatology*, 2020, **236**, 593–600.
105 F. Yang, X. Bai, X. Dai and Y. Li, *Regen. Med.*, 2021, **16**, 373–390.
106 P. Krzyszczyk, R. Schloss, A. Palmer and F. Berthiaume, *Front. Physiol.*, 2018, **9**, 419.
107 F. Liaqat, L. Xu, M. I. Khazi, S. Ali, M. U. Rahman and D. Zhu, *Ind. Crops Prod.*, 2023, **204**, 117372.
108 B. R. Albuquerque, M. A. Prieto, M. F. Barreiro, A. Rodrigues, T. P. Curran, L. Barros and I. C. F. R. Ferreira, *Ind. Crops Prod.*, 2017, **95**, 404–415.
109 M. N. Safdar, T. Kausar, S. Jabbar, A. Mumtaz, K. Ahad and A. A. Saddozai, *J. Food Drug Anal.*, 2017, **25**, 488–500.
110 C. Monton, S. Settharaksa, C. Luprasong and T. Songsak, *Rev. Bras. Farmacogn.*, 2019, **29**, 254–261.
111 F. Pittella, R. C. Dutra, D. D. Junior, M. T. P. Lopes and N. R. Barbosa, *Int. J. Mol. Sci.*, 2009, **10**, 3713–3721.
112 C. Zhao, X. He, C. Li, L. Yang, Y. Fu, K. Wang, Y. Zhang and Y. Ni, *Appl. Sci.*, 2016, **6**, 19.
113 M. Garcia-Vaquero, G. Rajauria and B. Tiwari, in *Sustainable seaweed technologies*, Elsevier, 2020, pp. 171–189.
114 M. C. Florczak, *Neurobiol. Aging*, 2015, **36**, 2577–2586.
115 I. E. Orhan, E. Atasu, F. S. Senol, N. Ozturk, B. Demirci, K. Das and N. Sekeroglu, *Ind. Crops Prod.*, 2013, **47**, 316–322.
116 M. A. López-Bascón and M. D. L. De Castro, in *Liquid-phase extraction*, Elsevier, 2020, pp. 327–354.
117 P. N. Kunene and P. N. Mahlambi, *J. Environ. Chem. Eng.*, 2020, **8**, 103665.
118 K. O. Fagbemi, D. A. Aina and O. O. Olajuyigbe, *Sci. World J.*, 2021, **2021**, 1–8.
119 P. T. Selvi, M. S. Kumar, R. Rajesh and T. Kathiravan, *Asian J. Res. Pharm. Sci.*, 2012, **2**, 76–79.
120 M. Rahman, S. Hossain, A. Rahaman, N. Fatima, T. Nahar, B. Uddin and M. A. Basunia, *J. Pharmacogn. Phytochem.*, 2013, **1**, 27–32.
121 W. Thong-On, T. Pathomwichaiwat, S. Boonsith, W. Koo-Amornpattana and S. Prathanturarug, *Sci. Rep.*, 2021, **11**, 22026.
122 A. Yaqub, Z. Iqbal, T. Toyota, N. Chaudhary, A. Altaf and S. R. Ahmad, *Clin Med Bio Chem*, 2020, **8**, 1–9.
123 Y. Shen, A. Liu, M. Ye, L. Wang, J. Chen, X. Wang and C. Han, *Chromatographia*, 2009, **70**, 431–438.
124 S. B. Bagade and M. Patil, *Crit. Rev. Anal. Chem.*, 2021, **51**, 138–149.
125 L. Gomez, B. Tiwari and M. Garcia-Vaquero, in *Sustainable seaweed technologies*, Elsevier, 2020, pp. 207–224.
126 C. Duval, *J. Parkinson's Dis.*, 2016, **6**, 685–698.
127 C. Duval, *Quantum Grav.*, 2014, **31**, 092001.
128 A. Bhatia, B. Singh, S. Wadhwa, K. Raza and O. P. Katare, *Pharm. Dev. Technol.*, 2014, **19**, 160–163.
129 M. Kumar, U. K. Mandal and S. Mahmood, *Dermatological formulations*, Academic Press, 1st edn, 2024.
130 E. Proksch, E. Berardesca, L. Misery, J. Engblom and J. Bouwstra, *J. Dermatolog. Treat.*, 2020, **31**, 716–722.
131 M. J. Blair, J. D. Jones, A. E. Woessner and K. P. Quinn, *Adv. Wound Care*, 2020, **9**, 127–143.
132 X. Liu, B. Testa and A. Fahr, *Pharm. Res.*, 2011, **28**, 962–977.
133 M. Kumar, A. Sharma, S. Mahmood, A. Thakur, M. A. Mirza and A. Bhatia, *J. Dispersion Sci. Technol.*, 2023, 1–14.
134 K. Sugibayashi, *Ski. Permeat. Dispos. Ther. Cosmeceutical Compd*, 2017, pp. 3–11.
135 M. S. Balda and M. R. García-Villegas.
136 S. Nafisi and H. I. Maibach, in *Emerging nanotechnologies in immunology*, Elsevier, 2018, pp. 47–88.
137 M. Elmowafy, *Colloids Surf., B*, 2021, **203**, 111748.
138 E. Arribas-López, N. Zand, O. Ojo, M. J. Snowden and T. Kochhar, *Int. J. Environ. Res. Public Health*, 2022, **19**, 3266.
139 Y. Y. Zhang, L. Chen, L. Zhang and L. Zhang, in *Annual Conference Proceedings of the World Federation of Chinese Materia Medica Committee (11)*, 2011, pp. 352–355.
140 S. Pattnaik, S. Mohanty, S. K. Sahoo and C. Mohanty, *J. Drug Delivery Sci. Technol.*, 2023, 104546.
141 K. Raza, B. Singh, S. Lohan, G. Sharma, P. Negi, Y. Yachha and O. P. Katare, *Int. J. Pharm.*, 2013, **456**, 65–72.
142 K. Raza, O. P. Katare, A. Setia, A. Bhatia and B. Singh, *J. Microencapsul.*, 2013, **30**, 225–236.
143 S. Chaturvedi and A. Garg, *J. Drug Delivery Sci. Technol.*, 2021, **62**, 102355.
144 M. S. Roberts, Y. Mohammed, M. N. Pastore, S. Namjoshi, S. Yousef, A. Alinaghi, I. N. Haridass, E. Abd, V. R. Leite-Silva and H. A. E. Benson, *J. Controlled Release*, 2017, **247**, 86–105.
145 O. Katare, K. Raza, B. Singh and S. Dogra, *Indian J. Dermatol. Venereol. Leprol.*, 2010, **76**, 612.
146 A. Okyar, M. Nuriyev, A. Yildiz, Z. Pala-Kara, N. Ozturk and E. Kaptan, *Arch. Pharmacal Res.*, 2010, **33**, 1781–1788.
147 J. Zhou, G. Feng, W. Zhou, A. Ren, Y. Wu, D. Zhang and H. Dai, *J. Orofac. Orthop.*, 2011, **72**, 457–468.
148 S. Sawatdee, K. Choochuay, W. Chanthorn and T. Srichana, *Acta Pharm.*, 2016, **66**, 233–244.

149 C. Choipang, T. Buntum, P. Chuysinuan, S. Techasakul, P. Supaphol and O. Suwantong, *Polym. Adv. Technol.*, 2021, **32**, 1187–1193.
150 J. Huang, X. Zhou, L. Xia, W. Liu, F. Guo, J. Liu and W. Liu, *Int. Wound J.*, 2021, **18**, 598–607.
151 J.-H. Lee, H.-L. Kim, M. H. Lee, K. E. You, B.-J. Kwon, H. J. Seo and J.-C. Park, *Phytomedicine*, 2012, **19**, 1223–1227.
152 U. K. M. M. Kumar, *J. Clin. Exp. Dermatol. Res.*, 2021, **12**, 1–7.
153 B. Alberts, *Molecular biology of the cell*, Garland science, 2017.
154 H. N. Wilkinson and M. J. Hardman, *Open Biol.*, 2020, **10**, 200223.
155 P. Shu, L. Tianzeng, L. Yeyang, C. Xiaodong, X. Julin, X. Yingbin and Q. Shaohai, *Acta Acad. Med. Mil. Tertiae*, 2005, **27**, 49–52.
156 A. Shukla, A. M. Rasik and B. N. Dhawan, *Phyther. Res.*, 1999, **13**, 50–54.
157 B. H. I. Ruszymah, S. R. Chowdhury, N. A. B. A. Manan, O. S. Fong, M. I. Adenan and A. Bin Saim, *J. Ethnopharmacol.*, 2012, **140**, 333–338.
158 B. S. Shetty, S. L. Udupa, A. L. Udupa and S. N. Somayaji, *Int. J. Low. Extrem. Wounds*, 2006, **5**, 137–143.
159 A. S. Ahmed, M. Taher, U. K. Mandal, J. M. Jaffri, D. Susanti, S. Mahmood and Z. A. Zakaria, *BMC Complementary Altern. Med.*, 2019, **19**, 1–7.
160 S. G. Jin, K. S. Kim, A. M. Yousaf, D. W. Kim, S. W. Jang, M.-W. Son, Y. H. Kim, C. S. Yong, J. O. Kim and H.-G. Choi, *Int. J. Pharm.*, 2015, **490**, 240–247.
161 H. A. Azis, M. Taher, A. S. Ahmed, W. Sulaiman, D. Susanti, S. R. Chowdhury and Z. A. Zakaria, *S. Afr. J. Bot*, 2017, **108**, 163–174.
162 A. S. Ahmed, U. K. Mandal, M. Taher, D. Susanti and J. M. Jaffri, *Pharm. Dev. Technol.*, 2018, **23**, 751–760.
163 S. Chatterjee, T. Prakash, D. Kotrsha, N. R. Rao and D. Goli, *Chin. Med.*, 2011, **2**, 138.
164 A. Shukla, A. M. Rasik, G. K. Jain, R. Shankar, D. K. Kulshrestha and B. N. Dhawan, *J. Ethnopharmacol.*, 1999, **65**, 1–11.
165 Y. Liu, J. Zhao, X. Mu, J. Deng, X. Wu, W. He, Y. Liu, R. Gu, F. Han and X. Nie, *J. Ethnopharmacol.*, 2024, **319**, 117266.
166 J. Somboonwong, M. Kankaisre, B. Tantisira and M. H. Tantisira, *BMC Complementary Altern. Med.*, 2012, **12**, 1–7.
167 V. Paocharoen, *J. Med. Assoc. Thai.*, 2010, **93**, S166–S170.
168 G. Calapai, *Eur. Med. Agency*, 2012, 44.
169 X. Feng, D. Huang, D. Lin, L. Zhu, M. Zhang, Y. Chen and F. Wu, *J. Investig. Surg.*, 2021, e202116068.
170 F. Zhang and W. Lineaweaver, *Ann. Plast. Surg.*, 2011, **66**, 581–582.
171 A. Devkota, S. Dall'Acqua, S. Comai, G. Innocenti and P. K. Jha, *Biochem. Syst. Ecol.*, 2010, **38**, 12–22.
172 L. Lu, K. Ying, S. Wei, Y. Fang, Y. Liu, H. Lin, L. Ma and Y. Mao, *Int. J. Dermatol.*, 2004, **43**, 801–807.
173 L. Lu, K. Ying, S. Wei, Y. Liu, H. Lin and Y. Mao, *Br. J. Dermatol.*, 2004, **151**, 571–578.
174 H. Rosen, A. Blumenthal and J. McCallum, *Proc. Soc. Exp. Biol. Med.*, 1967, **125**, 279–280.
175 J. C. Watkins and D. E. Jane, *Br. J. Pharmacol.*, 2006, **147**, S100–S108.
176 S. Jayanarayanan, S. Smijin, K. T. Peeyush, T. R. Anju and C. S. Paulose, *Chem.-Biol. Interact.*, 2013, **201**, 39–48.
177 F. Qi, L. Yang, Z. Tian, M.-G. Zhao, S. Liu and J. An, *Neural Regen. Res.*, 2014, **9**, 1275.
178 L. Wang, T. Guo, Y. Guo and Y. Xu, *Mol. Med. Rep.*, 2020, **22**, 2364–2372.
179 H. Yu, Z. Yin, S. Yang, S. Ma and R. Qu, *Phyther. Res.*, 2016, **30**, 469–475.
180 R.-H. Du, J. Tan, X.-Y. Sun, M. Lu, J.-H. Ding and G. Hu, *Int. J. Neuropsychopharmacol.*, 2016, **19**, pyw037.
181 X.-Y. Deng, H.-Y. Li, J.-J. Chen, R.-P. Li, R. Qu, Q. Fu and S.-P. Ma, *Behav. Brain Res.*, 2015, **291**, 12–19.
182 C. C. Barua, P. Haloi, B. Saikia, K. Sulakhiya, D. C. Pathak, S. Tamuli, H. Rizavi and X. Ren, *Pharm. Biol.*, 2018, **56**, 245–252.
183 C. Zhang, S. Chen, Z. Zhang, H. Xu, W. Zhang, D. Xu, B. Lin and Y. Mei, *Med. Sci. Monit.*, 2020, **26**, e920325–e920321.
184 S. Chen, Z.-J. Yin, C. Jiang, Z.-Q. Ma, Q. Fu, R. Qu and S.-P. Ma, *Pharmacol. Biochem. Behav.*, 2014, **122**, 7–15.
185 Y. Luo, C. Fu, Z. Wang, Z. Zhang, H. Wang and Y. Liu, *Mol. Med. Rep.*, 2015, **12**, 8294–8300.
186 A. Bandawane and R. Saudagar, *J. Drug Delivery Ther.*, 2019, **9**, 517–521.
187 M. Kumar, A. R. Hilles, S. H. A. Almurisi, A. Bhatia and S. Mahmood, *JCIS Open*, 2023, 100095.
188 M. Ghezzi, S. Pescina, C. Padula, P. Santi, E. Del Favero, L. Cantù and S. Nicoli, *J. Controlled Release*, 2021, **332**, 312–336.
189 B. S. Makhmalzade and F. Chavoshy, *J. Adv. Pharm. Technol. Res.*, 2018, **9**, 2.
190 A. S. Manjappa, P. S. Kumbhar, A. B. Patil, J. I. Disouza and V. B. Patravale, *Crit. Rev. Ther. Drug Carr. Syst.*, 2019, 1–58.
191 A. Parra, I. Jarak, A. Santos, F. Veiga and A. Figueiras, *Materials*, 2021, **14**, 7278.
192 P. A. Penttilä, S. Vierros, K. Utriainen, N. Carl, L. Rautkari, M. Sammalkorpi and M. Österberg, *Langmuir*, 2019, **35**, 8373–8382.
193 R. Paliwal, S. R. Paliwal, R. Kenwat, B. Das Kurmi and M. K. Sahu, *Expert Opin. Ther. Pat.*, 2020, **30**, 179–194.
194 M. Liu, J. Wen and M. Sharma, *Curr. Pharm. Des.*, 2020, **26**, 3203–3217.
195 V. R. Salvi and P. Pawar, *J. Drug Delivery Sci. Technol.*, 2019, **51**, 255–267.
196 I. Chauhan, M. Yasir, M. Verma and A. P. Singh, *Adv. Pharm. Bull.*, 2020, **10**, 150.
197 B. Begines, T. Ortiz, M. Pérez-Aranda, G. Martínez, M. Merinero, F. Argüelles-Arias and A. Alcudia, *Nanomaterials*, 2020, **10**, 1403.

198 N. S. Ayumi, S. Sahudin, Z. Hussain, M. Hussain and N. H. A. Samah, *Drug Delivery Transl. Res.*, 2019, **9**, 482–496.
199 L.-L. Wang, S. Huang, H.-H. Guo, Y.-X. Han, W.-S. Zheng and J.-D. Jiang, *Drug Des., Dev. Ther.*, 2020, **14**, 2125–2126.
200 S. Hiranphinyophat, A. Otaka, Y. Asaumi, S. Fujii and Y. Iwasaki, *Colloids Surf., B*, 2021, **197**, 111423.
201 N. H. Che Marzuki, R. A. Wahab and M. Abdul Hamid, *Biotechnol. Biotechnol. Equip.*, 2019, **33**, 779–797.
202 Y. Singh, J. G. Meher, K. Raval, F. A. Khan, M. Chaurasia, N. K. Jain and M. K. Chourasia, *J. Controlled Release*, 2017, **252**, 28–49.
203 W. Cai, P. C. Calder, M. F. Cury-Boaventura, E. De Waele, J. Jakubowski and G. Zaloga, *Nutrients*, 2018, **10**, 776.
204 J. Alvarez-Trabado, Y. Diebold and A. Sanchez, *Int. J. Pharm.*, 2017, **532**, 204–217.
205 S. Tamizharasi, A. Dubey, V. Rathi and J. C. Rathi, *J. Young Pharm.*, 2019, **1**, 205–209.
206 B. A. Witika, L. L. Mweetwa, K. O. Tshiamo, K. Edler, S. K. Matafwali, P. V. Ntemi, M. T. R. Chikukwa and P. A. Makoni, *J. Pharm. Pharmacol.*, 2021, **73**, 1427–1441.
207 R. Bartelds, M. H. Nematollahi, T. Pols, M. C. A. Stuart, A. Pardakhty, G. Asadikaram and B. Poolman, *PLoS One*, 2018, **13**, e0194179.
208 G. Sharma, K. Thakur, A. Mahajan, G. S. Randhawa, B. Singh and O. P. Katare, in *NanoAgroceuticals & NanoPhytoChemicals*, CRC Press, 2018, pp. 277–295.
209 A. Saxena and M. L. Kori, *J. Adv. Sci. Res.*, 2020, **11**, 27–34.
210 A. A. Kassem and S. H. Abd El-Alim, *Nanopharmaceuticals Princ. Appl*, 2021, vol. 2, 155–209.
211 M. Barani, E. Sangiovanni, M. Angarano, M. A. Rajizadeh, M. Mehrabani, S. Piazza, H. V. Gangadharappa, A. Pardakhty, M. Mehrbani and M. Dell'Agli, *Int. J. Nanomed.*, 2021, **16**, 6983.
212 P. Morganti, E. Ruocco, R. Wolf and V. Ruocco, *Clin. Dermatol.*, 2001, **19**, 489–501.
213 K. Raza, M. Kumar, P. Kumar, R. Malik, G. Sharma, M. Kaur and O. P. Katare, *BioMed. Res. Int.*, 2014, 1–10.
214 P. Desai, R. R. Patlolla and M. Singh, *Mol. Membr. Biol.*, 2010, **27**, 247–259.
215 S. Chatterjee, K. Ghosal, M. Kumar, S. Mahmood and S. Thomas, *J. Drug Delivery Sci. Technol.*, 2022, 104095.
216 S. Onoue, S. Yamada and H.-K. Chan, *Int. J. Nanomed.*, 2014, **9**, 1025.
217 L. B. Lopes, *Pharmaceutics*, 2014, **6**, 52–77.
218 S. B. Shirsand, M. S. Para, D. Nagendrakumar, K. M. Kanani and D. Keerthy, *Int. J. Pharm. Investig.*, 2012, **2**, 201.
219 R. Muzzalupo, L. Tavano, R. Cassano, S. Trombino, T. Ferrarelli and N. Picci, *Eur. J. Pharm. Biopharm.*, 2011, **79**, 28–35.
220 D. Aggarwal and I. P. Kaur, *Int. J. Pharm.*, 2005, **290**, 155–159.
221 N. Ravouru, P. Kondreddy and D. Korakanchi, *Curr. Drug Discovery Technol.*, 2013, **10**, 270–282.
222 J. Jiménez-López, I. Bravo-Caparrós, L. Cabeza, F. R. Nieto, R. Ortiz, G. Perazzoli, E. Fernández-Segura, F. J. Cañizares, J. M. Baeyens and C. Melguizo, *Biomed. Pharmacother.*, 2021, **133**, 111059.
223 M. Walunj, S. Doppalapudi, U. Bulbake and W. Khan, *J. Liposome Res.*, 2020, **30**, 68–79.
224 M. L. Moyá, M. López-López, J. A. Lebrón, F. J. Ostos, D. Pérez, V. Camacho, I. Beck, V. Merino-Bohórquez, M. Camean and N. Madinabeitia, *Pharmaceutics*, 2019, **11**, 69.
225 S. Mahira, N. Kommineni, G. M. Husain and W. Khan, *Biomed. Pharmacother.*, 2019, **110**, 803–817.
226 M. Chang, M. Wu and H. Li, *Drug Delivery*, 2018, **25**, 1984–1995.
227 A. Jose, S. Labala and V. V. K. Venuganti, *J. Drug Targeting*, 2017, **25**, 330–341.
228 X. Gai, L. Cheng, T. Li, D. Liu, Y. Wang, T. Wang, W. Pan and X. Yang, *AAPS PharmSciTech*, 2018, **19**, 700–709.
229 Z. Yang, L. Tian, J. Liu and G. Huang, *J. Liposome Res.*, 2018, **28**, 322–330.
230 A. Jafari, S. Daneshamouz, P. Ghasemiyeh and S. Mohammadi-Samani, *J. Liposome Res.*, 2022, 1–19.
231 M. M. Maniyar, A. S. Deshmukh and S. J. Shelke, *Asian J. Pharm. Res.*, 2022, **12**, 225–228.
232 V. Dave, D. Kumar, S. Lewis and S. Paliwal, *Int. J. Drug Delivery*, 2010, 81–92.
233 S. Jain, N. Patel, P. Madan and S. Lin, *Pharm. Dev. Technol.*, 2015, **20**, 473–489.
234 T. Limsuwan and T. Amnuaikit, *Procedia Chem.*, 2012, **4**, 328–335.
235 Z. Hou, Y. Li, Y. Huang, C. Zhou, J. Lin, Y. Wang, F. Cui, S. Zhou, M. Jia and S. Ye, *Mol. Pharm.*, 2013, **10**, 90–101.
236 A. R. Sahu and S. B. Bothara, *Int. J. Res. Med.*, 2015, **4**, 94–99.
237 N. Karimi, B. Ghanbarzadeh, H. Hamishehkar, F. Keyvani, A. Pezeshki and M. M. Gholian.
238 A. Riva, M. Ronchi, G. Petrangolini, S. Bosisio and P. Allegrini, *Eur. J. Drug Metab. Pharmacokinet.*, 2019, **44**, 169–177.
239 Š. Koudelka and J. Turánek, *J. Controlled Release*, 2012, **163**, 322–334.
240 K. V. Clemons, J. Capilla, R. A. Sobel, M. Martinez, A.-J. Tong and D. A. Stevens, *Antimicrob. Agents Chemother.*, 2009, **53**, 1858–1862.
241 A. K. Singh and S. S. Narsipur, *J. Transplant.*, 2011, 480642.
242 J. Pardeike, A. Hommoss and R. H. Müller, *Int. J. Pharm.*, 2009, **366**, 170–184.
243 T. Liu, Y. Lu, R. Zhan, W. Qian and G. Luo, *Adv. Drug Delivery Rev.*, 2023, **193**, 114670.
244 E. A. Madawi, A. R. Al Jayoush, M. Rawas-Qalaji, H. E. Thu, S. Khan, M. Sohail, A. Mahmood and Z. Hussain, *Pharmaceutics*, 2023, **15**, 657.
245 I. Theochari, A. Xenakis and V. Papadimitriou, in *Smart Nanocontainers*, Elsevier, 2020, pp. 315–341.

246 A.-M. Matei, C. Caruntu, M. Tampa, S. R. Georgescu, C. Matei, M. M. Constantin, T. V. Constantin, D. Calina, D. A. Ciubotaru and I. A. Badarau, *Appl. Sci.*, 2021, **11**, 4915.
247 B. Farasati Far, M. R. Naimi-Jamal, M. Sedaghat, A. Hoseini, N. Mohammadi and M. Bodaghi, *J. Funct. Biomater.*, 2023, **14**, 115.
248 M. Liu, X. Wei, Z. Zheng, Y. Li, M. Li, J. Lin and L. Yang, *Int. J. Nanomed.*, 2023, 1537–1560.
249 A. A. Shaikh, J. B. Pawar, S. J. Anbhule and V. V. Kakade.
250 S. Borkar, H. Yadav and A. Raizaday, *Nasal drug delivery*, **2023**, 361–379.
251 M. Kumar, R. Dogra and U. K. Mandal, *Curr. Drug Delivery*, 2023, **20**, 841–856.
252 M. Kumar, D. Kumar, S. Kumar, A. Kumar and U. K. Mandal, *Curr. Pharm. Des.*, 2022, **28**, 3212–3224.
253 D. Guimarães, A. Cavaco-Paulo and E. Nogueira, *Int. J. Pharm.*, 2021, **601**, 120571.
254 M. Kumar, A. Thakur, U. K. Mandal, A. Thakur and A. Bhatia, *AAPS PharmSciTech*, 2022, **23**, 244.
255 S. S. Chrai, R. Murari and I. Ahmad, *Biopharm*, 2001, **14**, 10.
256 T. M. Allen and P. R. Cullis, *Adv. Drug Delivery Rev.*, 2013, **65**, 36–48.
257 L. Sercombe, T. Veerati, F. Moheimani, S. Y. Wu, A. K. Sood and S. Hua, *Front. Pharmacol.*, 2015, **6**, 286.
258 X. Huang, M. Li, R. Bruni, P. Messa and F. Cellesi, *Int. J. Pharm.*, 2017, **524**, 279–289.
259 B. S. Pattni, V. V. Chupin and V. P. Torchilin, *Chem. Rev.*, 2015, **115**, 10938–10966.
260 C. Zylberberg and S. Matosevic, *Drug Delivery*, 2016, **23**, 3319–3329.
261 A. Bhatia, B. Singh, S. Bhushan and O. P. Katare, *Drug Dev. Ind. Pharm.*, 2010, **36**, 350–354.
262 A. Bhatia, B. Singh, K. Raza, A. Shukla, B. Amarji and O. P. Katare, *J. Drug Targeting*, 2012, **20**, 544–550.
263 M. Rahman, V. Kumar, S. Beg, G. Sharma, O. P. Katare and F. Anwar, *Artif. Cells, Nanomed., Biotechnol.*, 2016, **44**, 1597–1608.
264 S. Saesoo, I. Sramala, A. Soottitantawat, T. Charinpanitkul and U. R. Ruktanonchai, *J. Microencapsul.*, 2010, **27**, 436–446.
265 D. Paolino, D. Cosco, F. Cilurzo, E. Trapasso, V. M. Morittu, C. Celia and M. Fresta, *J. Controlled Release*, 2012, **162**, 143–151.
266 L. Feng, Y. Liu, Y. Chen, Q. Xiang, Y. Huang, Z. Liu, W. Xue and R. Guo, *Adv. Healthcare Mater.*, 2024, 2203201.
267 C. Singh, S. Purohit, M. Singh and B. L. Pandey, *J. Drug Delivery Res.*, 2013, **2**, 18–27.
268 M. Saini and J. K. Malik, *SAR J. Anat. Physiol.*, 2022, **3**, 9–16.
269 S. B. Sharma, S. Jain and K. Ganesan, *J. Drug Delivery Ther.*, 2019, **9**, 338–342.
270 R. Arshady, *J. Controlled Release*, 1990, **14**, 111–131.
271 P. Blasi, *J. Pharm. Investig.*, 2019, **49**, 337–346.
272 Y. W. Chien, *Novel Drug Delivery Systems*, CRC Press, Florida, US, 2nd edn, 1991.
273 B. S. Prasad, V. R. M. Gupta, N. Devanna and K. Jayasurya, *J. Glob. Trends Pharm. Sci.*, 2014, **5**, 1961–1972.
274 C.-Z. Zhang, J. Niu, Y.-S. Chong, Y.-F. Huang, Y. Chu, S.-Y. Xie, Z.-H. Jiang and L.-H. Peng, *Eur. J. Pharm. Biopharm.*, 2016, **109**, 1–13.
275 T. G. Mason, J. N. Wilking, K. Meleson, C. B. Chang and S. M. Graves, *J. Phys.: Condens. Matter*, 2006, **18**, R635.
276 O. Sonneville-Aubrun, J.-T. Simonnet and F. L'alloret, *Adv. Colloid Interface Sci.*, 2004, **108**, 145–149.
277 K. Bouchemal, S. Briançon, E. Perrier and H. Fessi, *Int. J. Pharm.*, 2004, **280**, 241–251.
278 S. F. Tan, H. R. F. Masoumi, R. A. Karjiban, J. Stanslas, B. P. Kirby, M. Basri and H. Bin Basri, *Ultrason. Sonochem.*, 2016, **29**, 299–308.
279 H. Li, Q. Peng, Y. Guo, X. Wang and L. Zhang, *Int. J. Nanomed.*, 2020, **15**, 3123.
280 M. Hanifah and M. Jufri, *J. Young Pharm.*, 2018, **10**, 404.
281 V. J. Mohanraj and Y. Chen, *Trop. J. Pharm. Res.*, 2006, **5**, 561–573.
282 S. Bhatia, in *Natural polymer drug delivery systems*, Springer, 2016, pp. 33–93.
283 M. Dadwal, D. Solan and H. Pradesh, *J. Adv. Pharm. Educ. Res.*, 2010, 381–387.
284 V. B. Kadam, K. B. Dhanawade, V. A. Salunkhe and A. Ubale, *J. Curr. Pharm. Res.*, 2014, **4**, 1318.
285 M. Kumar and U. K. Mandal, *Drug Delivery Lett.*, 2021, **11**, 195–202.
286 P. B. R. da Rocha, B. dos Santos Souza, L. M. Andrade, J. L. V. dos Anjos, S. A. Mendanha, A. Alonso, R. N. Marreto and S. F. Taveira, *J. Drug Delivery Sci. Technol.*, 2019, **50**, 305–312.
287 M. C. Kwon, W. Y. Choi, Y. C. Seo, J. S. Kim, C. S. Yoon, H. W. Lim, H. S. Kim, J. hee Ahn and H. Y. Lee, *J. Biotechnol.*, 2012, **157**, 100–106.
288 S. Liu, Y. Zhao, M. Li, L. Nie, Q. Wei, O. V. Okoro, H. Jafari, S. Wang, J. Deng and J. Chen, *Chem. Eng. J.*, 2023, 143016.
289 S. Narisepalli, S. A. Salunkhe, D. Chitkara and A. Mittal, *Int. J. Pharm.*, 2023, **631**, 122508.
290 R. M. Handjani-Vila, A. Ribier, B. Rondot and G. Vanlerberghie, *Int. J. Cosmet. Sci.*, 1979, **1**, 303–314.
291 J. Kemps and D. A. Crommelin, *Pharm. Weekbl*, 1988, **123**, 355–363.
292 M. Malhotra and N. K. Jain, *Indian Drugs*, 1994, **31**, 81.
293 P. Wichayapreechar, S. Anuchapreeda, R. Phongpradist, W. Rungseevijitprapa and C. Ampasavate, *J. Liposome Res.*, 2020, **30**, 197–207.
294 D.-W. Kim, M.-H. Cho, S.-Y. Park, J.-H. Lee, G.-W. Lee, M.-S. Park, J.-K. Park and U.-K. Jee, *J. Pharm. Investig.*, 2002, **32**, 291–297.
295 M. Kumar, Y. Ge, A. R. Hilles, A. Bhatia and S. Mahmood, *Int. J. Biol. Macromol.*, 2023, 123696.
296 Z. Ma, M. Kotaki, R. Inai and S. Ramakrishna, *Tissue Eng.*, 2005, **11**, 101–109.

297 M. Alavi and A. Nokhodchi, *Cellulose*, 2022, 1–17.
298 M. Momin, Z. Patel, S. Gharat, M. Altabakha, A. Ashames and S. Boddu, *Crit. Rev. Ther. Drug Carr. Syst.*, 2022, 83–118.
299 Z. Aytac and T. Uyar, *Appl. Polym. Nanofibers*, 2022, pp. 202–254.
300 C. Gao, L. Zhang, J. Wang, M. Jin, Q. Tang, Z. Chen, Y. Cheng, R. Yang and G. Zhao, *J. Mater. Chem. B*, 2021, **9**, 3106–3130.
301 L. Kumar, S. Verma, K. Joshi, P. Utreja and S. Sharma, *Future J. Pharm. Sci.*, 2021, **7**, 1–17.
302 O. Suwantong, U. Ruktanonchai and P. Supaphol, *Polymer*, 2008, **49**, 4239–4247.
303 O. Suwantong, U. Ruktanonchai and P. Supaphol, *J. Biomed. Mater. Res., Part A*, 2010, **94**, 1216–1225.
304 L. Zhu, X. Liu, L. Du and Y. Jin, *Biomed. Pharmacother.*, 2016, **83**, 33–40.
305 S. Anand, P. S. Rajinikanth, D. K. Arya, P. Pandey, R. K. Gupta, R. Sankhwar and K. Chidambaram, *Pharmaceutics*, 2022, **14**, 273.
306 L. Liu, Z. Ding, Y. Yang, Z. Zhang, Q. Lu and D. L. Kaplan, *Biomater. Sci.*, 2021, **9**, 5227–5236.
307 J. T. James, *Determination and manipulation of biologically active triterpenoid secondary metabolites in Centella asiatica*, University of Johannesburg, South Africa, 2013.
308 W. Han, L. Wang, J. Sun, Y. Shi, S. Cui, D. Yang, J. Nie and G. Ma, *ACS Appl. Bio Mater.*, 2013, 10418–10422.
309 N. Raval, P. Barai, N. Acharya and S. Acharya, *Artif. Cells, Nanomed., Biotechnol.*, 2018, **46**, 832–846.
310 B. Pamornpathomkul, W. Rangsimawong, T. Rojanarata, P. Opanasopit, C. Chaiyodsilp and T. Ngawhirunpat, in *MATEC Web of Conferences*, EDP Sciences, 2018, vol. 192, p. 1016.
311 K. Witkowska, M. Paczkowska-Walendowska, T. Plech, D. Szymanowska, B. Michniak-Kohn and J. Cielecka-Piontek, *Int. J. Mol. Sci.*, 2023, **24**, 17229.
312 A. G. M. Perez, J. M. Machado, K. C. Manhani, P. Leo, P. Noriega and M. H. A. Zanin, *SN Appl. Sci.*, 2020, **2**, 1–12.
313 P. Wang, Y. Wang, Y. Yi, Y. Gong, H. Ji, Y. Gan, F. Xie, J. Fan and X. Wang, *J. Nanobiotechnol.*, 2022, **20**, 259.
314 S. A. T. Opatha, R. Chutoprapat, P. Khankaew, V. Titapiwatanakun, W. Ruksiriwanich and K. Boonpisuttinant, *Int. J. Pharm.*, 2023, 123738.
315 Y. R. Wu, H. J. Choi, Y. G. Kang, J. K. Kim and J.-W. Shin, *Int. J. Nanomed.*, 2017, 7007–7013.
316 X. Chen, Y. Zhang, P. Zhao, Y. Chen, Y. Zhou, S. Wang and L. Yin, *Drug Dev. Ind. Pharm.*, 2020, **46**, 57–69.
317 N. Namviriyachote, V. Lipipun, Y. Akkhawattanangkul, P. Charoonrut and G. C. Ritthidej, *Asian J. Pharm. Sci.*, 2019, **14**, 63–77.
318 R. Kunjumon, G. Viswanathan, D. V. Jayasree, P. G. Biju, P. Prakash, B. C. P. Sasidharan and S. Baby, *Can. J. Chem.*, 2022, **100**, 396–404.
319 A. G. Bertollo, M. E. D. Mingoti, J. Medeiros, G. B. da Silva, G. T. Capoani, H. Lindemann, J. V. Cassol, D. Manica, T. Oliveira and M. L. Garcez, *Pharmacol. Res. - Mod. Chin.*, 2022, 100032.
320 M. Oboh, L. Govender, M. Siwela and B. N. Mkhwanazi, *Molecules*, 2021, **26**, 7243.
321 K. Wu, G. Yao, X. Shi, H. Zhang, Q. Zhu, X. Liu, G. Lu, L. Hu, W. Gong and Q. Yang, *Mol. Immunol.*, 2021, **130**, 122–132.
322 X. Liang, Y. N. Huang, S. W. Chen, W. J. Wang, N. Xu, S. Cui, X. H. Liu, H. Zhang, Y. N. Liu and S. Liu, *Pharmacol. Biochem. Behav.*, 2008, **89**, 444–449.
323 L. Luo, X.-L. Liu, R.-H. Mu, Y.-J. Wu, B.-B. Liu, D. Geng, Q. Liu and L.-T. Yi, *Brain Res. Bull.*, 2015, **114**, 62–69.
324 R. K. Verma, K. G. Bhartariya, M. M. Gupta and S. Kumar, *Phytochem. Anal.*, 1999, **10**, 191–193.
325 T. Hou, X. Li and C. Peng, *Neurosci. Lett.*, 2017, **646**, 56–61.
326 Y. Zhang, X. Meng and K. Liu, *J. Bioenerg. Biomembr.*, 2022, **54**, 9–16.
327 E. Fitrianda, E. Y. Sukandar, E. Elfahmi and I. K. Adnyana, *Asian J. Pharm. Clin. Res.*, 2017, **10**, 268–272.
328 A. E. Nugroho, N. Y. Lindawati, K. Herlyanti, L. Widyastuti and S. Pramono.
329 J. S. Guo, C. L. Cheng and M. W. L. Koo, *Planta Med.*, 2004, **70**, 1150–1154.
330 N. X. Nhiem, B. H. Tai, T. H. Quang, P. Van Kiem, C. Van Minh, N. H. Nam, J.-H. Kim, L.-R. Im, Y.-M. Lee and Y. H. Kim, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1777–1781.
331 N. Nowwarote, T. Osathanon, P. Jitjaturunt, S. Manopattanasoontorn and P. Pavasant, *Phyther. Res.*, 2013, **27**, 457–462.
332 J. Wan, X. Gong, R. Jiang, Z. Zhang and L. Zhang, *Phyther. Res.*, 2013, **27**, 1136–1142.
333 Y. He, X. Peng, L. Zheng, Y. Tang, J. Li and X. Huang, *J. Gastrointest. Oncol.*, 2021, **12**, 196.
334 S. C. Funes, M. Rios, J. Escobar-Vera and A. M. Kalergis, *Immunology*, 2018, **154**, 186–195.
335 J. Huang, X. Zhou, Y. Shen, H. Li, G. Zhou, W. Zhang, Y. Zhang and W. Liu, *J. Biomed. Mater. Res., Part A*, 2020, **108**, 69–80.
336 L. S. Wei, N. Musa, C. T. Sengm, W. Wee and N. A. M. Shazili, *Afr. J. Biotechnol.*, 2008, **7**, 2275–2278.
337 G. K. Sankar, K. Ramamoorthy, K. Sakkaravarthi and A. Elavarsi, *Der Pharm. Sin.*, 2010, **1**, 17–22.
338 M. Ramanathan, S. Sivakumar, P. R. Anandvijayakumar, C. Saravanababu and P. R. Pandian, *Indian J. Exp. Biol.*, 2007, **45**, 425–431.
339 G. K. Shinomol, *Neurotoxicology*, 2008, **29**, 948–957.
340 G. K. Shinomol and H. Ravikumar, *Phyther. Res.*, 2010, **24**, 885–892.
341 N. Dhas, H. S. Preetha, A. Dubey, G. Ravi, I. Govindan, A. Rama, A. Naha and S. Hebbar, *J. Appl. Pharm. Sci.*, 2022, **12**, 71–81.
342 R. Kunjumon, G. Viswanathan and S. Baby, *Brain Behav. Immun. Integr.*, 2024, 100043.
343 A. Roy and N. Bharadvaja, *Curr. Trends Biomed. Eng. Biosci.*, 2017, **5**, 1–5.

344 M. A. Barkat, Harshita, S. S. Das, S. Beg and F. J. Ahmad, *Nanophytomedicine Concept to Clin*, 2020, pp. 1–17.
345 S. Ghosh, B. Sarkar, C. S. Ranadheera and S. Thongmee, in *Nanotechnology and In Silico Tools*, Elsevier, 2024, pp. 75–87.
346 F. Ebau, A. Scano, M. L. Manca, M. Manconi, V. Cabras, M. Pilloni and G. Ennas, *J. Biomed. Mater. Res., Part A*, 2023, **111**, 300–308.
347 N. A. Jusril, S. I. Abu Bakar, K. A. Khalil, W. M. Md Saad, N. K. Wen and M. I. Adenan, *Evidence-Based Complement. Altern. Med.*, 2022, 1–18.
348 M.-S. Huang, P. Chanapongpisa, P. Yasurin, K. Kitsubthawee, J. Phetsom and I. Lindayani, *Appl. Sci. Eng. Prog.*, 2020, **13**, 11–18.
349 J. Huang, Y. Gong, K. Liu, J. Chen and X. Zhou, *Explor. Res. Hypothesis Med.*, 2023, **8**, 319–337.