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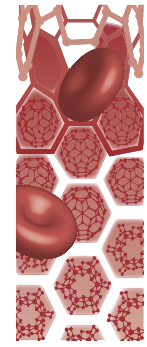

The significance of quercetin-loaded advanced nanoformulations for the management of diabetic wounds

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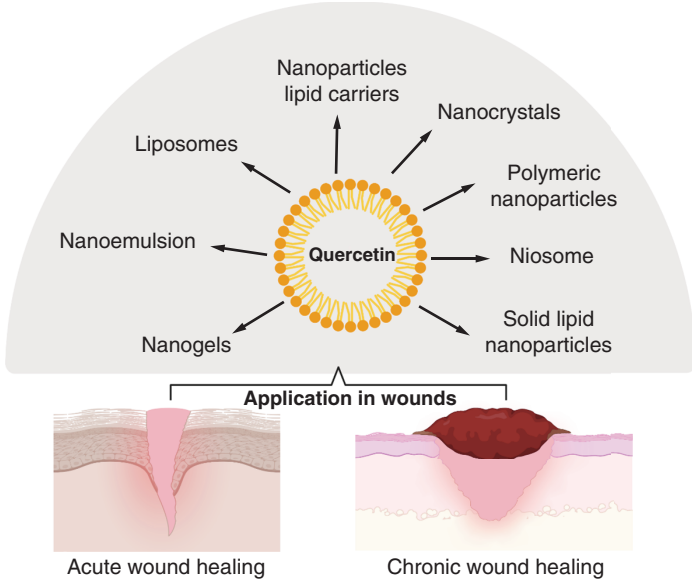
Quercetin is a well-known plant flavanol that exhibits multiple biological activities, including antioxidant, anti-inflammatory and anticancer activities. The role of quercetin in wound healing has been widely explored by a range of researchers in different models. However, the physicochemical properties, such as solubility and permeability, of this compound are low, which ultimately limits its bioavailability on the target site. To overcome these limitations for successful therapy, scientists have developed a range of nanoformulations that provide effective therapeutic potential. In this review, the broad mechanism of quercetin for acute and chronic wounds is covered. A compilation of recent advances on the horizon of wound healing via quercetin is incorporated with several advanced nanoformulations.

Graphical abstract:



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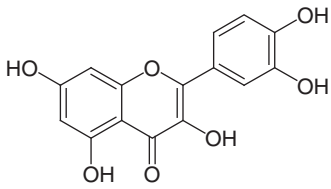

Figure 1. Chemical structure of quercetin.

Diabetes is a systemic disease that results in hyperglycemia due to a lack of circulating insulin hormone or the presence of cells or organs that are insulin resistant [1]. Various complications are associated with diabetes, including eye disease, cardiovascular disease, renal disorder and impaired wound healing [2]. Wound healing is an extremely intricate and well-coordinated process. It occurs in a series of overlaying phases – namely, hemostasis, inflammation, proliferation and remodeling [3] – employing various cell types and releasing many cytokines and growth factors [4]. When one or more of the healing processes are obstructed or damaged, wounds may become refractory. Additionally, the obstruction in the mechanism of wound healing of diabetic patients is complicated due to multiple symptoms, including cellular inflammation, vascular occlusion over deposition of extracellular matrix, cell aging and phenotypic abnormalities in macrophages taking part in the process [2]. Diabetic wounds pose major public health issues worldwide, including in the USA [1]. According to International Diabetes Federation, 415 million adults aged 20–79 years have diabetes globally, and this is expected to increase to 642 million by 2040 [2]. The WHO indicates that the prevalence of diabetes is increasing greatly in low- and middle-income countries such as China and India. In India, the prevalence of diabetes has been rising consistently since 1990 and rapidly since 2000. Data show that 77 million individuals had diabetes in 2019; by 2045, the number is expected to increase to more than 134 million [5].

Similar to cancer and neurodegenerative disorders, oxidative stress is strongly associated with the prevalence of diabetes. Numerous studies have demonstrated that oxidative stress plays a significant role in the onset, progression and development of diabetes and its related consequences [6]. Hence, the role of antioxidants in diabetes has received much attention. Among other flavonoids, quercetin (3,3′,4′,5,7-pentahydroxyflavone; QCN) is one of the potent compounds commonly found in fruits and vegetables (e.g., apples, berries, onions, seeds, nuts, flowers, barks, brassica vegetables, tea and leaves) that possess antiproliferative and anti-inflammatory activity [7,8]. The chemical structure of QCN is shown in Figure 1. QCN has therapeutic potential in glycolysis hindrance, osteoporosis, macromolecule synthesis, cardiovascular disease, pulmonary-related disorders, antiaging, various cancers and wound healing [9]. The application of QCN for wound healing is important mainly because of its free radical scavenging potential and ability to reduce inflammation. In addition, it enhances collagen production and protects tissues from oxidative damage. An effective skin regeneration procedure usually slows inflammation and may change the wound from acute to chronic [10]. Moreover, it can also inhibit histamine discharge and release and proinflammatory cytokine expression in mast cells, thus hampering the swelling of acute skin [2]. Recently, a study by Vinay *et al.* revealed that QCN ameliorated the antioxidant proportion in wounds of diabetic rats and activated the proliferation phase, which promoted rapid wound healing compared with a control group [11]. Also, in another study by Ahmed *et al.* showed QCN possess hypoglycemic and hypolipidemic potential in diabetic induced rat. This study also showed a significant improvement in wound healing in diabetic rats with the application of quercetin [12].

Various treatment options are available to heal wounds, including synthetic chemical compounds, but these have a range of limitations that reduce their efficacy. Conventional treatment options for diabetes treatment include antihyperglycemic agents; however, these possess major drawbacks such as severe hypoglycemia, weight gain, decreased therapeutic efficacy caused by improper or ineffective dosage regimen, low potency and altered side effects due to drug metabolism and a lack of target specificity, as well as issues with solubility and permeability [13]. To overcome these limitations, advanced nanoformulations have been proposed and investigated in different diseases including diabetic wounds. These advanced formulations offer a lot of advantages, including increasing drug solubility, reducing dosage, quick onset of action, controlled drug release, fewer side effects, optimized drug delivery, extended drug half-life, reduced patient variability and optimized bioavailability; all these properties improve the overall therapeutic efficacy. Hence, different research groups have developed various nanoformulations and tested them *in vitro* and *in vivo* to ensure an effective option for wound healing [14]. Such nanoformulations

include polymeric nanoparticles, nanoemulsions (NEs), liposomes (LPs), niosomes (NSs), solid-lipid nanoparticles, nanogels and nanocrystals, which have shown potential to improve the condition of wounds [14].

Therefore, this review covers the application of quercetin to heal diabetic wounds. The sequences and process involved in developing and treating acute and chronic wounds are discussed. In addition, the mechanism of how the quercetin acts against the development and generation of wounds is reviewed. Next, different approaches for wound treatment, such as advanced nanotechnological-based formulation, are covered. The last section focuses on current trends and challenges for diabetic wound management.

Topical delivery of QCN

Although lipophilic molecules can permeate by disrupting the stratum corneum (SC) layer quickly, the poor aqueous solubility of QCN makes it challenging to permeate through human skin. The partition coefficient is not a sufficient parameter to determine the skin absorption of a drug. However, various physical and chemical characteristics, such as molecular size, dosage form, Log P and aqueous solubility, play a crucial role in determining the absorption and permeation behavior of the drug across the skin barrier [15]. The antioxidant properties of QCN effectively scavenge free radicals, which are associated with the development of inflammation and improve the disease condition. However, QCN effectiveness for topical antioxidants is limited by its minimal skin permeability in addition to skin deposition.

Additionally, the effect of QCN is greatly limited due to poor hydrophilicity. Various researchers have tried to ameliorate QCN solubility with the addition of ethanol. In general, a greater concentration of ethanol is not recommended for the topical route due to skin irritation. Thus, to deliver QCN efficiently, a suitable carrier is required [16] and QCN incorporation in the collagen matrix was suggested before confirming the moderate release and optimal activity of QCN.

Furthermore, collagen allows for new cell development. Biodegradation of the collagen constituent follows a process similar to usual wound healing; native enzymatic pathways are associated with further degradation of embedded collagen without causing a harmful reaction. In studies on topical delivery of QCN, its characteristics of free radical scavenging exhibited significantly enhanced wound-healing efficacy and skin regeneration of tissue damaged by oxidative stress. In addition, administration via the topical route may be dependent on the drug's hydrophilic or lipophilic potentiality, along with molecular size. Drug administration through this route enables noninvasive, self-medication. Additionally, compared with oral or parenteral drug delivery, topical administration reduces repeated dosage regimens and promotes continuous maintenance of drug plasma concentration for a prolonged duration. Drug administration via topical routes has accomplished a longer journey, and considerable advancements in this area have been made. Thus, to deliver the optimal concentration of QCN to the wound area, researchers have incorporated QCN in different nanoformulations – such as NEs, nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), nanogels (NGs) and nanocreams – to enhance drug permeation through topical delivery [17,18].

Moreover, regarding topical administration, two inconsistent terms are usually resolved. First, SC is modified, which normally acts as a hurdle for drug permeation. Second, the drug accumulating within SC is forced to get distributed in deeper skin layer. NE has specific capabilities that can modify the SC layer and help the drug distribute into a deeper layer of the skin [19]. Further, drug permeation via the skin is invariably associated with the particle size of NEs. Lipid-based formulations such as NEs aid in drug delivery via topical administration because it is somewhat challenging to achieve permeability in the systemic circulation. Accordingly, surfactant-based emulsions act through other permeation methods. These types of transformable formulations regulate the skin's permeability, thereby enhancing skin permeation [20,21]. Moreover, NE based on surfactant tentatively interrupts the cell's disposition of SC if applied at a greater concentration and improves absorption of the drug through paracellular and transcellular mechanisms [18].

Another study carried out *in vitro* skin permeation by applying QCN SLN and NLC preparations; the vital distinguishing characteristic among these formulations is oleic acid availability. Comparable nonhomogenized developments (with and without oleic acid, incorporating equal lipid concentration as in the NLC and SLN preparations), having particle diameter within the micrometer range, were used as the control fabrications. The superior topical delivery of QCN observed from both the lipid based nanosystems compared to the control formulation (particles in the micrometer range) can be possibly explained by the increased surface area/contact surface of the active compound with the skin corneocytes, higher occlusive effect and increased hydration of the

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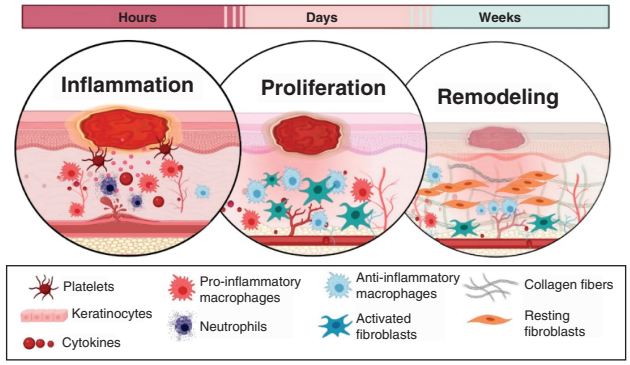

Figure 2. Phases of wound healing. This illustration shows a crucial cellular population's involvement in wound healing management.

SC that has been associated in general with lipid nanoparticles. Moreover, NEs consisting of semisolid components are fabricated in such a way that they aid NE delivery over the skin surface in the unaltered state [22].

Wound healing

The normal healing wound process comprises various well-organized interactions that occur at the molecular and cellular levels at different stages, including hemostasis, inflammation, migration and cell proliferation, in addition to tissue regeneration. Wound healing is considered a complicated process that is affected by several factors. At each stage of the healing process, various specific growth factors (GFs) and cytokines should interact with other GFs, their receptors and elements of extracellular matrix (ECM) at their target sites [23] (Figure 2). Wound healing occurs throughout the tissue after impairment, although it is focused on repairing missing or damaged tissue. The preliminary stage of healing activity is hemostasis, which begins immediately after the wound occurs and attempts to stop the hemorrhage and minimize microorganisms from spreading inside the body. Hemostasis is a process of coagulation followed by vasoconstriction, platelet accumulation and clotting, ultimately resulting in a scab, which protects the injured tissue [24]. During hemostasis, platelets release several GFs, such as EGF, TGF-β, IGF and PDGF. These GFs are associated with the stimulation of endothelial cells, fibroblasts and macrophages at the enclosed sites [25]. The inflammatory stage begins concurrently with hemostasis and is evidenced by the discharge of diverse proinflammatory cytokines, proteases, cationic peptides, reactive oxygen species and GFs, which clean the wound. GFs such as PDGF, TGF-β, EGF and FGF are involved in the predominant interaction between cells and their ECM, activating deposition, morphogenesis, enlargement and differentiation of the cell. After hemorrhage, healing activity is associated with the relocation and permeation of inflammation-induced cells into the wound. Macrophages, lymphocytes and neutrophils play several roles, including enhancement of the inflammatory reaction, hindrance of penetrating extracellular pathogens, removal of germs and activation of keratinocytes, fibroblasts and angiogenesis [26]. After hemorrhage and inflammation, fibroblasts and epithelial cells shift to the impaired site. At this time, epithelial cells remove dead cells, and fibroblasts produce the major constituents of the ECM, such as collagen, fibronectin, hyaluronic acid (HA), glycosaminoglycans and proteoglycans, which strengthen the skin [27]. As lymphatic vessel and capillary development progress, granulation tissue is also reproduced at the injured site (neovascularization). At the remodeling stage, the new tissue progressively matures until its characteristics and configuration are close to that of undamaged tissue. The eventual objective of the wound healing process is the remodeling of the impaired skin and reduced scarring [25].

Chronic wound healing

A chronic wound is defined as an injury that fails to follow the normal wound healing process in a sequential and timely manner. Factors contributing to incurable wounds include infection, necrotic tissue and the vascular supply. In addition, various physical and psychological factors, such as nutritional status (malnutrition), disease (e.g., diabetes, cancer, arthritis and renal impairment), age and mental health problems, can all impact wound healing [28]. Healing wounds is a pivotal clinical issue in diabetic patients and is the most common cause of minimal extremity excision. Persistent wounds include venous leg ulcers, pressure ulcers, arterial ulcers and diabetic foot ulcers (DFUs). Among these, DFUs are reasonably prevalent, with almost 20% of diabetic patients having at least one over their lifetime; the patients often require surgery, potentially causing chronic wounds. Peripheral neuropathy is predominantly associated with DFUs, both sensory and motor, along with vascular ailments with repeated moderate trauma related to higher glucose values.

When the four stages of wound healing are interrupted, healing is delayed, and many changes occur. Frequent complications associated with chronic injury are the secretion of matrix metalloproteinases (MMPs) and other proteases owing to the higher proportion of inflammatory cells. Consequently, cytokine deficiency occurs; specifically, GFs facilitate the required bimolecular and cellular signals before ordinary healing [23]. Macrophages are an important cell in the innate immune system that are required for wound repair. Evidence shows that their actions are altered in diabetic wounds. In typical injuries, macrophages shift to another phenotype stage, including proinflammatory to propreparative, eventually promoting tissue development. In diabetes, macrophages cannot activate tissue regeneration [29].

Diabetes creates high blood glucose-associated metabolic complications that hamper wound healing. These involve advanced glycation end-product deposition in the systemic circulation, which impedes the activities of skin and inflammatory cells and enhances ECM stiffness, oxidative stress, inhibition of micro- and macro-circulatory functions and induction of lower oxygen perfusion. Moreover, people with DFUs are more prone to repeated ulceration, amputation and mortality. These severe consequences have led to significant attention being paid to curing diabetic wounds and limb salvage over the past decade [30]. At the nonhealing edge of DFUs, impedance of migration, higher proliferation and insufficient differentiation of keratinocytes occurs. Fibroblasts exhibit a phenotypic transformation along with reduced migration and multiplication, but these have the potential to react to the supplementary delivery of cellular therapy and GFs [31].

During normal wound healing, the keratinocytes support wound reepithelialization via induced migration and mitosis at the wound site and surrounding area in the epidermis. Fibroblasts move to the impaired area adjacent to the wound as well. In chronic injuries, slow reepithelialization occurs due to microbial load, exudates, local ischemia, tissue hypoxia and extensive concentrations of inflammatory cytokines, causing a chronic inflammation. Furthermore, the interaction between cell at this stage is disturbed and probably exhibits elevated cellular senescence, in addition to reduced cellular response to GFs. Inflammatory cells are deposited at the wound site in a chronic wound; thus, disruption in the sequential healing process of a chronic inflammatory site thus occurs [32]. Impeded monocyte and neutrophil infiltration are important factors in persistent injuries. Neutrophils emit several enzymes, such as collagenase, that deteriorate elastase and ECM and damage prohealing factors. There is also depleted cellular keratinocyte and fibroblast activity at the periphery of the inflammation due to the extensive concentration of inflammatory cytokines, ECM depletion due to high MMP function and hindrance of prohealing elements, which further attract neutrophils and repeat the process. This unmanageable and repeated inflammatory feedback impedes wound healing, drastically slowing the process of reepithelialization [33]. Moreover, in normal wound healing, angiogenesis exists at an adequate equilibrium along the progression of vessel extension and enlargement, in addition to vessel remodeling and dormancy. Hyperglycemia can considerably influence this balance, impeding better wound healing, tissue maturation and restoration of a normal vascular system. For diabetic patients, the higher glucose level in the blood is the main reason for the various micro- and macro-vascular difficulties that eventually impact angiogenesis. Further, inadequate angiogenesis contributes considerably to the pathological process of delayed wound healing in diabetes, along with minor and major vascular disorders. Although a hyperglycemic state is linked to angiogenic deficiency, induced or reduced angiogenesis may occur in diabetes depending on the pathogenesis. Research has demonstrated that diabetes-associated modifications in the angiogenesis response may be either tissue or organ dependent. However, angiogenesis is reduced in diabetes. Consequently, development of new blood vessels is reduced, diminishing the appearance of inflammatory cells and GFs and ultimately leading to delayed wound healing [34]. The overall difference between normal and chronic wound healing is demonstrated in Table 1.

In the context of wound healing, the effects exerted by the anti-inflammatory and antioxidant properties of QCN relate to its therapeutic potential [11] and have shown tremendous ability to heal any kind of wound. QCN acts differently at each stage of wound healing (inflammatory, proliferation and remodeling stage) and improves the wound condition. At the inflammatory stage, QCN decreases inflammation and oxidative stress, which can slow the healing process [40]. In so doing, it aids in the migration of immune cells to the wound site, which is important for the removal of debris and the initiation of the repair process. In the proliferation stage, QCN initiates the growth and migration of new cells, which is necessary for wound repair [28]. By promoting the growth and migration of new cells, QCN closes the wound and begins the process of tissue regeneration. In the remodeling stage, QCN supports new blood vessel formation and collagen deposition, which are necessary for the development of new tissue. Through these processes, it strengthens the newly formed tissue and improve its resistance to future

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Table 1. Difference between acute and chronic wound healing.

Parameters	Acute wound healing	Chronic wound healing	Ref.
Common occurrence	Any age group	Older people suffering from pathological conditions such as diabetes mellitus, vascular disease and obesity	[23]
Healing duration	A few days to 1 month	1–2 years or longer	[35,36]
Physiological process (hemostasis, inflammation, proliferation and maturation)	Eventually results in restored structural integrity	Fails to proceed or is interrupted	[37]
Characteristics	• Scar formation on the epidermis • Apoptosis • Relocation of dermis	• Exudation • Repeated infection • Tissue necrosis • Decreased angiogenesis • Overproduction of reactive oxygen species	[23]
Re-epithelialization process	Rapid, due to keratinocytes support	Delayed because of bacterial load, local ischemia, tissue hypoxia etc.	[38]
Angiogenesis	Almost balanced	Significantly disturbed	[39]

injury [40]. A plethora of research has investigated the role of QCN at the various wound stages, showing significant therapeutic effects in the preclinical context; however, translation of QCN to the clinic remains to be explored.

Therapeutic approaches for diabetic wound healing

The self-remodeling potential of human skin after an injury may be altered under situations such as skin loss, severe burns, chronic injuries, incurable ulcers and diabetes. Improper healing can result in a chronic wound, increasing the possibility of infection and impacting the patient's well-being and quality of life. Chronic injuries such as ischemic wounds and venous ulcers are characterized by reduced self-regeneration, usually because of pathogenic colonization, vascular inadequacy and diabetes, leading to a problematic and delayed healing course [24]. Such wounds are among most painful, disabling and costly skin problems and are therefore an important clinical and social issue. Chronic impairments may necessitate longer hospital stays; procurement of highly specialized wound protection products, such as medicated dressings, increasing clinical costs. Although various medical processes have been examined, the therapeutic alternatives for chronic injuries are still insufficient. To overcome this problem, numerous approaches have been studied as potential treatments to heal these wounds [41,42].

Previously, honey-based medicaments were assessed in both experimental research and clinical settings to evaluate their wound healing action [43]. Topical dressings help to heal chronic wounds by reducing the microbial load and supporting a moist environment at the surrounding site. Similarly, antimicrobial agents delivered through the topical route have demonstrated minimal resistance compared with antibiotics [44]. Common topical antimicrobials include povidone-iodine, chlorhexidine, silver nitrate, silver sulfadiazine and peroxidase. Collagen-containing decellularized dressings transport collagen to facilitate a scaffold for keratinocyte and fibroblast migration around the wound. These dressings may be able to modify the environment surrounding chronic injuries by efficiently altering the function of cytokines and GFs and inhibiting GF degeneration [45]. Additionally, negative pressure wound therapy (NPWT) is a novel therapeutic option for DFUs. Preclinical findings have revealed that NPWT enhances blood flow; eliminates exudate, proinflammatory cytokines and pathogens from the wound area; and minimizes tissue edema. NPWT is used for severe diabetic foot impairments; however, it is restricted for patients suffering from ulceration of active hemorrhage [46]. Another important therapeutic approach for DFUs is hyperbaric oxygen therapy (HBOT), which helps elevate oxygen concentrations in hypoxic injuries, increase leukocyte activity, reduce activity of inflammatory cytokines and stimulate angiogenesis. This treatment involves the delivery of 100% oxygen as a complementary therapeutic approach for patients with complicated foot infections in soft tissue and osteomyelitis who have not responded to traditional therapy [47]. Revascularization is pivotal in diabetic and peripheral arterial patients who are predisposed to ischemic ulceration; however, this should be carried out before debridement or drainage [48]. The therapeutic approaches available and their benefits in diabetic wound care are shown in Table 2.

Mi *et al.* investigated the role of QCN in wound healing and demonstrated that cutaneous wounds were healed in the mice through the Wnt/β-catenin signaling pathway. These findings revealed that the proinflammatory cytokines were significantly reduced after administration of QCN. The increased level of glutathione in the QCN-treated wounds demonstrated the antioxidant potential of QCN. Interestingly, upregulated proteins such as Wnt and β-catenin showed the crucial role of QCN in the wound healing [52]. Figure 3 illustrates the QCN treatment

Table 2. Various therapeutic approaches for wound healing.

Therapeutic approaches	Significance in wound healing	Ref.
Topical dressings	Reduces bacterial burden Maintains a moist wound environment	[43]
Dressings containing topical antibiotics	Minimal antibiotic resistance	[49]
Decellularized collagen dressings	Keratinocyte and fibroblast migration to the wound site through collagen delivery Changes the chronic injury environment by altering the action of cytokines and growth factors Protects growth factors from degradation	[50,51]
Negative pressure wound therapy	Improves blood circulation Diminishes tissue edema Eliminates exudate, proinflammatory cytokines and pathogens from the wound site	[46]
Hyperbaric oxygen therapy	Elevates oxygen concentrations in hypoxic injuries Boosts leukocyte and fibroblast activity Slow regulation of inflammatory cytokines Promotes angiogenesis	[47]

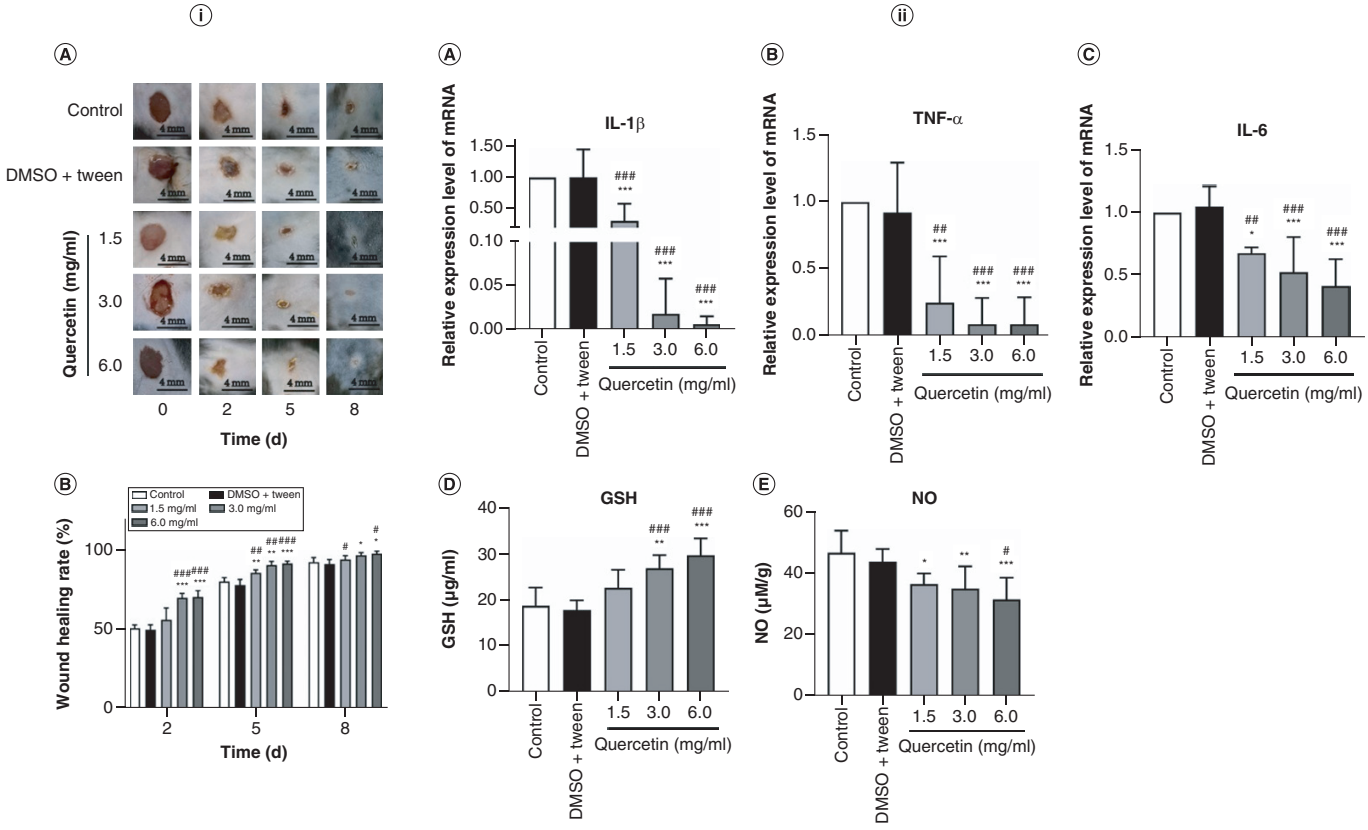

Figure 3. Various findings of quercetin to heal the wounds. (i) The treatment of animals with the quercetin (QCN) at different dose, the therapeutic effects of QCN can be clearly seen that it is dose-dependent effect **(A),** percentage wound healing with the different dose of QCN and compared with control group **(B)**; **(ii)** The comparison of QCN dose and its effects on the different inflammatory cytokines which indicated the anti-inflammatory and antioxidant effects of QCN **(A–E)**.
The figures were reproduced with permission [52].

in mice and its role in regulating the different inflammatory cytokines.

Mechanism of QCN in wound healing

QCN has exhibited several actions in molecular- and animal-based models, varying from preserving cells from UV irradiation to promoting restorative action in wound healing [53]. QCN may also have antiaging activity due to its anti-inflammatory properties. As a lipid peroxidation inhibitor, QCN protects skin from dehydration. Due to the resistance of MMP action, QCN may inhibit skin collagen from deteriorating during inflammatory

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feedback in response to external aging factors [54,55]. The broad range of biological actions associated with QCN, including collagen deposition, antioxidant and anti-inflammation activity, angiogenesis and fibroblast enlargement, it is considered useful for wound care. Topical application of QCN at a concentration of 0.3% remarkably accelerates wound closure, increases regeneration of the epithelial layer and diminishes oxidative stress [7]. Additionally, it promotes the protection of keratinocytes from exogeneous oxidizing agents, aids free radical scavenging activities, inhibits the depletion of endogenous antioxidants and after exposure to UV, impedes lipid peroxidation [56]. It also possesses a sufficient range of anti-inflammatory properties. It is more potent than other flavonoids in impeding activities on NF-kB and the emission of various proinflammatory cytokines. NF-kB is a transcription factor that plays a crucial role in the regulation of inflammation and immune response. It is triggered by the response of various cellular stresses and signals (exogenous and endogenous), including those associated with injury and tissue damage [57]. In the context of wound healing, NF-kB upregulates the inflammatory response by promoting the expression of various proinflammatory cytokines (TNF-α, IL-β) and chemokines [58]. These molecules initiate the process of tissue repair by recruiting the immune cells at the injury site. In addition, it also plays a critical role in differentiation and proliferation of cells during the proliferative stage of wound healing. It has been reported that it promotes the migration of fibroblasts and the development and formation of new blood vessels, which are highly important for tissue regeneration [59]. The role of NF-kB is not limited to this stage of wound healing; it also has effects in the remodeling stage, upregulating the production of collagen and extracellular matrix, which ultimately supports and strengthens newly developed tissue [60]. However, excessive or prolonged activation of NF-kB signaling can lead to chronic inflammation and delay wound healing. Therefore, the proper regulation of NF-kB signaling is crucial for optimal wound healing [61].

QCN exhibits antiaging properties on middle-aged keratinocytes and supports regeneration of terminally senescent cells. A wound treated with QCN should display rapid wound recovery due to the aforementioned biological characteristics [62]. In addition, the delivery of this compound also favors the regulation of VEGF, TGF-β1, IL-10, α-SMA, CD31, GAP-43 and PCNA concentrations. Slow-modulation of TNF-α has also been shown, revealing the anticipated QCN ability to heal injuries. Some findings have also demonstrated that QCN therapy ameliorated wound care by inhibiting the MAPK pathway [63].

QCN-loaded conventional approaches for wound healing

The antioxidant and free radical scavenging potential of QCN and its effective anti-inflammatory activity, even in low doses, highlight the potential utilization of this flavonoid for wound management. A complex physiological balancing mechanism is associated with wound healing. Application of QCN during wound healing is useful to suppress uncontrolled inflammation. Inflammation hampers the skin regeneration process and can transform the wound state from acute to chronic [54]. Various conventional approaches of QCN have been applied to wound healing. Traditional topical preparations such as gels, ointments, emulsions and creams are the main strategies for fabricating QCN [7,64]. In addition, wound dressings and skin grafts have been used to manage wounds [65]. In 2002, a study by Gomathi *et al.* examined *in vivo* healing ability of QCN on male albino Wistar rats. In this study, 1 mM concentration of QCN was incorporated into collagen films. The results indicates that QCN introduced collagen films and showed a remarkable level of wound contraction compared with the control group and the collagen-alone-treated group. Reduction of the wound surface in each group was 80, 57 and 60%, respectively. Furthermore, collagen containing QCN enhanced the concentration of hydroxyproline in the granulation tissue ranging between 0.78 in the control group and 1.84/100 mg granulation tissue. This reveals the increased collagen production in the granulation tissue. In 2010, Ahmed *et al.* examined healing of aphthous ulceration by applying QCN cream in 40 male patients in a randomized clinical trial. In this study, mouthwash containing benzydamine hydrochloride was applied to the control group and QCN cream was directly applied on their ulcers. After 10 days, when comparing the average ulcer size, the lesions in the QCN-treated group were smaller than those in the untreated group, and the size difference among two groups was significant [66]. Mehmet *et al.* topically applied QCN gel to improve wound healing in Wistar rats. Their results confirmed that QCN-loaded gel led to a significant improvement in wound healing compared with other groups, highlighted by enhancement and reduction of fibroblasts and inflammatory cells, respectively. However, collagen coalescence was similar between the treated groups [67]. In addition, Yin *et al.* also performed the wound healing efficacy of QCN in pressure ulcer lesions via topical administration. This study revealed that QCN hastened wound closure as shown by a cell scratch assay. Furthermore, in an ischemia–reperfusion (I/R) injury model, QCN therapy markedly expedited wound closure and decreased immune cell filtration and synthesis of proinflammatory cytokines [68].

The signaling experiment of their research exhibited treatment using this molecule hindered MAPK without activating NFκB. QCN treatment ameliorated the process of impairment healing in I/R lesions by preventing MAPK pathway. As a result, Yin *et al.* concluded that QCN might be a promising therapeutic compound for the management of pressure ulcers [68]. Bhatia *et al.* also examined the wound healing ability of isoquercetin-based cream on scald burn injury in rats. This research showed that the wound contraction rate was significantly elevated, and the duration of epithelialization was less in groups treated with isoquercetin-based cream compared with the control group. In this study, the most remarkable findings were achieved with isoquercetin cream at a concentration of 0.06% w/w. In a histological study, this concentration of isoquercetin revealed nearly full reepithelialization in addition to restructuring of the wound tissue [69]. Doersch *et al.* assessed the QCN impact on wound healing with alteration in αV and β1 integrin expression. In this study, 100 µl of 10 mM QCN solution was topically applied in C57Bl/6J mice. The results demonstrated that the wound healed in 14 days in both the QCN-treated and control group. However, QCN-treated animals showed the reduction in fibrosis and scar formation at the wound site, revealing effective therapeutic potential of QCN in wound healing [70]. Kant *et al.* showed the effectiveness of 0.3% quercetin ointment on diabetic wounds in rats. Their findings showed a notable reduction in expression levels of TNF-a, IL-1b and MMP-9 and increased IL-10, VEGF and TGFb1. Moreover, histopathological and immunohistochemical results showed better healing outcomes in diabetic wounds treated with QCN compared with untreated wounds. In our own investigation, diabetes wounds treated with QCN also exhibited early myofibroblast and epithelial layer development compared with diabetic control group wounds, contributing to the group's rapid contraction [3].

Ahmad *et al.* studied the potential effect of QCN on streptozotocin (STZ)-induced diabetic Wistar rats. When QCN was administered topically to hyperglycemic rats, blood glucose levels significantly decreased, demonstrating the substance's hypoglycemic action. An increase in wound contraction was observed in QCN-treated rats [12]. In a study by Taskan *et al.,* Wistar rats were divided into two groups; one group was administered QCN gel and the other group was administered vehicle. The results of study showed that the QCN-administered group demonstrated better wound closer compared with the vehicle group. Also, fibroblast cell counts were found to be higher in QCN-administered group; however, collagen synthesis was similar in both groups. This investigation revealed the therapeutic potential of QCN for the wound healing [67].

Novel topical nanoformulations of QCN for wound healing

The diverse biological activities of QCN (e.g., anti-inflammation, antioxidant effects, collagen accumulation, angiogenesis, fibroblast proliferation) suggest its effectiveness for wound care. The development of QCN nanoformulations exhibited various advantages, such as increasing the bioavailability by encapsulating QCN in the nanovechicles, which also increase solubility and penetration/permeation, thereby increasing bioavailability of QCN reaching the wound site [71,72]. These nanoformulations have demonstrated higher targeting ability to target tissue and superior controlled and sustained release behavior, which are important factors in would healing [73]. These nanoformulations also exhibited some disadvantages, such as long-term instability, complex preparation and expense, which makes these formulations less accessible to patients [74].

However, some cases of QCN application have been successful, as described in the next sections. Topical application of 0.3% QCN remarkably accelerates wound closure, promotes regeneration of the epithelial layer and reduces oxidative stress. Additionally, wounds treated with QCN demonstrated rapid wound healing [7]. Jangde *et al.* formulated a multiple-hydrogel system incorporating QCN-loaded LPs for wound treatment by applying an alternating proportion of gelatin and carbopol; they then examined various *in vitro* and *in vivo* parameters. The results indicated that the hydrogel markedly declined wound closure duration [75]. Jee *et al.* fabricated an NE complex containing QCN, several highly skin-permeable GFs and oxygen to evaluate their combined impact, which can improve the epithelialization and healing process of hyperglycemic wound by increasing the ratios of antioxidants and growth hormones across the wound area. As a result, QCN-incorporated hydrogel sped up recovery of keratinocytes and fibroblasts compared with traditional gel, and the generated synergistic efficacy had a long-term effect in chronic wound healing [76]. It is generally assumed that wound dressings should have optimal tensile strength, hydrophilicity and specified antioxidant and antimicrobial characteristics to hasten healing. Ajlam *et al.* prepared PVA-gelatin electrospun nanofibers incorporating QCN and ciprofloxacin with this objective. The outcome suggested that the formulation healed full-thickness injuries completely within 16 days of direct application. In addition, modulation of hydroxyproline and catalase proportions in granulation tissues by QCN ultimately boosted the wound healing process [77]. Choudhary *et al.* developed QCN-incorporated

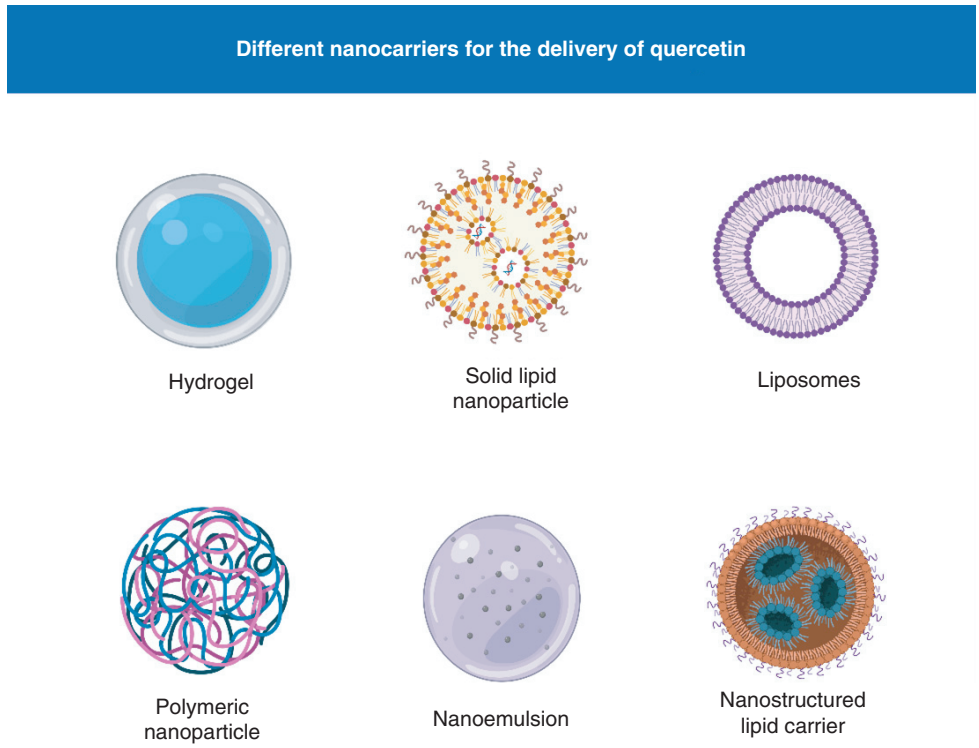

Figure 4. The different nanocarriers employed for the delivery of various therapeutics.

chitosan nanoparticles following the ionic gelation technique for a wound healing application. The fabricated nanoparticles were topically applied to a wound prepared with surgery, and several tests were assessed in the healing tissues. It has thus been shown that 0.03% QCN-nanoparticle-treated granulation tissue have several blood vessels, fewer inflammatory cells, sufficient collagen fiber mass and fresh epithelialization [78].

A recent study performed by Yi-Bing *et al.* evaluated the healing effects in an acute lung injury rat model using a QCN-loaded NG. In this study, QCN NG had a significant on injured rats by removing oxidative stress damage and impeding the regulating effects of mRNA and protein expression of inflammatory cytokines through inhalational administration of ultrasonic aerosol [79]. Another study by Jangde *et al.* developed QCN-loaded LPs using a thin-film hydration technique, and the authors concluded that this formulation achieved sustained drug release in wounds [80]. The overall summary of nanoformulations and their significance in wound healing is illustrated in Supplementary Table 1. Figure 4 shows the various nanocarriers employed for the delivery of QCN in wound healing.

Nanoemulsion

NEs are emulsions with particle sizes ranging from 50 to 200 nm. This dosage form is broadly applied in various biomedical fields, and due to the low droplet size, NEs reveal exceptional characteristics, including improved stability and tunable rheology. This delivery approach is frequently used in the fabrication of pharmaceutical formulations for intravenous, oral, topical and other modes of administration. They also appear as an appropriate carrier to deliver therapeutically active water-insoluble ingredients [81]. Regarding the advantages of NEs, research indicates that NEs are a valuable and effective drug carrier for delivery from nose to brain. This system of administration is also kinetically stable and not markedly affected by coalescence, creaming, sedimentation or flocculation during storage [82]. These preparations are generally nonirritating, and applying small amounts of active agents is harmless in humans [83]. NEs appear to be promising nanocarriers for drugs with particularly low water-solublity or that demonstrate stability problems, such as oxidation, hydrolysis and enzymatic degradation in a physiological environment.

Enhancing drug permeation and altering the biological hurdles is another significant achievement [84]. Considering natural compounds such as QCN and curcumin lipophilicity, NEs appear especially useful for administration

to the brain. Compared with conventional emulsions, delivery systems based on nanotechnology have exhibited greater surface area, higher drug solubility, minimal side effects controlled release of active pharmaceutical ingredient (API), and enhanced drug stability [85,86]. However, due reduced viscosity of NEs, they have minimal deposition at the applied area and are difficult to apply.

Polymeric nanoparticles

Polymeric nanoparticles have been widely used as nanocarriers due to their advantageous properties, including their easy construction and design, strong biocompatibility, wide range of structural options and remarkable bioavailability. This is particularly evident in the smart delivery of drugs, where they play a significant role due to their exceptional efficiency in delivering medicines to a precise location in the human body [87]. With this nanocarrier, drugs are protected from deterioration by the proteases present in the wound when embedded or conjugated with these polymeric nanocarriers, and they are released in a controlled manner to lower the frequency of administration. Nanoparticles will meet the demand for efficient delivery of biomolecules such as antibacterial drugs, growth factors and genes [88]. Polymeric nanoparticles can be prepared using different polymers, natural and synthetic [89]; natural polymers that are widely employed include chitosan, albumin, gelatin and alginate, and synthetic polymers include PLGA among many others [90]. In a study conducted by Choudhary *et al.* demonstrated the significant potential of QCN-loaded polymeric nanoparticles and excellent wound healing outcomes. These nanoparticles enhanced wound healing by altering cytokines and GFs involved in the inflammatory and proliferative phases of wound healing (Figure 5) [78]. In another *in vivo* study, diabetic rats were treated with topical and oral ferulic acid nanoparticles; the findings showed that wounds were significantly healed through treatment with these nanoparticles [91].

Liposomes

LPs are spherical-shaped nanocarriers that have been extensively studied for drug-delivery purposes. LPs consist of phospholipid bilayers enclosing a recognizable aqueous capacity, facilitating encapsulation of both hydrophilic and hydrophobic APIs [92]. This carrier's features significantly vary with the composition of lipid, size, surface charge and fabrication techniques. The common properties of LPs, such as biodegradability, biocompatibility and low toxicity, aid in enclosing both hydrophilic and lipophilic ingredients. Recently, researchers have studied encapsulation approaches associated with LPs to deliver drugs that respond as therapeutic facilitators to the targeted organs of the body [93]. This delivery system holds several advantages related to formulation and drug delivery. LPs enhance a drug's effectiveness and therapeutic window. Additionally, this nanocarrier helps to increase drug stability through the encapsulation technique, and this delivery system is fully biodegradable, toxin-free and nonimmunogenic for both systemic and nonsystemic delivery. LPs also minimize tissue exposure to toxic molecules. They can be coupled with ligands having site-specificity to achieve active targeting [94]. However, the it has also been shown that there is a risk of oxidation and hydrolysis of phospholipids, in addition to drainage and synthesis of incorporated molecules or drugs. Other limitations related to LPs are high production costs and reduced stability [94].

LPs can protect a wound, and after administration, they create a moist environment that is highly effective in impaired wounds (altered physiological conditions). Considering these advantages, LPs have been used globally in injury treatment and skin regeneration [95,96]. A study done by Xu *et al.* fabricated a novel LP formulation of silk fibroin with a hydrogel that potentially incorporated bFGF. This preparation significantly ameliorated the bFGF stability in wound fluids and supported the maintenance of cell proliferation activity with respect to conventional LPs. Moreover, LPs having hydrogel cores effectively promoted wound healing, especially by enhancing angiogenesis. Nunes *et al.* examined the wound healing efficacy of a LPs containing usnic acid. Research in a porcine model showed that the liposomal membrane prevented secondary infection. Further, better deposition of collagen along with cellularized granulation tissue appeared in the membrane treated with LPs. Thus, the unique membrane developed an approximate potentiality to the marketed product DuoDerm regarding increase granulation tissue remodeling and scar repair.

Nanocrystals

Nanocrystals are colloidal systems in which pure drug crystals are emulsified with the minimum concentration of surfactant for stabilization. These nanocarriers have shown positive effects, increasing drug loading by 100% [97]. Some studies have also reported that these nanocarriers improve the overall physicochemical properties of a drug. Nanocrystals may increase the cutaneous bioavailability of less soluble therapeutics [98]. To increase bioavailability,

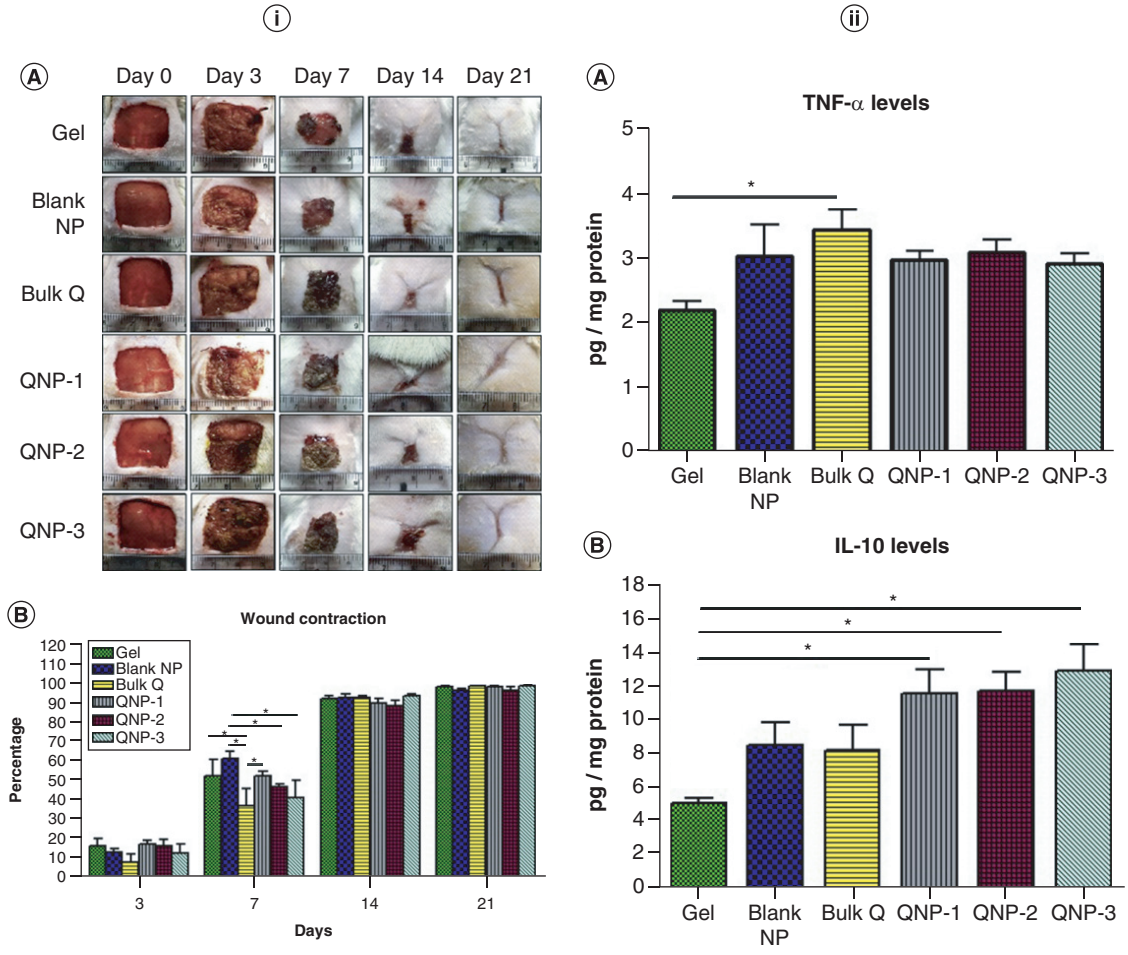

Figure 5. ***In vivo*** **findings of quercetin polymeric nanoparticles for wound healing. (i)** Photographs of animals treated with different concentrations of QCN-nanoparticles and compared with blank nanoparticles **(A),** The effect of topical application of QCN on the wound contraction **(B); (ii)** The effect of QCN topical application on different inflammatory cytokines such as TNF-α **(A),** and IL-10 levels **(B)**.
Figures were reproduced with permission [78].
NP: Nanoparticles; QCN: Quercetin.

nanocrystals work by increasing kinetic saturation solubility and, as a result, the concentration gradient between the topical formulation and the skin. Additionally, their enormous surface area leads to fast dissolution. As a result of bioavailablity to the skin, nanocrystals exhibit greater adhesion and longer retention [99]. Quercetin smartCrystals® have greater SC skin deposition and have potential for use in sunscreen products. There is limited literature on nanocrystals for the delivery of QCN for wound healing. However, some research groups have explored their role in other diseases *in vitro* and *in vivo*. In addition, Liu *et al.* demonstrated the biological effects of QCN nanocrystals against A549 cells. The findings of their study demonstrated a size-dependent effect of nanocrystals against A549 cells and that QCN nanocrystals significantly increased the anticancer effects at the cellular level; notably, the results were considerably influenced by the size of nanocrystals [100]. In addition, Kakran *et al.* investigated the long-term physical stability of QCN nanocrystals designed by using three methods: high pressure homogenization, bead milling and cavi-precipitation. The results demonstrated that first two methods produced QCN nanocrystals that were stable for 180 days, whereas the cavi-precipitation-produced nanocrystals were unstable and did not show the optimal zeta potential value. Therefore, these types of nanocarriers should be developed using a method in which the formulation remains stable [101].

Solid lipid nanoparticles

SLNs are lipid-based nanocarriers prepared using solid lipids and emulsifiers [102,103]. This carrier is submicron, with a particle size <1000 nm. It has various benefits, including protection of the molecule from unsuitable environmental conditions, easier production on a larger scale by applying a high-pressure homogenization method, biodegradability and biocompatibility [104]. They also have longer physical stability, prolonged drug circulation time and maintenance of controlled and sustained drug release. Several studies have demonstrated that SLNs have better potential as adjuvants. However, this carrier is also appropriate for liver disorders because of its specific accumulation in that organ [105]. In addition, it has also been shown to enhance the permeation and retention duration of drugs in tumor tissues, promoting drug bioavailability. This delivery system also has some disadvantages; owing to its crystalline structure, it has a low potential for drug encapsulation, and there is a possibility of drug discharge during storage due to the crystallization process. Another drawback is drug expulsion during the initial stage. Other limitations include insufficient clinical studies and minimum drug entrapment for hydrophilic drugs [106]. It has been reported that QCN nanoparticles can reduce injuries caused by intestinal mucositis due to methotrexate [107].

Nanostructured lipid carriers

NLCs are a dispersion system composed of different lipids (solid and liquid lipid) and emulsifiers [108]. The structure of NLCs is highly disordered, which gives them the ability to encapsulate and load a higher drug. According to reports, NLCs prevent oxidation or hydrolysis of medication and ensure controlled release. These nanocarriers can be administrated by various routes, including oral, parenteral, topical and intranasal [109]. The wide applications of these nanocarriers have been investigated and explored in a range of diseases and conditions. NLCs are the best candidates for increasing drug bioavailability, treating inflammatory bowel illnesses and decreasing drug-induced toxicity because they exhibit lower particle disintegration and longer gastrointestinal tract (GIT) residence time after oral administration. In pulmonary applications, they can evade local defenses and accumulate in the lung. They have little or no toxic effect, and increase ocular bioavailability when applied to eyes [110]. Because they are formed from nonirritating, nontoxic lipids that are easy to sterilize, they can also be used on damaged skin. Due to the occlusive nature on the skin, NLCs also enhance skin moisture. The occlusive film that NLCs create when they stick to the skin promotes reduction in transepidermal water loss and an increase in skin water content, which makes it easier for drugs to permeate into and through the skin [97].

Chen developed QCN-loaded NLCs to take advantage of a drug's protective effects against reactive oxygen species-mediated skin damage. The amount of QCN deposited into the epidermis and dermis from NLCs after 12 h of an *in vivo* skin permeation study was much higher than that of QCN solution (1.52 and 3.03 times, respectively). After the application of NLCs, the SC loosened and opened skin pores, which facilitated drug permeation in skin, according to histological analysis of skin samples [111]. In addition, Liu *et al.* showed an improvement in QCN release from QCN-loaded nanostructured lipid carrier. After oral administration of this carrier, it was found at greater concentrations in lungs, liver and kidney compared with the control group [112].

Niosomes

NSs are considered one of the best nanocarriers prepared from synthetic nonionic surfactants. This delivery system contains hydrophilic head and lipophilic tail groups, which impact the encapsulation efficiency of the drug [113]. NSs behave similarly to LPs, extending the flow of incorporated molecules and metabolic steadiness. Similar to LPs, the characteristics of NS rely on the bilayer concentration and its fabrication technique. The difference between LPs and NS is that NS are developed from single-chain surfactant (uncharged) and cholesterol, whereas LPs are fabricated from double-chain phospholipids (charged or neutral). Cholesterol quantity in LPs is much higher compared with NS, and thus the drug entrapment ability of LPs is lower compared with NS [114–116].

NS administration has potential as a drug carrier for several disorders. Additionally, NSs may be a promising vehicle for low-absorption drugs because they increase the drug's bioavailability by bypassing the gastrointestinal tract's physiological barrier through the transcytosis mechanism in intestinal tissues [117]. In addition, compared with LPs, NS have various advantages, such as better stability, cost–effectiveness and convenience in fabrication and scale-up. Moreover, this carrier is stable, mainly due to its fabrication substances – nonionic surfactants, which are more physically and chemically reliable than lipids. The NS delivery system also has some disadvantages. A previous study revealed that although an increase in their alkyl chain length can lead to a reduction in toxicity, enhancement in the polyoxyethylene chain elevates the toxicity [118].

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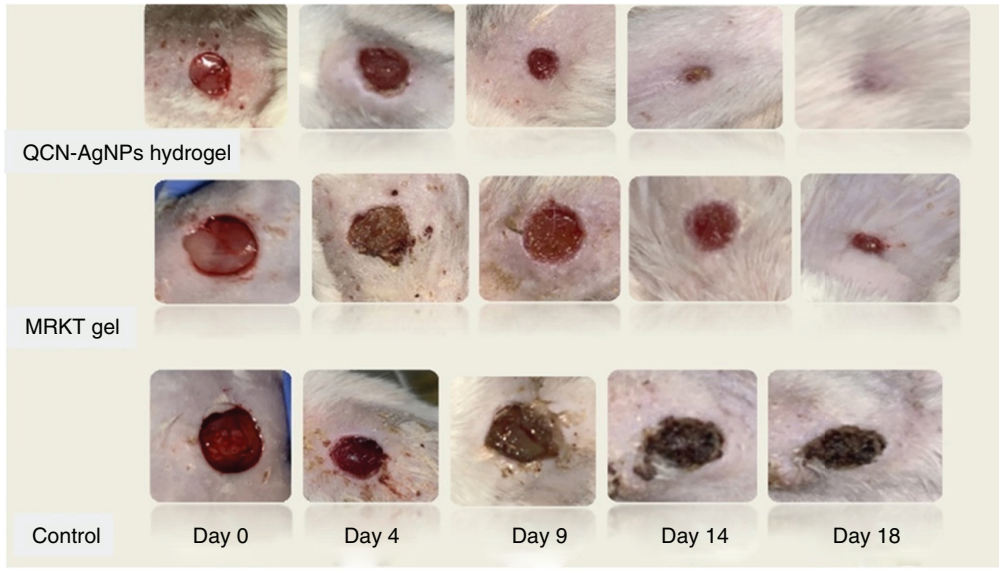

Figure 6. Comparison of the different treatment groups and their effects on the wounds from day 0 to 8.
Reproduced with permission [40].
AgNP: Gold nanoparticle; QCN: Quercetin.

Nanogels

NGs are promising drug carriers in therapeutics, macromolecules and diagnostics [105]. These nanoparticles consist of a hydrogel crosslinked with hydrophilic polymer chains, either physically or chemically. This drug-delivery system can hold a higher quantity of water because of the availability of hydrophilic functional groups [119]. As with other nanocarriers, NGs have some advantages and some limitations. Due to their hydrophilic nature, this delivery system is biocompatible with better incorporating ability for different compounds, such as, inorganic, organic nanoparticles and biomacromolecules (proteins and DNA) [120,121]. Furthermore, NGs can encapsulate more than one bioactive agents within one delivery system and can provide excellent therapeutic outcomes [122]. Owing to properties such as softness, stimuli-response behavior and swelling, NGs prevent the *in vivo* degradation and elimination of encapsulated biological molecules, thereby supporting the delivery process before receiving a stabilized and prompt feedback at the target area. NGs have limitations associated with optimizing the degradation process, biodistribution and toxicity of components [123]. It is also expensive to completely remove both surfactants and solvents at the final stage of the fabrication process. Moreover, traces of surfactant may remain and can have undesirable side effects, and scale-up is difficult because of mean size and weight [124].

Nanohydrogels as nanostructures for wound dressing have various benefits, such as better hydrophilicity and flexibility, higher mechanical power, tunable structure and the capacity to absorb a wound's exudate to improve oxygen permeation and obstruct wound dehydration [125]. Because of their porous arrangement, they represent another valuable nanostructure for facilitating prolonged and controlled administration [126]. A study performed by Liand *et al.* fabricated a nanohydrogel using alginate gum. Adhesive nanohydrogels exhibit the potential to bind with impaired tissues and can act as a hemostat and facilitate a microenvironment to provide cell enlargement, migration and differentiation [127]. Badhwar *et al.* showed the therapeutic effects of QCN-loaded silver NPs in hydrogel, and their findings revealed that a wound was completely healed by the hydrogel in 18 days. Figure 6 shows the effects of QCN-based advanced formulation *in vivo* study.

Regulatory perspectives on the application of QCN for wound healing

QCN is not regulated by the major regulatory authorities, such as the US FDA, EMA and Therapeutic Goods Administration. Despite showing therapeutic potential against various diseases and conditions, including wound healing, the gap for translation remains to be filled. Because it is a dietary supplement, it cannot be regulated as drugs because its safety and effectiveness may not be fully explored. Thus far, the FDA has not approved the claim that quercetin can heal wounds. Researchers are exploring the potential of this compound in different cells (*in vitro*) and animals (*in vivo*). The findings of such claims have been described and covered in different sections of

this article. In contrast, the FDA has approved various wound care products such as hydrogels, hydrocolloids, foam dressings, transparent films, collagen and biological dressings that contain the synthetic compounds. However, it is recommended that these approved products should be used under the guidance of a healthcare professional.

Current trends & challenges

Chronic wounds constitute a vital healthcare difficulty such as financial expenses and have a damaging effect on morbidity. The public health care funding has been revealed in India, which is 5% of the annual gross domestic product, with higher than 80% of healthcare budgets received from out-of-pocket payments. These figures do not indicate the financial expenditure, dissatisfaction and disturbed quality of life suffered by chronic wound sufferers. Therefore, patients have difficulty managing their condition, affecting quality of life and medical expenditures [128]. Once bacterial balance has been achieved, the application of topical antibacterial should be stopped, because longer treatment courses of these therapeutic agents may impede healing action of a wound and induce antimicrobial resistance [129]. It has been extensively reported that the use of phytochemicals and naturally extracted ingredients are a remarkable innovation for healing of chronic wounds. Complementary and alternative medicine is a promising way to ameliorate clinical and therapeutic challenges of untreatable chronic injuries. Researchers must realistically assess whether phytochemicals are useful wound healing agents. Sadly, one hurdle to wound treatment is the scarcity of knowledge possessed by physicians and other healthcare professionals on this subject [65].

The physiological environment of the wound tissue also poses challenges for effective and successful therapy. These challenges are classified into various categories based on pathological conditions [130]. The presence of different biomarkers and change in their levels affects the overall healing of the wound. For example, there are changes in pH, cytokine, GF and oxygen levels in the diseased condition or the microenvironment of diseased tissue [130]. If the pH in diseased conditions increases, the possibility of wound treatment is impaired; better wound healing is reported in many cases with the lower pH, which is close to neutral. Similarly, a certain oxygen level is required for a wound to heal, and this is not available in diseased tissue. Oxygen deprivation at levels >30 mm Hg eventually slows fibroblast proliferation and collagen formation [26]. This allows bacteria to grow and worsens the condition of the tissue or wound. Another challenge is to increase fibroblast production and proliferation, which increases the GF level necessary for effective wound healing [131]. Considering all the evidence, the literature has shown promising results in preclinical studies using QCN to treat wounds; however, there is a lack of clinical evidence to support its use in wound treatment. Therefore, more research is needed to determine its safety and effectiveness in humans.

Conclusion

Wound healing is a complex series of events that starts with an injury that results in the formation of granular tissue, skin regeneration and ultimately the closure of the wound. The healing time varies depending on the type of wound and the body's response to treatment. In most cases, established therapies successfully treat wounds; however, in the worst cases where no treatment is effective, amputation is required. We have reviewed the literature to show the potential of QCN in preclinical models, and the findings of the studies show promising results. QCN may be a successful treatment for wound management. We conclude that the correlation between preclinical findings and therapeutic efficacy of QCN to patients as a clinical translation is inevitable for further confirmation of its effectiveness. Hence, there is a great opportunity to investigate this potential compound in wound management.

Future perspective

Despite the important research in this domain, there is a need to fill the gaps, understand the drawbacks and associated complications and address the scientific questions to improve public health. In addition, advances in contemporary therapies through nanotechnology and cell-based therapy require pharmaceutical scientists' attention to explore novel possibilities. Existing therapies for wound healing, such as the development of artificial skin, have huge potential to heal and regenerate wounds and tissue. Therefore, exploiting pluripotence and self-renewal might be the best resource to develop effective wound healing therapies. In addition, the application and design of 3D printing with the support of biodegradable and safe polymers to generate artificial skin could have great potential to dress and heal wounds. The development of 3D skin organoids could be an alternative to various dressings as well. Stem cell therapy could be a significant opportunity due to the possible support of multifaceted mechanisms such as angiogenesis, cell proliferation, fibroblast synthesis and, notably, the significant potential to vary the wound microenvironment. Moreover, inclusion of gene-editing methods such as CRISPR along with nanotechnology may

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lead to advances in wound treatment. Secretomeengineering is a novel technique that involves using natural cell components such as extracellular vesicles, red blood cell membranes and white blood cell membranes to create advanced therapies loaded with QCN. By utilizing these natural membranes and components, scientists can develop highly effective cell-based therapies. Hence, by exploring all possibilities and investigating advanced approaches, QCN may provide excellent outcomes in wound treatment.

Executive summary

Quercetin
- Antioxidant potential: quercetin (QCN) has been established as an antioxidant compound that has been explored by a range of researchers due to its inherent characteristic of scavenging free radicals.
- Anti-inflammatory: QCN is effective in reducing inflammation.
- Proliferation and remodeling: QCN alters both these stages, which upregulate healing of any injury, including wounds.

Wound healing
- Hemostasis: this stage of wound healing is rapid, initiating by closing the wound.
- Inflammatory phase: this is the second stage of wound healing and starts immediately after the occurrence of an injury. It both controls the bleeding and reduces the chances of infection.
- Proliferative phase: in this phase, the wound is regenerated and rebuilt through the formation of collagen and extracellular matrix.
- Maturation phase: also known as a remodeling phase of wound healing, this is the stage when a wound closes completely.

Mechanism of wound healing
- Reduction of different cytokines: marked reduction of various inflammatory cytokines have been reported (e.g., TNF-a, IL-1b and MMP-9), along with increased IL-10, VEGF and TGFb1.
- Regulation of NF-kB: this is critical at all stages of wound healing; therefore, it should be properly regulated for optimal wound healing.
- Altering MAPK pathway: QCN has shown potential for improving wound care by inhibiting the MAPK pathway.

Topical delivery of QCN
- Advanced formulations: different formulations were reviewed, such as polymeric nanoparticles, nanoemulsions, liposomes, niosomes, solid-lipid nanoparticles, nanogels and nanocrystals; these have already been shown to have potential to improve the condition of wounds.
- US FDA approved wound healing products include hydrogels, hydrocolloids, foam dressings, transparent films, collagen and biological dressings that contain the synthetic compounds.

Challenges & future perspective
- Physiological challenge: chronic wounds pose a challenge for effective and successful treatment.
- Translation: the effectiveness of QCN needs to be explored for translation to the clinic.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/nnm-2022-0281

Financial & competing interests disclosure

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