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Chemistry

An overview of the healing potential of silver nanoparticles in the treatment of diabetic wounds

Uma visão geral do potencial cicatrizante de nanopartículas de prata no tratamento de feridas diabéticas

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ABSTRACT

Silver is a metal known for its antimicrobial and antibacterial properties, and when reduced to the nanoparticle scale, there is an increase in its surface area, which enhances these properties. As a result, silver nanoparticles have been widely studied and used in wound treatment, especially in cases of chronic infections and infected wounds, such as those found in people with diabetes. The purpose of this study was to provide an updated overview of the potential of silver nanoparticles and their applications in diabetic wound treatment. A search was conducted in the PubMed Database, ranging over the last five years, using the descriptors and Boolean markers: silver nanoparticles AND wound healing AND diabetes. The search resulted in 54 articles, of which 14 were selected to compose this review according to the proposed criteria. From the studies included in this review, it was possible to observe that among many nanostructures containing AgNPs, hydrogel and spray were the most used for topical application *in vivo*. Of the analyzed articles, AgNPs showed promising results for the healing of diabetic wounds, showing anti-inflammatory and antibacterial properties.

Keywords: Metallic nanoparticles; Antibacterial; Healing properties

RESUMO

A prata é um metal conhecido por suas propriedades antimicrobianas e antibacterianas, e que quando reduzida para a escala de nanopartículas, ocorre o aumento de sua área superficial, o que potencializa essas propriedades. Em função disso, as nanopartículas de prata têm sido amplamente estudadas e utilizadas no tratamento de feridas, especialmente em casos de infecções crônicas e feridas infectadas, como as encontradas em pessoas com diabetes. O objetivo deste estudo foi investigar uma visão geral atualizada do potencial das nanopartículas de prata e suas aplicações no tratamento de feridas diabéticas. Foi realizada uma pesquisa na base de dados PubMed, no intervalo de tempo de 2020 a 2023, usando os descritores e marcadores booleanos: silver nanoparticles AND wound healing AND diabetes. A pesquisa resultou em 54 artigos, dos quais 14 foram selecionados para compor esta revisão de acordo com os critérios propostos. A partir dos estudos incluídos nesta revisão, foi possível observar que dentre muitas nanoestruturas contendo AgNPs, hidrogel e spray foram a mais utilizadas para aplicação tópica in vivo. Dos artigos analisados, as AgNPs apresentaram resultados promissores para a cicatrização de feridas diabéticas, apresentando propriedades anti-inflamatórias e antibacterianas.

Palavras-chave: Nanopartículas metálicas; Antibacteriano; Propriedades cicatrizantes

1 INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases worldwide. According to the International Diabetes Federation (IDF), in 2021, around 537 million adults (20-79 years old) are living with diabetes, with an expected increase to 643 million by 2030. Wound healing in diabetics is affected by hyperglycemia in various metabolic structures. Among some, the synthesis of proteins, migration and perspectives of keratinocytes and fibroblasts are interrupted, in addition to the balance in the reactive oxygen species (ROS) generation, affecting the blood supply in peripheral nerves, leading to sensory and motor dysfunctions, and causing the risk to develop diabetic foot ulcer (DFU). (Burgess et al., 2021).

In addition to conventional drugs on the market, more current developments using nanotechnology are beneficial for the development of new drugs and delivery systems using nanostructures. Metallic nanoparticles have been considered an option for antibiotics, and among them, silver nanoparticles (AgNPs) are one of the most studied for their antibacterial properties (Liu et al., 2023). Metal nanoparticles have attracted great interest due to their unique properties, such as large contact surface area, high conductivity, and distinct chemical characteristics (Pereira, 2022). Promisingly, AgNP reduces foci of inflammation and healing time, demonstrates increased collagen deposition and migration of macrophages and fibroblasts, improving remodeling in the wound area, as AgNP induces the migration of keratinocytes from the edge of the wound to its center (Toczek et al., 2022).

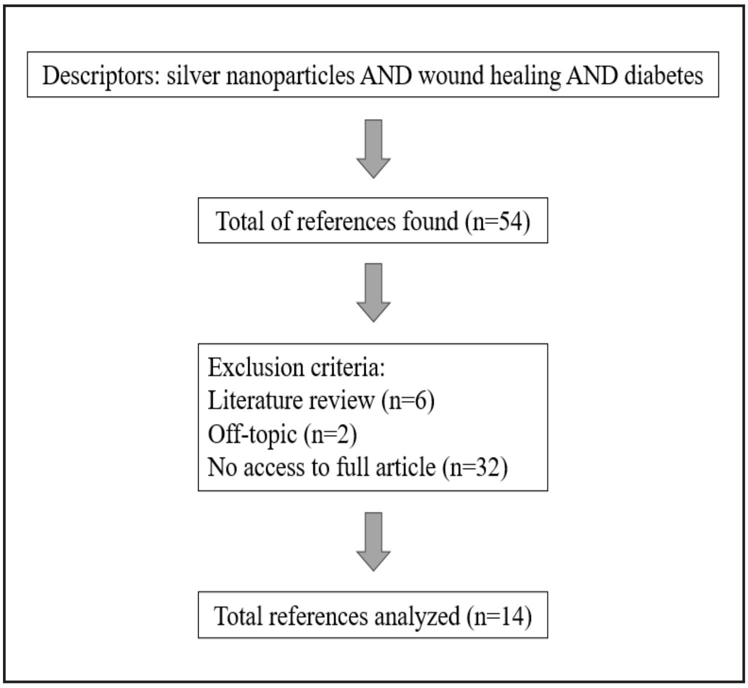
In this context, the present work aims to carry out an exploratory and qualitative bibliographic research on the application of AgNPs in the treatment of diabetic wounds.

2 MATERIAL AND METHODS

This study is characterized as an exploratory, integrative literature review type. A research was carried out in the Pubmed database, published within the last five years, using the Boolean descriptors and markers: silver nanoparticles AND wound healing AND diabetes.

The inclusion criteria used to select the articles were: articles published in Portuguese and English, with free access to the full article on the online platform, which used silver nanoparticles with healing properties for diabetic wounds. Literature reviews and off-topic articles were excluded. Articles that performed isolated evaluations, without proposing an *in vitro* or *in vivo* model to analyze healing properties in diabetic wounds were also excluded from the study.

Figure 1 – Flowchart with article selection strategy



Source: Author's construction (2023)

After searching the database, titles and abstracts were evaluated, and those that met the inclusion criteria were selected to be read in full. The search resulted in 54 articles, of which 14 were selected to be included in the review, according to the proposed criteria. Figure 1 presents the flowchart with the selection strategy of the articles included. The articles that make up this study were published in the years between 2020 and 2023.

3 RESULTS AND DISCUSSION

From the articles analyzed, it was observed that the nanostructures containing silver nanoparticles for diabetic wound healing most used were gel/hydrogel and spray (Table 1), representing 43% and 14%, respectively. Regarding the test models, 71% performed *in vivo* tests, while 29% only *in vitro*.

In the study of Kumar, Houreld and Abrahamse (2020), it was evaluated the combined effects of green synthesized silver nanoparticles (G-AgNPs) and photobiomodulation (PBM) (laser irradiation at 830 nm with 5 J cm^{-2}) on fibroblastic cells with the normal and diabetic wound (WS1). For the green synthesis method was used a non-toxic extract of *Aloe arborescens* with anti-inflammatory, antimicrobial and antioxidant properties. In cell viability, the concentration of 12 µg/mL of G-AgNPs reached the minimum inhibitory concentration (MIC) in Gram-positive and Gram-negative strains, being then used in the remaining tests. Both in normal and diabetic wound cells, there was greater cell migration within 24 hours with the use of G-AgNPs, irradiated or non-irradiated. The same was observed in the percentage of wound closure. However, diabetic wounds closed completely in 48 hours only in the model treated with the combination of irradiated laser and G-AgNPs. There was no change within 48 hours in the mechanisms of cell proliferation in the S phase - when DNA synthesis occurs - during the healing processes. By fluorescence microscopy, no structural adverse effect of G-AgNPs and PBM was observed. Thus, the use of combined therapy with G-AgNPs and PBM showed promise results for the treatment of normal and diabetic wounds, however, the same remains to be proven in *in vivo* models.

Table 1 – Publications that composed the study presented in chronological order

Year	Author	*In vitro/In vivo* Model	Nanocomposite
2020	Chen et al.	*In vitro / In vivo*	L-AgÅP gel
	Kumar, Houreld & Abrahamse	*In vitro*	Silver nanoparticles (G-AgNPs)
2021	Scappaticci et al.	*In vivo*	Spray of G-AgNPs
	Zhang et al.	*In vivo*	Epidermal growth factor spray with nanosilver dressing
2022	Chai et al.	*In vitro/ In vivo*	Regenerative antibacterial hydrogel of TA and AgNPs
	Mei et al.	*In vitro/ In vivo*	Hydrogel system (M@M–Ag–Sil-MA)
	Nagarjuna et al.	*In vivo*	Dressing with GC-AgNPs patches
	Permyakova et al.	*In vivo*	Superabsorbent CUR/CS/Ag foams
	Ruffo et al.	*In vitro*	Biocompative hydrogel carboxymethilcellulose- AgNP
	Younis, Mohamed & El Semary	*In vivo*	Silver nanoparticles (G-AgNPs)
	Zhang et al.	*In vivo*	AgNPs with Themoplastic polyurethane
2023	Balcucho et al.	*In vitro*	Bio-AgNPs and CuONPs films
	Fathil & Katas	*In vitro*	AgNPs/Lactoferrin hydrogels
	Zeng et al.	*In vitro / In vivo*	Hydrogel CINPS and Hydrogel AgNWs

Source: Organized by the authors (2023)

Also using the green synthesis method, Scappaticci et al. (2021) tested the effectiveness in healing diabetic wounds of spray formulations of AgNPs by green synthesis from pomegranate peel extract (GS) compared with AgNPs prepared by the traditional chemical method (CS). Under *in vitro* conditions, GS and PS (pomegranate spray) showed greater antimicrobial activity against *S. aureus* and *C. albicans* compared to CS in a previous study of the same group. The MIC values against *C. albicans* were 781 and 0.18 (PS), 68.75 and 16.87 (GS), and 0.25 and 1.12 (CS), and for *S. aureus* 391 and 0.37 (PS), 67.5, and 0.26 (GS), and 0.5 and 0.56 (CS). For the *in vivo* method, Wistar rats were induced to diabetes, and after, two surgical excisions with a 1.5 cm diameter were made. Affecting the wound on the back, *Staphylococcus aureus* and *Candida albicans*, adjusted to 104 CFU/mL, were pipetted directly into the lesion. Rats were topically treated twice a day (GS-CS-PS), with untreated animals or animals treated with silver sulfadiazine (Sulf) being used as controls, and analyzed at 2, 7 and 14 days of treatment. Significant healing activity of GS and CS can be observed after 7 days of treatment, which was demonstrated by PS after 14 days compared to the other groups. Regarding CFU, there was a reduction for *S. aureus* in all treatments after 14 days, however, no formulation had an influence on the reduction of viable cells of *C. albicans*. PS demonstrated a statistically significant increase in the inflammatory infiltrate after 7 days of treatment, suggesting that PS healing was due to a pro-inflammatory response, corroborating the myeloperoxidase (MPO) enzyme dosage, which remained the same on days 2 and 7 post treatment, while the other formulations progressively reduced MPO, with no inflammatory response and no MPO in all groups after 14 days. Overall, GS and CS show considerable potential for the treatment of diabetic wounds, with better healing after 7 days of treatment than commercial silver sulfadiazine.

Younis, Mohamed and El Semary (2022) investigated the ability of cyanobacterial species to produce silver nanoparticles (AgNPs) and its wound-healing properties in diabetic animals. Methods based in UV–visible and FT-IR spectroscopy and electron microscopy techniques investigated AgNPs' producibility by *Synechocystis* sp. when supplemented with a silver ion source. AgNPs were evaluated for their antimicrobial, anti-oxidative, anti-inflammatory, and diabetic wound healing along with their angiogenesis potential. The results demonstrated the cyanobacterium biosynthesized spherical AgNPs with a diameter pore ranging from 10 to 35 nm. The produced AgNPs exhibited wound-healing properties verified with increased contraction percentage, tensile strength and hydroxyproline level in incision diabetic wounded animals. AgNPs treatment decreased the epithelialization period, amplified the wound closure percentage, and elevated collagen, hydroxyproline and hexosamine contents, which improved angiogenesis factors' contents (HIF-1, TGF-1 and VEGF) in excision wound models. AgNPs intensified catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) activities, and glutathione (GSH) and nitric oxide content and reduced malondialdehyde (MDA) levels. IL-1β, IL-6, TNF-α, and NF-κB (the inflammatory mediators) were decreased with AgNPs' topical application. In conclusion, the AgNPs biosynthesized from *Synechocystis* sp. exhibited antimicrobial, anti-oxidative, anti-inflammatory, and angiogenesis promoting effects in diabetic wounded animals.

Chen et al. (2020) prepared a carbomer gel soaked in large AgÅPs (L-AgÅP-gel) and evaluated the *in vitro* antibacterial efficacy and healing in an *in vivo* model. The Ångstrom scale was present in particles < 20 nm, which could vary in general in size >20 nm, being known as large AgÅPs. The incorporation of L-AgÅP into the gel was confirmed by Scanning Electron Microscope (SEM) micrographs, and its sphere size ranging from 0.72 nm to 16.8 nm according to the Transmission Electron Microscope (TEM) micrograph. The L-AgÅPs incorporated in the carbomer gel were about 15.2% of the total weight of the L-AgÅPs gel (0.152 g g^{-1}) and doping with L-AgÅPs increased the thermal stability of the carbomer gel. Antibacterial activity using Staphylococcus aureus and Pseudomonas aeruginosa showed that the antibacterial activity was more potent in the L-AgÅPs gel compared to the AgNPs gel. Moreover, L-AgÅPs-gel caused significant increases in the reactive oxygen species (ROS) generation in bacterial colonies, being more effective with N-acetylcysteine (NAC) antioxidant co-treatment, with greater inhibition of ROS than when only treated with NAC. In the *in vivo* test, wound repair was evaluated in streptozotocin-induced diabetic mice with full-thickness excisional wounds. As a result, the L-AgÅPs-gel had the shortest time to wound closure, with the lowest degree of scar formation, and the highest collagen deposition and skin cell proliferation compared to the other groups of mice treated with AgNPs gel and blank gel. The greater antibacterial potential was observed *in vivo* treatment, in addition to anti-inflammatory responses, where immunohistochemical staining revealed that the

L-AgÅPs gel was more competent than the AgNPs gel to suppress the expression of pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α). In the mouse burn model, topical application of L-AgÅPs-gel also exhibited greater antibacterial and anti-inflammatory activity than AgNPs-gel and blank gel.

Zhang et al. (2021) studied the efficacy of epidermal growth factor when applied alone and in combination with nano-silver dressing in the treatment of diabetic foot wounds. Thus, 160 patients with diabetic foot wounds were selected for the study and randomly divided into four groups: A combination group with 40 patients who received a spray (40 IU cm^{-2}) of human epidermal growth factor associated with the nanosilver dressing. The epidermal growth factor group with 40 patients, received only the spray on the wound surface. Nanosilver dressing group with 40 patients, received only the nanosilver dressing. And the control group was treated with ordinary surgical dressing. Each group received a dressing change every other day, and the time required for wound repair at each stage of healing was observed. In the second and fourth week of treatment wound exudate was collected for bacterial culture. In stage 1 of healing, there was no significant difference in time for all groups. For healing stages 2 and 3, the combined group and epidermal growth factor showed a shorter healing time when compared to the control group. The combination group showed a shorter wound healing time than the epidermal growth factor group. In the epidermal growth factor group, the positive bacterial culture rate of wound exudate was similar to that of the control group, which was significantly higher than the combination group and the nanosilver dressing group. Nanosilver mainly exerts an antibacterial effect on wounds and can provide a favorable microenvironment for wound healing by reducing infection and inflammatory response. In conclusion, the nanosilver dressing combined with epidermal growth factor for diabetic foot treatment can inhibit bacterial proliferation, better control wound infection, accelerate epidermal growth and granulation tissue formation and promote wound healing. It is an ideal method for diabetic foot treatment that deserves to be promoted in clinical practice.

In the study by Chai et al. (2022), a kind of regenerative antibacterial hydrogel (RAH) was developed from thioctic acid (TA) as a pharmaceutical molecule for diabetes treatment and AgNPs as antibacterial material. In *in vitro* experiments, RAH could eliminate reactive oxygen species due to the antioxidant properties of thioctic acid, decrease oxidative damage, attenuate cell apoptosis, and retain cell proliferation efficiency. In the *in vivo* experiments, RAH had a significant therapeutic effect on chronic diabetic wounds by accelerating collagen deposition, epithelialization, vascularization and suppressing the infection of multidrug-resistant bacteria. In conclusion, this work provides an example of drug hydrogel systems formed by medicinal molecules to significantly promote therapeutic effects with good biocompatibility and regeneration.

Mei et al. (2022) investigated a photocurable methacryloxylated silk fiber hydrogel (Sil-MA) system coencapsulated with metformin-loaded mesoporous silica microspheres (MET@MSNs) and silver nanoparticles (AgNPs), developed to accelerate diabetic wound healing. The antibacterial of the M@M-Ag-Sil-MA hydrogel was carried out against the *Staphylococcus aureus* and *Escherichia coli* strains, where it was possible to observe a reduction in the number of colonies when cultured with the M@M-Ag-Sil-MA hydrogel system compared to the Sil-MA hydrogel system. Furthermore, it was possible to observe that bacteria cultured with the Sil-MA and M@M-Sil-MA hydrogel system can form an intact and dense biofilm, while in the M@M-Ag-Sil-MA hydrogel system, we can observe only sporadic non-biofilm forming bacteria. These results confirmed that the antimicrobial activity of the M@M-Ag-Sil-MA hydrogel releasing AgNPs provided a continuous environment that promoted bacterial inhibition for wound healing. The M@M-Ag-Sil-MA hydrogel was tested *in vivo* on diabetic mouse models to promote wound healing. The hydrogel systems (Sil-MA, M@M-Sil-MA and M@M-Ag-Sil-MA) were injected into the wounds, and the healing process could be observed. The results showed that all wounds in which each of the hydrogels administered showed some noticeable shrinkage of the wound area, but specifically the M@M-Ag-Sil-MA hydrogel showed a faster healing rate compared to the other hydrogel systems. In conclusion, was synthesized and characterized an injectable M@M-Ag-Sil-MA hydrogel system that can be used for diabetic wound healing.

Nagarjuna et al. (2022) studied the healing ability of wounds impregnated with gallocatechin (GC) and silver nanoparticles (AgNPs) in diabetic rats. The rats were divided into five groups: group I with non-diabetic rats, received only gauze dressing; group II with diabetic rats, received only gauze dressing; group III with diabetic rats, received gauze dressings impregnated with 13.06μmol of the GC-AgNPs; group IV with diabetic rats, received gauze dressings impregnated with 26.12μmol of the GC-AgNPs, and Group V with diabetic rats, received gauze dressings impregnated with silver sulfadiazine (AgS). Wound healing characteristics were observed from 15 to 18 days after the start of the trials. Immunofluorescence (Wnt3a/β-catechin, Bcl2, Caspase-3 and Bax) and immunohistochemistry (Gsk-3β, C-FOS, Caspase-9 and PCNA) studies were performed to detect the presence and prevalence of different cellular proteins involved in cell proliferation and apoptosis during wound healing. While mRNA and immunofluorescence or immunohistochemistry assays reveal that Wnt3a and β-catenin levels were higher with Gsk-3β and c-fos levels were lower in Group III and Group IV diabetic rats compared to Group II diabetic rats. In addition, the levels of apoptosis markers such as caspase-3, caspase-9 and Bax were reduced, while the levels of anti-apoptosis marker (Bcl-2) and proliferation marker (PCNA) were increased in Group III and Group IV diabetic rats compared with Group II diabetic rats. GC-AgNPs were proven to considerably help wound healing in a series of experiments. Thus, the results showed that the molecular mechanisms behind gallocatechin-silver nanoparticle patches in enhancing wound healing are mediated by GSK3β-mediated Wnt/β-catenin signaling. As a result of increased β-catenin signaling, it leads to decreased apoptosis and increased cell proliferation during the wound healing process.

In the study by Permyakova et al. (2022), the synthesis and characterization of pure curdlan-chitosan foams (CUR/CS), and foams containing silver nanoparticles

(CUR/CS/Ag) and their effect on skin repair in diabetic mice was performed. Diabetic mice were randomly divided into two groups: curdlan-chitosan group and curdlan-chitosan-Ag group. Two 1 cm x 1 cm wounds were opened on the spine of the mice, one for control, untreated, and the other for the test, receiving foam with CUR/CS or CUR/CS/Ag for 10 days. The use of CUR/CS led to a decrease in wound size, but complete healing was not observed. At the same time, the use of CUR/CS/Ag foam was found to significantly accelerate healing already in the first 10 days after treated. Wounds treated with CUR/CS/Ag showed complete healing after 24 days, accompanied by new vessel formation of different diameters and significant re-epithelialization. At the same time, CUR/CS-induced healing was only 20%, and the control showed an increase in wound area of more than 20%, which is associated with inflammatory processes. As a conclusion of the study, the authors reported that the developed CUR/CS/Ag can meet the needs of clinical practice and may have future medical applications for wound treatment, especially in diabetic patients.

Ruffo et al. (2022) synthesized a biocompatible hydrogel (HyDrO-DiAb) composed of carboxymethylcellulose loaded with silver nanoparticles (AgNPs) for the treatment of diabetic foot ulcers. In this study, AgNPs were obtained by a green synthesis and, then, were dissolved in a CMC hydrogel that, after a freeze drying process, becomes a flexible and porous structure. The *in vitro* and in *ex vivo* wound healing activity of the obtained HyDrO-DiAb hydrogel was evaluated.

Zhang et al. (2022) studied the effect of silver nanoparticles with thermoplastic polyurethane (TPU/NS) on the rehabilitation of diabetic patients with open fractures of lower extremities. Thus, treated diabetic patients (n = 98) with open fractures of the lower extremities in the hospital were analyzed retrospectively from June 2015 to December 2021. TPU/NS nanocomposites were prepared for postoperative treatment of diabetic patients with open fracture of lower extremities. First, the cultured *Staphylococcus aureus* and *Escherichia coli* were used to test the antibacterial effect of TPU/NS dressing *in vitro*. After using TPU/NS dressing (observation group) and traditional dressing (control group), the inflammatory reaction, clinical treatment, functional rehabilitation, and adverse reactions in patients were compared. As results were obtained, TPU/NS dressing effectively inhibited the growth of bacteria with a minimum inhibitory concentration of 2 μg/mL. The usage of TPU/NS dressing reduced the inflammatory reaction by reducing the positive rate of bacteria after the dressing on the seventh day postoperatively. Besides, the times of dressing, stopping time of wound exudation, wound healing time, length of hospital stay, and VAS score in the observation group were lower than those in the control group; the incidence of adverse reactions after treatment was lower in the observation group as compared with the control group (17.07% vs. 35.09%). Meanwhile, the functional rehabilitation and life quality of patients in the observation group were better TPU/NS dressing treatment. The conclusion was TPU/NS dressing has the function of promoting the postoperative recovery of patients by inhibiting the bacterial infection of the wound, thus improving the limb function and life quality. As a result, there was a tremendous potential to apply the constructed TPU/NS membrane to diabetic patients with open fractures, especially those with soft tissue injuries.

Balcucho et al. (2023) demonstrated the biosynthesis of polymer-nanoparticle composites and their potential as bioactive films for Methicillin-resistant *Staphylococcus aureus* (MRSA) treatment. Thus, was developed bio-based silver (Bio-AgNPs) and copper oxide nanoparticles (CuONPs) polymer composites using a microbially produced polyester from the Polyhydroxyalkanoates (PHAs) family. Poly (3-hydroxyoctanoate) -co-(3-hydroxyhexanoate) (PHO) was synthesized by Pseudomonas putida and functionalized in situ with Bio-AgNPs or ex situ with CuONPs. PHO-CuONPs films did not inhibit MRSA growth, while a reduction of 6.0 log CFU/mL was achieved with PHO-Bio-AgNPs synthesized from silver nitrate ($AgNO_3$) solution at 3.5 mM. Exposure of human fibroblast cells (HFF-1) to the bioactive films did not induce notable cytotoxicity and genotoxicity, as seen by viability higher than 79% and no significant changes in basal DNA damage. However, exposure to

PHO-Bio-AgNPs induced oxidative DNA damage in HFF-1 cells. No hemolytic potential was observed, while platelet aggregation was promoted and desired for wound healing.

Fathil and Katas (2023) developed a dressing that could effectively aid in the wound healing process and prevent bacterial infections by exerting both antibacterial and anti-biofilm effects. Silver nanoparticles (AgNPs) and lactoferrin (LTF) have been investigated as alternative antimicrobial and anti-biofilm agents, respectively, while dicer-substrate short interfering RNA (DsiRNA) has also been studied for its wound healing effect in diabetic wounds. In this study, AgNPs were complexed with LTF and DsiRNA via simple complexation before packaging in gelatin hydrogels. The hydrogels demonstrated positive antibacterial and anti-biofilm effects toward the selected Gram-positive and Gram-negative bacteria. The hydrogel containing AgLTF in 125 g/mL was also non-cytotoxic on HaCaT cells for up to 72h of incubation. The hydrogels containing DsiRNA and LTF demonstrated superior pro-migratory effects compared to the control group. In conclusion, the AgLTF DsiRNA-loaded hydrogel possessed antibacterial, anti-biofilm, and pro-migratory activities. These findings provide a further understanding and knowledge on forming multipronged AgNPs consisting of DsiRNA and LTF for chronic wound therapy.

Finally, a study by Zeng et al. (2023) explored a gelling mechanism, fabrication method, and functionalization for broadly applicable food biopolymers-based biogels that unite the challenging needs of elastic yet injectable wound dressing and skin bioelectronics in a single system. They combine our biogels with functional nanomaterials, such as cuttlefish ink nanoparticles and silver nanowires, to endow the biogels with reactive oxygen species scavenging capacity and electrical conductivity, and finally realized the improvement in diabetic wound microenvironment and the monitoring of electrophysiological signals on skin. This line of research work sheds light on preparing food biopolymers-based biogels with multifunctional integration of wound treatment and smart medical treatment. The results verify that our CINPs@ NSFG can fill deep wounds with varied shapes and achieve a perfect fit for the wound in a three-dimensional space.

3 CONCLUSIONS

From the present literature review, it was possible to observe that the main AgNPs structures with the purpose of diabetic wound healing were gel/hydrogel and spray for topical *in vivo* application, followed by nanostructured foams, dressings, patches and film. In the analyzed articles, AgNPs showed promising results for the healing of diabetic wounds *in vitro* and *in vivo* models, showing anti-inflammatory and antibacterial properties, in a non-toxic and effective way. It demonstrates that nanotechnology is a promising tool to expand the use of metallic nanoparticles, such as silver nanoparticles, for healing purposes in diabetic wounds.

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