TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 16
Number 2 *Spring 2023*

30-38

2023

Is Nanotechnology an Effective Treatment for Diabetic Wounds?

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Abstract

Diabetes Mellitus is increasingly impacting millions of adults worldwide. Multiple complications are associated with the disease, including non-healing chronic wounds. Treatment of diabetic wounds and foot ulcers is a complex challenge, as standard treatment options are ineffective. This review focuses on the use of nanotechnology as a treatment option. Nanomaterials include inorganic and organic nanoparticles as well as nanofilms and fibers. Analysis of the benefits of these nanoparticles will be discussed which include their antimicrobial, anti-inflammatory, antioxidant, and wound healing capabilities. A critical overview of the possible benefits will be assessed from in vitro and in vivo studies. Overall, this class of treatment options seems promising, but more research is necessary to determine long efficacy.

Introduction

As of 2021, an estimated 537 million adults have diabetes worldwide, and the numbers continue to rapidly increase (IDF Diabetes Atlas, 2021). Diabetes includes Type 1, Type 2, and Gestational diabetes. In Type 1 diabetes the body doesn't produce enough insulin and is often diagnosed at a young age. It accounts for 5- 10% of diabetes cases. Type 2 diabetes involves the dysregulation of insulin. While genetics plays the only role in type 1 diabetes lifestyle choices add to genetic factors in adults with Type 2 diabetes.

Diabetes is an illness that affects various organ systems as well as arterial and vascular functions. Diseases such as diabetic retinopathy, diabetic neuropathy, and kidney failure are all complications of diabetes mellitus (Thiruvoipati & et al., 2015). An important issue for diabetic patients is painful wounds that have trouble healing. These diabetic wounds often develop at the feet, being referred to as "diabetic foot ulcers" but can also develop in other parts of the body. Quite often, these wounds necessitate lower extremity amputations in patients. Standard treatment methods including bandages, topical creams, and medications don't work well against these chronic wounds. Researchers have been working to develop new methodologies to reduce the difficulties that are associated with chronic wounds. The application of nanomaterials as a treatment option shows promise in the future of diabetic wound treatment. This review will focus on metal-based nanoparticles, lipid-based nanoparticles, and biopolymer-based nanomaterials as some of the forms of nanoparticle therapies in treating diabetic wounds. It will attempt to assess whether nanoparticles are effective in the treatment of diabetic wounds, by analyzing the benefits and potential risks of this treatment choice.

Methods

Evidence-based research was gathered from scholarly journals accessed via databases including ProQuest, EBSCOhost, and Science Direct, with access granted via Touro college. All relevant research publications were gathered and analyzed for information on nanoparticles for the treatment of diabetic wounds.

Chronic Wounds

The wound healing process consists of several steps, hemostasis, inflammation, proliferation, and remodeling (Grubbs & Manna, 2022). Diabetic wounds may have issues at any of these stages which will then prolong the healing process. Individuals diagnosed with diabetes are at risk for developing peripheral artery disease (PAD). PAD is the blockage of the vessels that carry blood to the lower extremities which results in decreased blood flow. One cause for the lack of proper healing is insufficient vascular flow, which is critical for healing (Okonkwo & DiPietro, 2017).

Additionally, the immune system involved in wound healing appears to malfunction in diabetic patients. Macrophages and monocytes are important cells of the innate immune system that play a role in wound healing. Normal wounds have shown macrophages switch from a proinflammatory phenotype (M1) to a pro-repair phenotype (M2) during the healing process. This ensures a proper transition to allow for the regrowth of tissue. However, it is believed that in diabetic wounds this process is altered and the M1 macrophages are extended causing a prolonged inflammation stage and preventing the wound from continuing to heal. In a study performed on mice with diabetic-induced wounds researchers observed the pro-inflammatory phenotype of macrophage activity even at day 10 post-injury. The healthy group showed a transition to the healing phenotype of macrophages on day 5 post-injury. As a result of this, the diabetic mice had increased inflammatory cytokines, diminished levels of growth factor, and decreased angiogenesis resulting in impaired wound healing (Mirza & Koh, 2011).

MicroRNA 21 (miRNA 21) is the microRNA that plays an important role in the transition of the macrophages from the inflammatory phenotype to the reparative phenotype. Levels of miRNA 21 are reduced in diabetic wounds and therefore prevent the normal conversion in the phenotype of the macrophages. The reduced levels also impact the migration of fibroblasts and keratinocytes to the wound. Fibroblasts and keratinocytes are cells that execute regrowth and re-epithelialization in wounds and respond to increased levels of miRNA 21. Based on this, the decreased levels of miRNA at the wound play a role

in the increased inflammatory stage and decreased healing (MacLeod & et al., 2016).

Hyperglycemia causes decreased vascular flow and damage to endothelial cells via the production of reactive oxygen species (ROS). Abnormally high levels of ROS cause oxidative stress on cells and lead to cell death (Burgess & et al., 2021).

When wounds do not heal properly it can result in an increased risk of infections and biofilm formation. Additionally, there is evidence that diabetic skin has higher rates of bacterial colonization (Jagadeesh & et al., 2017). Overall, there are multiple factors associated with reduced wound healing in diabetic patients.

Forms of Treatment

There are many forms of treatment that attempt to improve the healing of diabetic wounds. For something to be considered an effective treatment method, it should include certain properties; the ability to absorb exudate, allow for effective water vapor transmission and contain antibacterial and anti-inflammatory properties. Additionally, having a drug loading capability, elasticity and strength are also beneficial. The treatment method should also provide a moist environment for wound healing. However, most wound treatment options do not contain all these properties, and diabetic wounds that are treated with conventional methods often produce scarring (Shalaby & et al., 2022). It is important to protect diabetic wounds from any microbe, as any infection will further complicate the healing process. Simple dressings can provide protection to the wound while it attempts to heal (Whittam & et al., 2016). Other treatment options include topical medications, gene therapy, and oxygenation therapy. Larval therapy has also been tested for aiding the healing process of chronic wounds. The larvae consume dead tissue from diabetic wounds and their secretions have been shown to contain antibacterial peptides which improve wound healing (Romeyke, 2021).

Nanotechnology

Nanotechnology is a recent introduction to treating diabetic wounds. Nanoparticles range from 1 to 100 nm in size, giving them the benefit of having a large surface area to volume ratio. The micro size of the particles allows for them to have unique properties when interacting with compounds (Maneesha & et al., 2016). Numerous nanoparticles are being tested which provide unique improvements to healing. The main classifications for nanoparticles are carbon-based, metal-based, semiconductor, ceramic-based, lipid-based, and polymeric (Ibrahim & et al., 2019). This review will focus mainly on metal and lipid-based nanoparticles. Metal-based nanoparticles such as gold and silver nanoparticles show anti-bacterial and anti-inflammatory properties (Pangli & et al., 2021). Zinc oxide nanoparticles are studied for drug delivery as well as for biocompatibility (Huang & et al., 2017). Lipid nanoparticles have been analyzed for use as a drug delivery system. Biological polymers have also been tested for incorporation into nano-formulations that can be applied for wound healing. Nanoparticles can be applied to the wound either topically or injected, and formulated into films, fibers, and gels.

Synthesis of Nanoparticles

The process of synthesizing nanoparticles differs for organic and inorganic particles. Metal nanoparticles are inorganic and can be produced via physical and chemical methods. Chemical synthesis involves the use of a reducing agent, and the type of agent used affects the character of the nanoparticles formed (Ghazali & et al., 2014). There are harmful effects that synthesizing metal nanoparticles has on the environment and their toxicity is an issue. Therefore, there has been much research for finding alternate safe methodologies to form metal nanoparticles rather than using chemical reducing agents.

Bio-mediated methods of synthesizing metal nanoparticles involve using biomaterials as the reducing agents which reduces the toxicity and damage to the environment. Zinc nanoparticles have been produced using extracts of Dovyalis caffra fruit as a bio-mediated reducing agent (Adeyemi & et al., 2019). Another biological method for synthesizing gold nanoparticles is using Magnolia kobus and Diopyros kaki leaf extracts. The rate of reaction was higher, compared to using a chemical-reducing agent. They also showed that the temperature of the reaction and the concentration of the plant extract affected the size and shape of the particle. This gave a way to control the desired size and shape of the nanoparticles being synthesized (Song & et al., 2009). An interesting plant extract that has also been used for gold nanoparticle synthesis is that of Chamaecostus cuspidatus. This plant possesses interesting qualities in the treatment of diabetes, and in India, it is referred to as "the insulin plant". The gold nanoparticles that were synthesized showed anti-diabetic effects and did not show toxicity when tested in vivo (Ponnanikajamideen & et al., 2019). Plant-based reducing agents seem optimal as compared to microbe-derived reducing agents since they require less purification and have fewer harmful side effects. There are hundreds of other bio-mediated ways that have been discovered to synthesize metal nanoparticles, including the use of bacteria, fungi, algae, and plant extracts as reducing agents.

Metal Nanoparticles

Silver Nanoparticles (AgNP)

Silver nanoparticles have been widely researched and shown to have antimicrobial and anti-inflammatory properties. Silver had a long history of being used in wound treatment but with the introduction of antibiotics, it became less popular. Recently, there has been renewed interest in using silver nanoparticles for their antibacterial properties, because of an increase in antibiotic resistance. Silver nanoparticles can be used alone or in conjunction with antibiotic treatment.

One method for observing the antibacterial effect that silver nanoparticles have was done using AgNP synthesized from cyanobacteria. These silver nanoparticles were tested for anti-MRSA capability in diabetic wounds. At low concentrations, the nanoparticles showed promising action against MRSA infection. Additionally, when using a combination of AgNP combined with 0.5% chloramphenicol, a strong antibiotic, there was practically 100% anti-MRSA activity. This was significant; indicating that combinations of AgNP with antibiotics produced significantly better antibacterial capabilities than antibiotics alone (Younis & et al., 2022).

Another example of AgNP's antibacterial properties is its effects on gram-negative bacteria. These silver nanoparticles were synthesized with sodium citrate to stabilize them. Gram-negative bacteria are often antibiotic resistant and therefore make controlling and treating these strains of bacteria quite challenging. Hospitals are frequently challenged by the spread of these bacteria. P. aeruginosa is a gram-negative strain of bacteria that causes many nosocomial infections, contributes to biofilm production, and is resistant to many forms of antibiotic treatment. Three strains of P. aeruginosa were shown to have significant susceptibility to the treatment of AgNP at 5.0 micrograms/ml concentration. Even more impressive were the results of silver nanoparticles on hospital strains of these bacteria which had shown resistance toward 11 types of antibiotic treatment. When these hospital strains were treated with 5.0 micrograms/ml concentration of AgNP there was 99.9% bacterial death, after 12 hours. Addressing the toxicity factor, these particles showed low toxicity at 5 micrograms/ml when tested. However, for extra safety, the concentration levels should be even lower when using them as a coating for medical devices, and the release of the silver ions should be slow (Salomoni & et al., 2017). This experiment shows the success of silver nanoparticles even on difficult-to-treat hospital-associated strains of resistant bacteria.

A study observing the wound healing potential of silver nanoparticles involved the bio-mediated synthesis of AgNP using Carica papaya extract. Using plant-based synthesis helps lower the risks of toxicity of the nanoparticles. The AgNP was tested in vivo on rats with streptozotocin-induced diabetes on excision wounds. The group that was treated with topical application of the nanoparticle solution showed the best wound healing. The other groups included treatment with povidone-iodine, an extract of Carica papaya leaves, and a control group that did not have as good of an outcome as the nanoparticles. After 14 days these biosynthesized silver nanoparticles successfully closed the wound by 100%, whereas other forms of treatment only partially reduced the wound area (Chandnani & et al., 2022).

Another method tested AgNP on human dermal fibroblasts that were taken from live donors and tested in vitro. The particles produced a decrease in wound inflammation by lowering the expression of the levels of Interleukin IL-6 levels. This decrease was observed when using concentrations of AgNP at 0.25 and 2.5 micrograms/ml. These interleukins are important in the inflammatory response of the immune system against invading pathogens. An issue with overexpression of these interleukins can cause chronic inflammation problems (Ambrozova & et al., 2017). As discussed previously, the decreased healing of diabetic wounds stems from increased and prolonged inflammation.

Gold Nanoparticles (AuNP)

Gold Nanoparticles (AuNP) have also been evaluated for their antimicrobial, and anti-inflammatory properties. One study used AuNPs that were synthesized from Acalypha Indica plant extract. The AuNPs were embedded within the cotton fabric and tested via in-vitro and in vivo uses. The gold-nanoparticle-coated cotton was tested on strains of E. coli and St. epidermidis and after 24 hours the zone of inhibition (ZOI) was analyzed. Zone of inhibition tests the effect of antibacterial treatment on the growth of the bacterial colonies. The AuNP-coated cotton showed antibacterial properties, creating zones of inhibition against E. Coli (26mm diameter) and S. Epidermidis (31 mm diameter). These were the highest ZOIs when compared with other control forms of antibacterial treatment such as Acalypha indica extract-coated cotton (Boomi & et al., 2020).

The research also showed the antioxidant properties of the extract of gold nanoparticles via an in-vitro study. Free radicals cause damage to cells, and it is important to find methods that use antioxidants to protect against the damage of free radicals. A DPPH solution which is a compound that has stable free radicals was used to analyze the antioxidant properties of gold nanoparticles. As The

concentration of AuNp extract increased; the antioxidant abilities also increased. When tested, he extract containing the gold nanoparticles had an Ic50 value of 16.25 µg/mL. For DPPH an extract that produces a value of IC50 that is between 10-50 mg/ml is considered to have strong free radical scavenging abilities. The gold nanoparticles showed highly significant antioxidant capabilities. The wound-healing properties of these AuNP were tested in vivo on mice containing diabetic-like wounds. When compared with a control group the mice whose wounds were treated topically with AuNP extract, exhibited much better healing. This treatment seemed to improve blood vessel formation and collagen matrix remodeling, both of which allowed for faster wound healing and skin regeneration. Additionally, the nanoparticles shortened the inflammation stage of the wounds, which helped with the healing (Boomi & et al., 2020). An extended inflammatory stage is a critical issue of diabetic wounds as discussed earlier. Treatment that is successful in reducing the stage of inflammation in these wounds is promising.

Another study using nanoparticles made from leaf extract of Physalis peruviana produced similar results in the treatment of diabetic wounds. This study also tested the in-vitro aspect of gold nanoparticles against different strains of gram-positive and gram-negative bacteria, as well as a strain of gram-positive fungus. As the concentration of AuNPs increased so did their zones of inhibition against all strains that were tested. The zones of inhibition were the best detected against the gram-positive fungus (C. albicans) and S. aureus and B. subtilis gram-negative (E. Coli). The zones of inhibition for P. aeruginosa were slightly less, but the gold nanoparticles showed antimicrobial properties. When tested against E. coli the gold nanoparticles were as effective as many forms of antibiotics tested. The wound healing potential was tested on rabbits who had diabetic-like wounds. The test compared the results of treatment with standard cotton versus gold nanoparticle-embedded cotton. The rabbits treated with the cotton containing the nanoparticles portrayed faster-wound healing at the 6-day mark compared to the control group. After 14 days the wounds treated with gold nanoparticles were fully healed without signs of infection thus portraying the wound-healing advantage of the AuNPs (Stephen & et al., 2022).

Zinc Oxide Nanoparticles

Zinc oxide nanoparticles are a group of inorganic nanoparticles with promising antibacterial properties. Zinc oxide has been approved as "safe for use" in biological applications and is cheaper compared to other types of inorganic nanoparticles. In one study zinc oxide nanoparticles were tested against different strains of gram-positive, gram-negative, and biofilms in-vitro. The researchers found that using a 500nm particle size of ZnO-NP was more effective as compared to smaller sizes. In gram-negative bacteria such as E. Coli and P. aeruginosa, there was 50% bacterial death when treated with 500 µg/ml of zinc oxide nanoparticles. At 1000mg/ml with 24-hour incubation, no colonies survived. For gram-positive bacteria, S. aureus 92% were killed when treatment comprised 500 µg/ml of ZnO-Np, and 98% with 1000 µg/ml of ZnO-NP. After 24 hours of incubation with the nanoparticles, there were no colonies. Significantly, ZnO-NPs were effective against MRSA, drug-resistant S. aureus. After treatment of 750 µg/ml and 6 hours of incubation, there were few surviving colonies. The zinc-oxide nanoparticles also showed success against biofilms when tested on established biofilms of P. aeruginosa and S. aureus. With increasing dosage strength of ZNO-NP, there was diminished biofilm formation and survival. Interestingly it was shown using scanning electron microscopy, that the ZnO-NP fights bacteria by attacking the bacterial cell membrane, as seen by S. aureus where after a minimal dose of ZnO-NP the membrane was completely disarranged (Rashmirekha & et al., 2014).

A second part of the study tested the in vivo antibacterial properties of zinc oxide nanoparticles in the treatment of S. aureus infections in mice. After treatment with ZnO-NP, the bacterial burden was significantly reduced compared to the control. The rats treated with the Zinc oxide nanoparticles exhibited reduced inflammation and improved skin composition in the infected wounds (Rashmirekha & et al., 2014).

Titanium Dioxide Nanoparticles (TiO2 NP)

Titanium Dioxide Nanoparticles have also been tested for their diabetic wound healing capabilities. This class of metallic oxide- nanoparticles is stable and exhibits minimal toxicity. Green synthesis of TiO2 NPs is a safer method for producing these particles. In one study TiO2 NPs were made from Ocimum sanctum, a plant extract, and embedded into a chitosan gel-based drug delivery system. This provided a uniform dispersion of the particles when applied topically to a wound. This experiment was performed in vivo on rats with Streptozotocin-induced diabetes and excision wounds. The rats were split into groups with a control group, a treatment of just chitosan gel, a group treated with Tio2 nanoparticles in chitosan gel, and a group that received a treatment of silver sulfadiazine, a topical antibiotic. The control group exhibited inflammation in the wound while the other three groups didn't show signs of infection or pus formation. The group

that was treated with the zinc oxide nanoparticle gel as well as the ones treated with the silver sulfadiazine showed the best wound healing after 7, 14, and 21 days. The least inflammation was in the groups treated with TiO2 NPs gel, which is likely due to the anti-inflammatory properties of chitosan combined with the titanium oxide. The measurement of the wound contraction of the diabetic wounds clearly shows the success of the Titanium dioxide nanoparticles with chitosan gel. Overall, this experiment was successful in demonstrating the possibility of using Titanium oxide nanoparticles for improved healing (Ahmad & et al. , 2022).

Lipid Nanoparticles

Lipid-based nano formulations can be classified into two main groups, liposomes and lipid nanoparticles. They function similarly but are structurally different. Liposomes consist of a lipid bilayer with an aqueous center, while lipid nanoparticles don't have that aqueous middle. The preferred method of synthesizing solid lipid nanoparticles is via high-pressure homogenization which reduces the size of the sample to a small particle (Kumbhar & et al., 2022). Lipid nano formulations possess unique characteristics that make them an ideal drug delivery system for diabetic wounds. Firstly, their small size and lipid makeup allow them to deliver drugs in a regulated manner and advance the interaction between the drug and the wound site. Additionally, the lipid-based particles share similar composition to bodily lipids and allow for successful tolerability as a drug delivery system and making them biodegradable (Dilara & et al., 2017).

Lipid nanoparticles are amongst the most widely researched organic nanoparticles and have many useful features. Lipid nanoparticles as drug delivery systems improve wound healing of diabetic wounds for multiple reasons. These particles were shown to have better wound penetration compared to other drug delivery systems. Additionally, they also can carry and deliver a wide variety of drug molecules and increase the half-life of the drugs (Matei & et al., 2021). One study incorporated lipid nanoparticles as a carrier for siRNA to diabetic wounds. A critical issue in the healing of diabetic wounds is extensive inflammation. Overproduction of the TNF alpha cytokine by the macrophages promotes fibroblasts in the wound to produce the MCP-1 chemokine which then signals an increase of macrophages and monocytes to the wound increasing inflammation in an inflammatory loop. siRNA therapy blocks the overproduction of TNF alpha thereby directly improving the healing process. This study showed the success of using lipid nanoparticles as the vehicle of transport for siRNA therapy. Wound cultures were prepared to mimic characteristics of a real diabetic wound, including a macrophage- fibroblast culture that exhibited the cytokine properties of a real wound. The lipid nanoparticles delivery of siRNA sequence was successful in reducing both the TNF alpha cytokine as well as the Mcp-1 chemokine thereby successfully reducing two inflammatory factors of diabetic wounds (Kasiewicz & al., 2016).

Another study researched the use of tissue scaffolds together with the drug simvastatin combined in a lipid-based carrier. The data showed these lipid particles were successful in encapsulating the simvastatin. Additionally, the results showed that it was a stable delivery in combination with the tissue scaffolds treatment. The success of the study in vitro diabetic wound models proved the feasibility of lipid-based drug delivery systems (Dilara & et al., 2017).

Additionally, solid lipid nanoparticles (SNL) were tested as a drug delivery vesicle for ATRA (all-trans retinoic acid) in an in-vivo study. ATRA has been shown to have some wound-healing properties however it can also be harmful to wounds if applied for more than a short time period. Chitosan is a polysaccharide compound that has low toxicity, biocompatibility and can control the release of drugs. The study attempted to evaluate chitosan film for drug administration method but because of the low solubility of ATRA (hydrophobic) in chitosan (which is hydrophilic), the researchers sought other delivery systems for incorporating the ATRA. One key benefit of solid lipid nanoparticles is that they can bind both hydrophilic and hydrophobic drugs. The ATRA was incorporated into solid lipid nanoparticles delivered to the chitosan film. This encapsulation prevents the overdosage of the drug to the wound while incorporating chitosan. The SNL-ATRA chitosan treatment helped the healing process by increasing the collagen deposition in the wounds. It also appeared to reduce the infiltration of neutrophils into the wounds, which helped healing, as diabetic wounds often have increased infiltration of neutrophils which cause inflammation and a reduced rate of healing. There was no sign of skin inflammation from the ATRA which was critical in proving that the SLN were successful in delivering the ATRA in a way that was regulated and sustained. This is another example where the use of lipid nanotechnology as a drug delivery system helped healing of diabetic wounds (Valquíria & et al., 2020).

Polymeric Nanoparticles

An additional class of organic nanomaterials include Biopolymeric nanoparticles, which as a group include proteins and polysaccharides, and may consist of chitosan, collagen, silk fibroin to name a few. The benefit of using

biopolymeric nanoparticles is that they are biodegradable and biocompatible (Sundar & et al., 2010) . They have been used successfully as a drug delivery system, and as a carrier for other treatments.

In one study, cellulose nanocrystal films were tested, since nanocellulose is a biopolymer that can be extracted from a variety bacteria and plants. It was used as an antimicrobial wound dressing film using cellulose nanocrystals as a drug delivery system for curcumin. Nanocellulose is an excellent material for wound dressings due to its impressive compressive properties and excellent ability to absorb exudate. Curcumin increases levels of growth factor β1, a protein involved in cell growth and proliferation. This compound also protects skin cells from oxidative damage. The film containing curcumin improved wound healing in a diabetic rat model after 7 days of topical application. The film was 99.9% effective at inhibiting bacterial growth at the wound, which is important for wounds where bacteria infect and impair healing. Compared with the control group the treated wounds also showed fewer inflammatory cells. Cellulose film was an effective system for curcumin and was successful in treating method for diabetic wounds (Woei & et al., 2018).

An in vivo study testing the use of silk fibroin/chitosan scaffolds containing adipose-derived stem cells (ADSC) to treat diabetic wounds. Rats with diabetic-induced wounds were split into a control group, a silk fibroin/chitosan scaffold grafts group, and a group that was given the ADSC-containing grafts. The group treated with the ADSC scaffold grafts showed the highest levels of wound size contraction. This was likely due to the properties of the ADSC which increased cell infiltration, epithelialization, and angiogenesis, all playing an important role in improved wound healing (Wu & et al., 2018).

Nanomaterials in various forms can be integrated into a variety of methodologies for the possible treatment of diabetic wounds, implemented for treatment in many different forms. Biopolymer films are effective as they are flexible and often contain wound-healing agents. They are also biodegradable and usually transparent allowing for monitoring of the wound healing without constant opening of the film. Nanofiber-based dressings have a high surface-to-area ratio and are therefore effective in drug delivery. These dressings also have a diameter size that is similar to that of the extracellular matrix, which aids in cell proliferation, adhesion to the skin, and wound healing. Hydrogels consist of networks of linked polymers and high moisture content. They are effective at providing a moist environment for the wound, absorbing exudate, and preventing infections. Using biopolymer-based hydrogels for drug delivery seems to lower the toxicity issues with many drugs. Their composition allows for them to be malleable and adhesive making them an ideal choice for a wound dressing Biopolymer-based foams and bandages are flexible and have high absorbency for wounds with exudate. They can also deliver drugs and other therapeutic agents (Alven & et al., 2022).

Harmful Effects of Nanoparticles

Recently studies have shown that nanoparticle treatment is a safe and effective way to treat chronic wounds; however, there is still concern over the safety of using nanomaterials. Before implementing a new class of treatment options, it is vital to ensure the safety of the treatment. It is also important that the possible risks are clearly understood by the user. The challenge with evaluating the safety of nanoparticles lies in the newness of this treatment. It is hard to make a definite conclusion about safety when there hasn't been enough time to fully evaluate all the lasting effects. A big concern of nanoparticle therapy is the concern of toxicity. The issue of toxicity arises mostly regarding metal-based nanoparticles. Silver nanoparticles as explained earlier contain many important anti-microbial and anti-inflammatory properties. They have also been shown to have associated toxicity. Research testing their toxicity is limited to in vitro studies as well as short-term in vivo studies on animals. Therefore, it is challenging to understand the ramifications that these silver nanoparticles would have on complex wounds over an extended period of time. Studies have found that the silver nanoparticles disassociate with silver ions and the ions cause the toxicity (Edwards-Jones, 2022). However, despite issues with toxicity, there have been attempts to minimize the toxicity of silver nanoparticles by using stabilizing agents during the synthesis of the particles. Additionally, when testing silver nanoparticles in vitro it appeared that the biologically synthesized silver nanoparticles caused less cytotoxicity compared with chemically synthesized ones. It also appears that the toxicity causes an increase in the production of reactive oxygen species ROS (Desai & et al., 2022).

An in vivo study tested the toxicity factor of green synthesized gold nanoparticles. Researchers took mice and injected them with treatments of the biologically synthesized nanoparticles and orally injected them daily for 10 days. After 10 days, the mice did not exhibit any symptoms of toxicity. Furthermore, when the kidneys, liver, and lungs of the mice were tested they did not show increased toxicity compared with the control group of mice. These results agreed with others showing that biologically synthesized nanoparticles were not toxic to cells (Kumar & et al., 2017).

Titanium oxide nanoparticles must be carefully regulated as extensive application can cause cytotoxicity of the dermis and aging of the skin. This is caused by oxidative stress from increased free radicals and the diminished collagen (Pormohammad & et al., 2021).

Solutions for the issue of toxicity may include using biological mediated factors for the synthesis. Also, lowering the concentration of the particles can reduce the risk. It appears that research into the toxicity risk of using nanoparticles for practical treatment is still in the early stages. The information on the long-term negative effects of the usage of the compounds investigated in this review will require further elucidation before a better understanding of the various short-term and long-term health risks is better understood.

Conclusion

In conclusion, nanotechnology seems promising in the future of diabetic wound treatment. The diversity of nanomaterials ranges from inorganic to organic and can be incorporated into many different forms of treatment. Based on in vitro and in vivo animal studies, these particles exhibited anti-microbial, anti-inflammatory, and wound-healing capacities. The concern for the toxicity of these nanoparticles needs to be further researched. Using biological mediated reducing agents, as well as, lowering the concertation of nanoparticles in treatment may help reduce risks of toxicity. Extensive research should be implemented before this can be used as a widespread treatment option.

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