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Application of Medicinal plants loaded Nanoparticles in the Treatment of Diabetic Wound

Nikita Shinde, Jaydeep Pawar*, Dnyandev Gadhave, Shital Bosale.

Department Of Pharmaceutics, HSBPVT's GOI College of Pharmacy (Affiliated to Savitribai Phule Pune University), Kashti, Dist. Ahmednagar, 414701, Maharashtra, India.

Abstract: Herbal medicines has achieved acceptance throughout the world in recent times. In different parts of India, ethnomedicinal plants are used to treat several ailments. In many clinical or research area, herbal medicines are considered for its less side effects than the synthetic medicines. Plants are better source of novel bioactive molecules with therapeutic effect. In the past few decades, the combination of nanoparticles from the plant sources have demonstrated to be an efficacious and alternative method for the innovative production of nanoparticles. In this article, the importance of nanoparticles as a drug carrier to the target site and incorporating the herbal drugs into novel drug delivery system are studied. The review also focused on to increase the adherence of topical application. Herbal drug with a great potential of wound healing activity especially in the diabetic complications is seems to be a challenging part. The herbal drugs imparting the activity to increase the growth factors and reducing the oxidative stress during wound healing part has studied.

Keywords: Wound healing, Diabetic wound, Ethnomedicinal plants, novel strategy, nanoparticulate drug delivery system.

Introduction:

Wound may be defined as an injury to living tissue caused by a cut or other impact, typically one in which the skin is cut or broken. Wound healing occurs in various processes such as haemostasis, inflammatory phase, proliferative or fibroblast phase, and remodelling of tissues. It is always challenging to treat the different types of wounds with less side effects of applied medicines at a target site. The review identified that the different authors studied wound healing activity of different medicinal plants as it has fewer side effects than the synthetic medicines. Although there are established limitations when it comes to the herbal medicines. There are several factors that limit the herbal medicines to achieve the potential bioavailability. Factors such as incorrect method of preparation, potential overdose of herbal medicine, improper identification of plant, risk of toxicity, improper knowledge about the standardization methods etc., are the limitations of the herbal medicines[1]. To overcome some of these limitations, Novel Drug Delivery plays an important role. Nanotechnology and nanoscience are the keys of novel drug delivery methods for the herbal constituents as they enhance the penetration, stability of formulation, therapeutic effect, develop the distribution of active constituents within the tissue.

Biologists are incorporating the nanotechnology which describes the engineering and manipulation of entities in 1- 100 nm range and are utilizing its potential to elaborate new therapeutics and diagnostics. Incorporating this tendency of size definition, Nanoparticulate drug delivery system is a notable experiment to conduct together a wide range of drug delivery systems for the delivery of active pharmaceutical ingredient through a variety of route of administration, diagnostics and vaccines in the treatment or anticipation of disease[2].

Diabetes is a chronic, metabolic disorders that is characterized by too much sugar in blood (high blood glucose), which leads over time to serious damage to heart, blood vessels, eyes, kidneys and nerves. Patients with such diseases are highly increased with the risk of growing foot ulcers. A diabetic foot ulcer is an open sore or wound that obtain in approximately 15% of patients with diabetes. Most of the patients face the complications such as limb amputation. The cost of healing a single ulcer is US$8000 and that of infected ulcer is US$ 17,000 and the major amputation cost is about US$54000. To avoid the surgical treatments, it is necessary to find out the non-invasive remedies with the lower cost[3].

Considering non-invasive remedies, the novel graphene oxide-polyhydroxy butyrate-sodium alginate composite scaffold was composed by solution casting into which two herbal active constituent such as curcumin and *Gymnema sylvestre* was added to achieve healing of normal and diabetic wounds for better tissue repair application[4]. Another herbal extract such as *Malva sylvestris* extract having antioxidant, anti-inflammatory, wound healing, anti-microbial, hepatoprotective, anticancer, antinociceptive properties. Polyurethane (PU) based on nanofibers wound relieving with Malva sylvestris extract were prepared and tested for their effects on the diabetes wound healing process. The extract containing nanofibers (15% w/w) showed 70.66% and 69.83% antibacterial activity against *E. coli* and *S. aureus* bacteria, respectively[5].

The previous studies reported, the topical application having a poor compliance due to its delaying effect. But in case of wound complication, topically administered drugs are effective in rapid wound contraction at the wound area. Topical drug treatment was found to be promising for the skin disease such as psoriasis, phthisis, squamous cell carcinoma etc. To increase and maintain the stability of drug molecule, different nano carriers play an important role namely liposomes, nanoparticles, dendrimers and nano emulsion[6].

Types and classification of Nanomaterials:[7]

1. **Carbon based nanomaterials**: These materials are morphologically classified as carbon nanotubes, carbon nanofibers, fullerenes.

   i) **Carbon nanotubes:** Carbon nanotubes has wide spectrum in biomedical application and have been considered as a new generation nanoprobe. It is sustainable for biosensing application as they have high conductivity, chemical stability and sensitivity. The attention towards the carbon nanotubes increased rapidly as it is used to delivered the drug moieties into the living cells. It makes easy to penetrate the drug across the cell membrane non-invasively due to their natural morphology[8]. It is reported that carbon nanotubes were useful to delivered the drug for the diagnosis and treatment of cancerous tumour at tumour site[9].

   ii) **Carbon nanofibers:** These are the cylindrical shaped nanostructures with graphene layers arranged as stacked cone, plates or cups. It is considered as a safe biomaterial as it exerted positive results in clinical area. Carbon nanofibers produced by the electrospinning with triethyl phosphate and calcium nitrate tetrahydrate containing β-tricalcium phosphate nanoparticles which enhanced the degradation property of carbon nanofibers in biological environment[10].

   iii) **Fullerene:** It is another carbon-based material consist of sp^2 carbons. Fullerenes are advantageous for physiological application as it has a unique physical and chemical feature[11]. It is reported that fullerenes play a role of MRI contrast agents and function of quenching and generation ROS in particular condition. Functionalized fullerenes deactivate pathogenic microbial cells and malignant cancer cells[12].

2. **Inorganic based nanomaterials:** Inorganic nanoparticles have vital role in the biomedical application. These materials are nothing but the

   metal nanoparticles. Inorganic nanoparticles such as **iron oxide nanoparticles** play an important role as an MRI contrast enhancer. **Plasmonic nanoparticles** are additional novel group which are used in biomedicine as it has distinctive feature. **Semiconductor quantum dots** are applicable alternative fluorescently categorized nanoparticles[13]. Inorganic nanoparticles are used when the polymeric nanoparticles fail to assessed biocompatibility. **Ceramic nanoparticles** provide great thermal and chemical stability than the polymeric nanoparticles. Thus, to avoid the denaturation of labile agents, encapsulation of drug within ceramic particles are needed as it offers protection from getting contaminate[14].

3. **Organic based nanoparticles:** **Dendrimers** are the synthetic polymers having stereoscopic, highly branched and understandable construction. Several studies revealed the drug conjugation to the dendrimer surface. They are considered as a good carrier for drug delivery[15]. **Micelles** are a group of amphiphilic surfactant fragments, that automatically accumulate in water rounded vesicles. It has a hydrophobic centre therefore they can segregate hydrophobic drugs until they are released by any drug delivery mechanism. Micelles can form in water with the polymers having segments of interchanging the hydrophilic and hydrophobic nature[16]. **Liposomes** have properties that make them multifaceted drug carrier for lipid soluble or water-soluble drugs. It consists of a material with low intrinsic toxicity and it can be prepared with the large scope of chemical composition and sizes. Liposomes have both hydrophilic and hydrophobic compartment, hence the drug with hydrophilic nature can be entrapped in the hydrophilic or aqueous core and drug with hydrophobic nature can be incorporated into hydrophobic core of phospholipid bilayer[17]. **Noisomes** having higher stability than the liposomes because niosomes are prepared by using non-ionic surfactants rather than phospholipids. It can be used to delivered the drug at target site. The approach for selecting the niosome is considerably increased as it has shown great transdermal drug delivery[18].

4. **Composite based nanomaterials:** Composite based nanoparticle is the class of hybrid nanofibers or metal organic frameworks. From the last decades, **metal organic frameworks** are considered large profile area of the nanotechnology system. It is porous in nature as its size ranges in between 0.4 to 3nm. Metal organic frameworks are used to delivered the therapeutic agents. Its is reported that, metal organic frameworks are advantageous for gas delivery in healthcare application. Nitrous oxide is one of the important molecules for biological purpose as its release from the entrapped material is interesting for many in-vivo and in- vitro application[19]. **Hybrid nanofibers** have great application in bioscience as due to their excellent properties like high porosity, exhibit large specific surface area, favourable biocompatibility. It is reported that, hybrid nanofibers helps to extend the drug release and packed inorganic materials increases cell adhesion, proliferation, mechanical properties of the nanofibers[20].

Mechanism of herbal nanoparticles on diabetic wound:

In diabetic wound, due to high blood glucose level, the blood vessels get stiffen and this situation restrict the oxygen and nutrients to reach to the blood vessels which makes the wound healing difficult. Overexposure of oxygen leads to produce the reactive oxygen species (ROS). ROS is a form of free radical that include one oxygen atom and other reactive species such as superoxide and peroxide. These reactive species reduce the oxygen and resulted in higher inflammation. In long term lack of oxygen may cause cell death which further result in possible necrosis and amputation. To overcome such problems, the herbal drug with the strong activities such as antioxidant, anti-inflammatory, antimicrobial, etc is needed. Some herbal drugs are unstable in the skin pH hence to maintain their stability at the wound area, enclosing the herbal drug into nanoparticle is beneficial as it increases the penetration of the herbal drug, increase the stability and surface area. The entrapment of herbal drug in the nanoparticle carries the drug at the target site. After reaching to the target site, the type of nanoparticle in which the drug is entrapped gets degraded in the cellular fluid that led to release the herbal drug at the injured area.

Through the literature survey mechanistic assumption has made on the activity of herbal drug nanoparticles in the treatment of diabetic wound healing as follows:

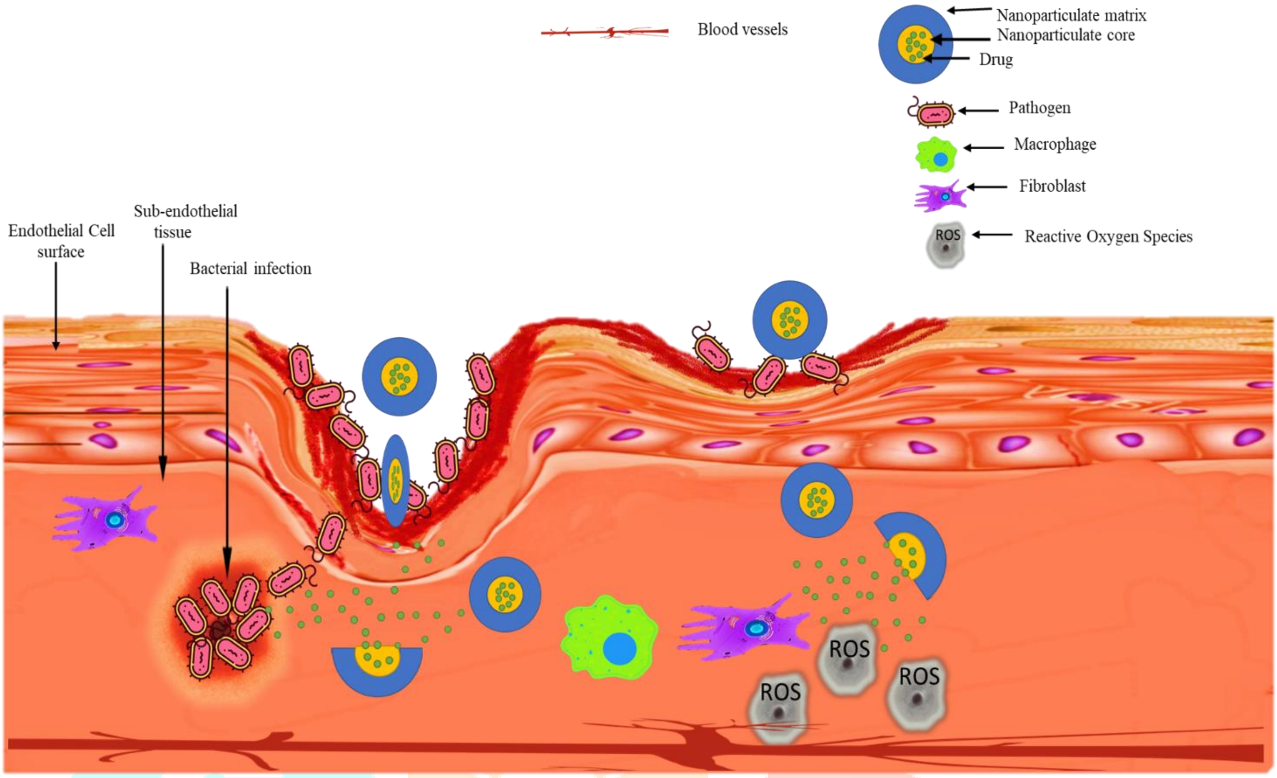
In case of normal wound, bacterial infection release chemokines in the endothelial cell surface (Chemotaxis occur). These chemokines attract the phagocytic cell i.e., neutrophil. Then neutrophil attached to the endothelial cell surface and entered into subendothelial tissue to reach the site of bacterial infection. Once the neutrophil reached the infection site, it engulfs the bacteria and reduce bacterial infection. But in case of hyperglycaemic condition, Chemotaxis gets reduced that affect the neutrophil adherence and therefore impaired the phagocytosis process and result in delayed wound healing. To prevent such consequences, when the herbal drug nanoparticles are applied to the diabetic wound area, it will penetrate the endothelial cell surface and starting act against the factors delaying the diabetic wound healing such as bacterial infection and oxidative stress.

The synergistic effect of antibacterial and antioxidant properties of herbal drug extract will result in effective healing of diabetic wound. For the autolytic debridement the development of hydrogels, transparent films and hydrocolloids are effective as it moist the healing environment which promotes granulation, epithelization, cools the wound and relief the pain[21].

Metal nanoparticles such as silver, copper and gold have majority of trend. Out of them silver nanoparticles have wide application in the clinical area. These metal nanoparticles are prepared by the chemical and physical methods. For the preparation of silver nanoparticles chemical reduction is mostly used method to get stable, colloidal dispersion in water or organic solvents. Silver nanoparticles enclosing curcumin in it was studied. The hydrogel formulation of this curcumin-silver nanoparticles was studies for its antibacterial activity[22]. Another study revealed the biosynthesis of gold nanoparticles using *Woodfordia fruticose*. This herbal drug complexed with the Carbopol to formulate an ointment. This resulted in increased level of hydroxyproline and therefore collagen fibers developing the tensile strength and wound healing process[23].

Mechanistic Diagram:

Fig.



Activity of Herbal drug nanoparticle in Diabetic skin wound

Different Herbal Nanoparticles used in diabetic wound complication:

1. Curcumin, a constituent of *Curcuma longa* Linn. Belonging to the family *Zingiberaceae*. Curcumin is well-known for anti-inflammatory[24] and anti-oxidant activity. So, according to the investigator, the use of curcumin to treat the diabetic wound would be beneficial. Novel nanohybrid scaffolds was prepared comprising chitosan nanoparticles. Freeze dried method was employed to prepare the scaffolds. This strategy was useful to improve the stability and solubility for appreciable wound healing. The morphology of curcumin- chitosan scaffold nanoparticles (CUR-CSNPs) was studied. Biodegradability, biocompatibility, in-vitro drug release and in vitro wound healing studies were performed. At the end of the study, it was identified that the novel CUR-CSNPs acted significantly to contract the wound in test group as compare to the control group and placebo scaffold group.

2. Silver and ceramic oxide nanoparticles with the *Lawsonia inermis* extract in it and *Lawsonia* extract activity was studied in diabetic condition. Silver nitrate and cerium acetate stalk solution was prepared (AgNO3-1.5gm) in 100ml purified water and 20ml *L. inermis* extract was added to 50ml AgNO3solution and kept at oven with temperature maintained at 40℃ for 12hrs. Cerium oxide solution was prepared with cerium acetate in 100ml purified water and 40ml extract was added dropwise in the above stalk solution with stirring for 2hrs then wash with distilled water to remove unwanted compounds. The product was kept in oven at 120℃ for 12hrs. At the end the material was exposed to strong heat at 200℃ for 2hrs. The characterization of nanoparticles using X-ray diffraction, Fourier Transform Infrared Spectroscopy, Particle size analyser, Field Emission Scanning electron microscope and High-Resolution transmission electron

microscope was studied. In vivo sub-acute oral toxicity study of nanoparticles was examined using female Swiss albino mice. Histopathological examination of isolated organs was studied. From the resulted data it has been revealed that these herbal mediated nanoparticles are effective in diabetic condition[25].

3. *Sambucus nigra L*. fruit extract incorporated into gold nanoparticles in the diabetic rats was studied. The gold nanoparticles were synthesized with *Sambucus nigra L*. fruit extract by reducing gold ions from hydrogen tetrachloroaurate solution. Characteristics of synthesized herbal mediated gold nanoparticles was examined using UV-vis spectroscopy, Transmission electron microscopy and Laser Doppler micro-electrophoresis technique was used to study the zeta potential of gold nanoparticles. Activity of synthesized nanoparticles was examined in male Wistar rats. Histopathological study was performed on isolated organs, protein content was measured using Bradford method and anti-oxidant activity of nanoparticles was examined[26].

4. *W. somnifera* leaf extract having anti-diabetic activity hence the study aimed to synthesize platinum nanoparticles enclosing *W. somnifera* drug to examine the antidiabetic activity in male albino rats. To study characteristics of nanoparticles, UV-vis spectroscopy, x-ray diffraction study and FTIR were used. Antidiabetic activity of the synthesized platinum nanoparticles with *W.somnifera* herbal drug was found to be effective[27].

5. Aqueous extract of *Nigella sativa* was incorporated into silver nanoparticle to determine the anti-inflammatory and antioxidant effect in diabetic neuropathy. The silver nanoparticles with *N. sativa aq*. Extract were prepared by using chemical reduction method. The characteristic evaluation of nanoparticles was studied using Scanning Electron microscopy and UV-vis spectroscopy. The effect of synthesized herbal mediated silver nanoparticles was evaluated in experimental rats. In histopathological study, the changes in brain tissues of diabetic neuropathic rats. In biochemical analysis glucose level was measured. The study provides an evidence that synthesized herbal mediated silver nanoparticles exhibit the promising antidiabetic effect[28].

6. Another Herbal nanoparticle effect of on diabetic complication was studied. *G.sylvestreR.Br*. has antidiabetic activity. The formation of gold nanoparticles with *G.sylvestreR.Br*. was prepared and examined its effect in male Wister albino rats. Characterization of gold nanoparticles was analysed by using UV-visible spectroscopy, FTIR spectroscopy, High-resolution transmission electron microscopy. After the treatment of the synthesized nanoparticles, modest change has been observed with islet cells in terms of regeneration, vacuolation and invasion of connective tissues as compared to that of diabetic control group[29].

7. *Sargassum swartzii* is known for potential antidiabetic effect and using this information, gold nanoparticles with *Sargassum swartzii* was synthesized. The effect was studied using male Wistar albino rats. UV-vi spectroscopy, FTIR spectroscopy, High-resolution transmission electron microscopy and x-ray diffraction methods were used to determine the characteristics of gold nanoparticles. Cytotoxicity assay was performed to determine the toxicity effect on cell upon exposure to gold nanoparticles. Fasting blood glucose levels, serum insulin, haemoglobin and glycosylated haemoglobin levels in diabetic treated rats with gold

nanoparticles were significantly decreased compared to the control group. Histopathological study was performed on isolated organ tissues and micrographs of tissues were captured using microscope Olympus BX51. Statistical analysis was performed using one-way analysis of variance followed by Bonferroni's multiple comparisons test where appropriate[30].

8. *Calendula officinalis* belonging to the family *Asteraceae* is another herbal medicinal plant. *Calendula officinalis*-loaded PCL/gum Arabic nanocomposite scaffolds was prepared. The PCL[Poly(ε-caprolactone]/*C. officinalis* solution was prepared using PCL that dissolved in acetic acid under magnetic stirrer. Then *C. officinalis* extract were slowly added into PCL solution and mixed for 1hr. Similarly, PCL/*C. officinalis* /GA (gum Arabic) solution was prepared using GA powder dissolving into formic acid and plant extract were added to the above solution. Then fabrication of these two solutions were carried out. In the evaluation parameters, morphological characterization, mechanical properties, porosity of the nanocomposite scaffold were studied. Degradation behaviour of the nanocomposite scaffolds was regulated by different ratios of GA. By examined all these parameters the study identified this scaffold a potential for tissue regeneration[31].

9. Green synthesis of silver nanoparticle using *Tephrosia tinctoria* was studied for its antidiabetic activity. This plant was rich in phenol and flavonoid group of compounds. The stem part of the plant was powdered and mixed with 300ml of distilled water and kept for 2hrs and then centrifugation was carried out at 5000rpm for 10 mins. The material deposited was collected followed by filtration with watt man filter paper no. 1. Then 100ml of 1mm silver nitrate was mixed with permeate and incubated at 37℃ in Rotary shaker for 24hrs. Again, the mixture was centrifuged at 9000 rpm for 10 min. Purification was performed using distilled water and centrifuging at 9000rpm for 10 min for each cycle. The synthesized nanoparticles were analysed by UV-vis spectroscopy. Characteristic features were studied using X-ray diffraction, scanning electron microscope, transmission electron microscope and Bruker – Alpha-T FTIR spectrum was used to study the functional group. To determine the antidiabetic activity the glucose uptake assay was performed. This green synthesis of silver nanoparticles was found to be cost effective and eco-friendly[32].

10. *Holoptelea integrifolia* leaf extract was prepared and mixed with the silver nitrate solution to prepare the *Holoptelea integrifolia* incorporated silver nanoparticles. Up to 2 mm of silver nitrate solution was prepared by solubilising the silver nitrate in 75ml of distilled water. From this stalk solution, 50ml of AgNO3 solution was mixed with 100ml of *Holoptelea integrifolia* leaf extract. The synthesis of Ag nanoparticles was confirmed by observing the colour change from light green to colloidal black colour. To determine the phenolic content, flavonoid content and antioxidant activity measurement, quantitative biochemical assay was performed. UV-visible spectrophotometer, X-ray diffraction, FTIR spectrophotometer and Field Emission Scan Electron Microscopy was used to determine the characteristic features of silver nanoparticles. By performing biological studies, author revealed the promising activity of biosynthesized silver nanoparticles that they can be potential used as an antidiabetic, anti-inflammatory, antiradical and antimicrobial agent[33].

11. Gold nanoparticles with the *Chamaecostus cuspidatus* leaves extract were used to determine the antidiabetic and antioxidant properties of this nanoparticles. 1mm of Chloroauric acid was 10ml of powder plant extract to synthesized gold nanoparticles. Orbital shaker was used to keep the mixture at room temperature. Characterization of the synthesized gold nanoparticles was studies using UV-vis spectrophotometer, X-ray diffraction and Scanning electron microscopy. The thermal analysis of the nanoparticles was performed using Thermogravimetric analysis. Free radical scavenging activity of the nanoparticles was estimated by using DPPH, nitric oxide, Superoxide, lipid peroxidation, hydroxyl radical scavenging assay. Acute toxicity study was performed by oral administration of nanoparticles to the animals for 10 days. To study antidiabetic activity adult male Wistar mouse were used. For Biochemical analysis blood sample was collected and serum was separated. From the above studies, the experimental results revealed the hypoglycaemic effect of plant extract and role of biosynthesized gold nanoparticles in wound recovery[34].

12. *Syzygium cumini* was investigated as an antidiabetic and antioxidant possessing herbal plant. This plant has great potential against free radicals hence this plant was widely used to prepare metal nanoparticles by increasing the antioxidant capacity of the formulation. Using the aq. extract of leaves or seeds of the plant, silver nanoparticles by adding silver nitrate in the extract was synthesized. It was observed that leaf extract contains polyphenols and more other constituents than seed extract. Similarly, gold nanoparticles were synthesized using plant aq. Extract. Also, the fruit extract of this plant was used to synthesized silver nanoparticles and characteristic parameters was studied using different techniques such as XRD, UV-vis spectrophotometer, FTIR, TEM.[35] [35- mittal AK, et al. 2014],

13. Another study investigated the hypoglycaemic effect by combining to phytomedicines, named as *Mulberry* leaf and *Pueraria Lobata*. This herbal extract was incorporated into selenium layered nanoparticles for oral delivery. MPE-SeNP was prepared by using solvent diffusion method and particle size, entrapment efficiency and drug loading were characterizes using analytical methods. On oral administration the synthesized nanoparticle showed significant antidiabetic effect in diabetic rats, great intestinal permeability of the drug, suitability in transepithelial transport and enhanced pancreatic function[36].

14. The extracted Pterocarpus marsupium Roxburgh heartwood has been used to study the effect of wound healing in a diabetic mouse model. Enclosing this herbal extract in chitosan nanoparticles, hydrogel as a novel diabetic wound healing formulation was prepared. These nanoparticles exhibit efficient therapeutic effect on both diabetic and non- diabetic rats. The formulation showed great effect of antimicrobial property against Gram positive and Gram-negative bacteria. PM-CNPsH-1 enhanced granulation tissue and angiogenesis which was observed in histopathological evaluation[37].

15. Enhancement in antidiabetic and antimicrobial activity of the plant *Ocimum basilicum* and *Ocimum sanctum* (*L*.) was prepared by synthesizing silver nanoparticles. Leaf extract of both the plant was analysed for α-amylase and α-glucosidase. The leaf extract was added dropwise to the 45ml of silver nitrate solution and stirred. Colour of the solution turned to brown colour solution confirmed the synthesis of silver nanoparticles. Characterization of the synthesized nanoparticles was investigated using analytical methods.

The biosynthesized silver nanoparticles exhibit greater antibacterial properties than the crude extract and potential antioxidant effect from the plant extract helps to conduct the further study. In this way, combining both the plant extracts showed potential activity in the diabetic complication and hence this study was the great evidence of the antioxidant and antidiabetic activity of the biosynthesized silver nanoparticles[38].

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