

## GREEN NANOTECHNOLOGY APPROACH FOR THE DEVELOPMENT OF HERBAL-BASED NANOPARTICLES IN WOUND HEALING

Smrutiranjana Dash<sup>1</sup>, Kushagra Jha\*<sup>2</sup>, B. Meenal<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India.

<sup>2</sup>Research Scholar, Bachelor of Pharmacy, Department of Pharmacology, Naya Raipur, Chhattisgarh, India.

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**\*Corresponding Author: Kushagra Jha**

Research Scholar, Bachelor of Pharmacy, Department of Pharmacology, Naya Raipur, Chhattisgarh, India.

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### ABSTRACT

Wound healing is a complex biological procedure that happens in numerous stages, together with tissue remodelling, proliferation, inflammation and haemostasis. Conventional technique of curing wounds frequently have difficulty such as antibiotic resistance, cytotoxicity, and not enough tissue regeneration. Green nanotechnology, which uses plant-based reducing and capping agents to make nanoparticles, has become a sustainable and biocompatible option. This review methodically analyses the green synthesis of herbal-derived nanoparticles, including silver, gold, zinc oxide, copper oxide, and titanium dioxide nanoparticles, sourced from medicinal plants such as aloe vera, curcuma longa, centella asiatica, azadirachta indica, and camellia sinensis. The wound healing mechanisms of these nanoparticles are examined, including antimicrobial activity, anti-inflammatory properties, antioxidant effects, promotion of collagen synthesis, stimulation of angiogenesis, and re-epithelialization. The research highlights the integration of herbal nanoparticles into advanced delivery systems called as hydrogels, nanofiber scaffolds, and transdermal patches. The matter associated with standardization, scalability, toxicological assessment, and regulatory clearance have been taken into consideration in this work. The aim of the literature review is to emphasize the potentiality of using plant-mediated synthesis of nanoparticles as an eco friendly approach for the development of the next generation of wound healing treatments.

**KEYWORDS:** Green nanotechnology, nanoparticles, wound healing, herbal medicine, silver nanoparticles, phytochemicals.

## 1. INTRODUCTION

Wound healing is an underlying physiological process crucial for maintaining skin integrity and avoiding infection that leads to tissue injury. It entails a coordinated series of biological processes—comprising haemostasis, inflammation, proliferation, and tissue remodelling that are tightly regulated by a variety of growth factors, cytokines, and cellular signals.<sup>[1]</sup> Even though there are a lot of products for wound care, chronic wounds like diabetic ulcers, pressure sores, and venous ulcers are still a big problem for doctors all over the world. These wounds are frequently made worse by microbial infections, biofilm formation, and chronic inflammation.<sup>[2]</sup> Traditional wound therapy, such as topical antibiotics, antiseptics, and artificial dressings, have become more ineffective and more toxic due to antibiotic resistance, cytotoxicity, and limited regenerative efficacy.<sup>[3]</sup> This has led to demand for other, more greener methods to treat wounds. Herbal medicine, that has been utilized for many years in traditional healing, possesses a lot of bioactive phytoconstituents which have been demonstrated to have antimicrobial, anti-inflammatory, antioxidant, and tissue-regenerative effects.<sup>[4,5]</sup> Nanotechnology particularly at the nanoscale (1-100 nm), has transformed drug distribution and biological material science through making it feasible to enhance bioavailability, target delivery, and controlled release of therapeutic agents.<sup>[6]</sup> Nanoparticles possess distinctive physicochemical characteristics, including substantial surface-area-to-volume ratios, quantum effects, and adjustable surface chemistry, which enhance the therapeutic efficacy of traditional agents.<sup>[7]</sup> When these principles are applied to herbal bioactive compounds, the resulting herbal nanoparticles show much better stability, permeability, and effectiveness than the bulk versions. Green nanotechnology, which is the use of biological materials like plants, microorganisms, and their extracts to make nanoparticles, has become a safe and cheap alternative to traditional chemical and physical synthesis methods.<sup>[8]</sup> Plant-mediated synthesis, specifically, utilises the varied phytochemical components found in medicinal plant extracts—such as flavonoids, terpenoids, alkaloids, polyphenols, and reducing sugars—which function concurrently as reducing, capping, and stabilising agents during nanoparticle formation.<sup>[9]</sup> A comparable diversity of phytochemicals has been extensively recorded in medicinal plants investigated for their pharmacological attributes, exemplified by ginkgo biloba, which possesses a broad array of flavonoids (quercetin, kaempferol, isorhamnetin) and terpenoids (ginkgolides, bilobalide) that impart antioxidant and anti-inflammatory effects.<sup>[10]</sup>

The converging of herbal medicine and nanotechnology shows a notable development for wound care. Herbal nanoparticles combine the biological activity of herbs with the capabilities of nanoparticles as carriers to deliver the active ingredients, which results in increased resistance to infection, anti-inflammatory action, accelerated wound healing, etc. The intention of the review is to summarize green approaches to nanoparticles synthesis, their description, wound healing mechanism, and clinical applications along with existing problems and future perspectives.

Nanotechnology has stirred up many aspects of society and industry by permitting the development of products that are not only extralong lasting, but also smarter, safer, and cleaner for use in fields such as daily living, healthcare, agriculture, and communication.<sup>[11]</sup> Nanotechnology has consistently yet extremely convert industries over the globe.

Its impact is especially noticeable in growing nations, where nano scale innovations have inflated swiftly over the past decade. While the notion itself isn't new, nanotechnology has now advanced into a flexible, established technology driving process in quite a few sectors.<sup>[12]</sup> Nanomaterials are more often than not used in two ways in everyday products.

They can either be add on to live matter to magnify their solidity, durability, or functionality, or they can be used straight to grow fragment edge devices that take dominance of their unique features. The adjustability and efficiency of

nanomaterials make them a motivation at the back of the future creation, with the prospective to transform just about every industrial sector. The human body is engulfed by the skin, acknowledge as its largest organ, wrapping an area of about two square meters in an average adult. It serves as a precautionary shield for the internal organs from the exterior environment. In addition to providing protection, the skin helps retain body moisture, regulates temperature, enable sensory awareness, maintain fluid balance, and acts as the first line of protection in opposition to damaging microorganisms.<sup>[13]</sup>

A wound means the breaking or damage of the upper layer of the skin or mucosa, which can occur due to an injury, burn, or any problem in the body. Wound can appear in multiple forms, such as clean incision from sharp objects, jagged laceration from blunt force, abrasions caused by friction, and contusions or bruises from impact.<sup>[14]</sup> To heal this broken tissue, the body has a complex and controlled process, which is divided into four stages: haemostasis, inflammation, proliferation, and remodelling. Wound entails the disruption or destruction of the superficial layer of the skin and mucous membrane which results from trauma, burns, or complication within the body. Wound can exist in various categories such as a clean incision from sharp objects, a rough cut from blunt object, a rough cut from blunt objects, abrasion from rubbing against surfaces and a contusion from an impact injury.<sup>[5]</sup> The process through which the damaged tissues are repaired is complicated and coordinated, involving four phases: haemostasis, inflammation, proliferation, and remodelling.

Haemostasis is the first stage in this approach. It occurs while blood vessels come together and platelets form a clot of blood in order to stop the flow of blood. This clot act as a starting point for fresh cells and emits vital growth regulators such as pdgf and tgf, which attract healthy immune cells to the wound's site.<sup>[15,16]</sup> After this, the wound becomes inflamed. This is when neutrophils and macrophages (white blood cells) come to the wound site and clean it by eating the bacteria and debris that are there. They let out reactive oxygen species, or ros<sup>[17]</sup> during this process. This is the most important step, and oxidative stress can get too high, which is why persistent wounds often get stuck here. Green nanotechnology, such as nanoparticles composed of neem or turmeric, is very extremely beneficial here. Such nanoparticles function similar to antioxidants and reduce inflammation, which accelerates out the recovery of the injury in contrast to the normal time it requires over a wound to recover.<sup>[18,19]</sup> After inflammation, the growth stage (proliferation) starts. This occurs as fresh skin and blood vessels grow. Research findings demonstrate that novel herbal-coated metal nanoparticles can expedite the wound-healing process by stimulating the production of vegf (the factor responsible for blood vessel formation) and promoting cell proliferation.<sup>[17,18]</sup> Ultimately, a transformation occurs, which is whenever young collagen (type iii) transforms into fully developed and powerful collagen (type i).

This renders the dermis powerful once again. Green nanotechnology is also beneficial here as it avoids significant damage after healing.<sup>[19]</sup> If the body fails to follow this entire procedure, the wound will develop into a chronic wound. Green nanotechnology, on the opposite side, has a double advantage: the metallic ions present in it eliminates microbes and the herbal ingredients assist in helping the wound heal rapidly and entirely.<sup>[19,20]</sup>

## 2. MATERIALS AND METHODS

This study is based on an extensive review of previously published literature sourced from google scholar, pubmed, scopus, springer, nature, research gate, and standard reference books.

### 3. Essential terms in nanoscience and nanotechnology

Table No.1.

Terms	Description	Reference
Nanotechnology	Nanotechnology is a process in which basic attributes of science is used to produce smaller particles at a minute scale of nanometers	[21]
Nanomanufacturing	Nanomanufacturing is the scalable and cost-efficient production of nanoscale materials and devices	[22]
Nanoscale	The range of 1 to 100 nanometers (nm) is where materials show distinct physical, chemical and biological properties because of their larger surface area and quantum effects	[23]
Nanomaterials	Nanomaterials are substances with at least one dimension ranging from 1 to 100 nanometers (nm) and have a larger surface area to volume ratio ( $>60 \text{ m}^2/\text{cm}^3$ ) compared to bulk materials.	[24]
Aspect ratio	The aspect ratio of an element is determined by dividing its longest dimension by its shortest dimension	[25]
Nanospheres	Nanospheres are solid nanoparticles made of polymer or other materials used as drug carrier	[26]
Nanorod	Nanorods are tiny structures made at the nanoscale, where each of their dimensions typically falls between 1 and 100 nanometers.	[27]
Nanofiber	A nanofiber is defined as a fibrous material with a diameter less than 100 nm, often exceeding it by at least a hundredfold.	[28]

### 4. Modern techniques and approaches for the synthesis of nanoparticles

You can make nanoparticles in a lot of different ways, such as by using physical chemical, or biological methods. There are now many ways to make nanoparticles with different surface structures. Some of these methods are biosynthesis, physical synthesis, photochemical synthesis, sonochemical synthesis, electrochemical synthesis, green synthesis, sol-gel synthesis, and chemical synthesis.<sup>[29]</sup> Biological methods are becoming more popular because they are cheap, easy to use, and give you more control over the nanoparticles shape, size, and other properties.<sup>[30]</sup> The bottom up and top down methods are the two main ways to make nanoparticles. A lot of people use the bottom up metho. It uses chemical and physical processes to put atoms or molecules together to make nanostructures that are very complex. This method is similar to how natural biological system wok, where chemical forces build important structures. Scientists use methods like atomic vapour condensation and liquid atom coalescence.<sup>[31]</sup> To make nanoparticles with specific sizes and properties. The top-down method begins with large pieces of material and, over time, uses different physical processes to break them down into nanoparticles. This method requires large, costly machinery, rendering it impractical for mass production. It is mostly used for research in labs and is based on how to grind things. These methods don't work well with soft materials though.<sup>[33]</sup>

#### 4.1. Leading techniques for creating natural product nanomedicine to support wound healing

Many different methods have been created to make nanomaterials because they can be used in many different fields of research and business. Depending on the shapes and sizes of the nanoparticles you want. Different methods use different chemical, physical, or biological ways to make synthesis accurate and useful.<sup>[33]</sup> Biomedicine that uses natural products is now made in a way that is good for the environment, using plants and biopolymers. This system increases the speed of tissue repair, controls inflammation, and boosts antimicrobial activity when we combine therapeutic phytochemicals with nanoscale carriers. There are different ways to do it, and one of them is the green synthesis method, which uses plant extracts to lower the amount of metal ions like (ag, zno). Another way is for natural substances like chitosan and alginate to break down into small pieces on their own. Sometimes these nanoparticles are mixed with a hydrogel and put on the wound. This keeps the wound wet and lets the drug out slowly. The nanoparticles

keep their shape, their surface properties are good, and their antioxidant and antimicrobial properties are very good thanks to all of these methods. This is why infection doesn't happen, and they also help make collagen and new blood vessels. These nanoparticles are loaded with plant-based polyphenols or proteins like lactoferrin, which makes them work even better. They are put into a biodegradable hydrogel (chitosan/pva) and put on the wound. The speed at which the drug is released can be controlled by changing the strength of the hydrogel.<sup>[34]</sup> systems made in this way close the wound quickly, help new skin grow, and don't hurt the body. Before these medicines can be used correctly, they need to be researched so that they can be given out easily in the market. We use techniques like tem/sem, dls, ftir, and xrd to learn more about their properties and shape. Researchers test these medicines on bacteria and animal wound healing models in the lab to see if they really work.<sup>[35]</sup> There are different kinds of nanostructured formulations that have specific properties that are needed for natural wound healing.

## 5. Wound healing: phases and challenges

### 5.1. Phases of wound healing

There are four distinct stages of wound healing that overlap: haemostasis, inflammation, proliferation, and remodelling.<sup>[1,2]</sup> The body's first response to tissue damage is to stop bleeding. Platelets stick together to start coagulation cascade and make a fibrin clot that temporarily closes the wound and gives cells a place to grow.<sup>[36]</sup> After the body stop bleeding, inflammation starts. At this point, neutrophils and macrophages go to the wound site. These cells eat dead cells, bacteria, and other trash. They also let out pro inflammatory cytokines (tnf- $\alpha$ , il-1 $\beta$ , il-6) and reactive oxygen species (ros). These are important for getting rid of bacteria, but they need to be carefully controlled so they do not hurt tissue.<sup>[37]</sup> During proliferation, fibroblast move and multiply, collagen is made, the extracellular matrix (ecm) is laid down, new blood vessels form, and the epithelial layer is rebuilt. Tgf- $\beta$ , vegf, and egf are some of the growth factors that control this process.<sup>[38]</sup> The last stage is called remodelling. It involves replacing collagen type iii with collagen type i and making the wound saller, which causes scar tissue to form that is biomechanically similar to normal skin.<sup>[39]</sup>

### 5.2. Challenges in conventional wound management

There are still some problems with wound care, even though it has gotten better. Chronic wounds, like diabetic foot ulcer, venous leg ulcer, and pressure ulcers, affect millions of people all over the world. These injuries make people sick, lower their quality of life, and cost a lot of money to treat.<sup>[2]</sup> The main issues are: microbial injection and biofilm formation are two of the main things that slow down the healing of wounds. Biofilm producing organisms, such as staphylococcus aureus, pseudomonas aeruginosa, and candida species, demonstrate considerable resistance to conventional antibiotics, rendering standard treatments ineffective.<sup>[3]</sup> Taking care of wounds is getting harder because more and more pathogens are resistant to many drugs. Macrophages that are working too hard and making too many ros cause inflammation that doesn't go away. This slows down tissue regeneration and makes wounds last longer.

Traditional anti-inflammatory drugs may stop inflammation in a board way, which can block important healing signals.<sup>[37]</sup> Other things that can cause chronic wounds are bad angiogenesis and ecm remodelling, which make it hard for oxygen and nutrients to get to the tissue that are healing the wound. Disruption of growth factors leads to inadequate advancement in wound healing.<sup>[38,40]</sup>

## 6. Green nanotechnology: principles and phytochemical basis

### 6.1. Principles of green synthesis

The green synthesis of nanoparticles uses biological system like plant extracts, microorganisms, enzymes, and biomolecules that work as both reducing and stabilising agents to make nanoparticles. This way, bad chemicals are kept out of the environment and the damage they do is kept to a minimum.<sup>[8]</sup> The main ideas behind green nanotechnologies and the twelve principles of green chemistry are very similar. They all focus on safety, less waste, renewable feedstocks, and atom economy.

In plant mediated synthesis, you mix plant extract with precursor metal salts like silver nitrate, chloroauric acid, or zinc acetate. You keep the pH, temperature, and time the same. The extract has phytochemicals like polyphenols, flavonoids, terpenoids, and reducing sugars that help metal ions change into zero valent metal atoms come together to make nanoparticles. The same phytochemicals that act as caps on the surface of the nanoparticles to keep it from clumping together also keep the particles biological activity.<sup>[9,41]</sup> You can use a colour change to keep an eye on the reaction, and uv-visible spectrophotometry to make sure nanoparticles are forming. The localised surface plasmon resonance (LSPR) of silver between 400-450nm, serves as an indicator of successful nanoparticle synthesis.<sup>[42]</sup>

### 6.2. Key phytochemical constituents involved in green synthesis

The green synthesis approach is based on the fact that medicinal plants have a wide range of phytochemical constituents. There are a few types of compounds that are very important:

Flavonoids, such as quercetin, kaempferol, and rutin, have many hydroxyl groups that can reduce metal ions and chelate metal atoms. This makes them very good at reducing and stabilizing agents. Many medicinal plants used in green synthesis, such as *Camellia sinensis*, *Morinda citrifolia*, and *Azadirachta indica*, contain these compounds.<sup>[43]</sup>

Flavonoids like quercetin and kaempferol, which are well-known for their antioxidant and anti-inflammatory effects in *Ginkgo biloba*,<sup>[10]</sup> also help make plant-mediated nanoparticles work.

Terpenoids and terpene lactones found in numerous aromatic plants are also recognized as reducing and capping agents in biosynthesis. The effects of these compounds on the surface chemistry of nanoparticles may affect biological interactions at the wound site.<sup>[44]</sup> Polyphenols and tannins are excellent electron donors and possess the capability of reducing metal ions. Antioxidant properties retained after adsorption on the surface of nanoparticles improve their ROS scavenging capability, which plays an important role in wound healing.<sup>[45]</sup> Alkaloids and saponins have been known to play roles in nanoparticle stability, especially in plants like *Solanum trilobatum* and *Tinospora cordifolia*.<sup>[46]</sup>

## 7. Medicinal plants used in green synthesis for wound healing

A wide range of medicinal plants have been investigated for the green synthesis of wound-healing nanoparticles. Selected plants of particular significance are reviewed below.

**Table no.2.**

SI. No	Plant name	Chemical constituents	Activity	Reference
1.	<i>Azadirachta indica</i> (neem)	Flavonoids, tannins, nimbidin, azadirachtin	Antibacterial, antioxidant, anti-inflammatory, anti-cancerous, anti-diabetic	[47,48]
2.	<i>Curcuma longa</i> (turmeric)	Curcumin	Anti-inflammatory, anti-oxidative, hepatoprotective, anti-diabetic, anti arthritis	[49,50]

			activity, neuroprotective, anti-microbial, anticancer activity.	
3.	<i>Calendula officinalis</i> (pot marigold)	Flavonoids, triterpenoids	Anti-inflammatory, healing-regenerative activity, anti-genotoxic, genotoxic, anticancer, cardio protective, gastroprotective, antiprotozoal, anthelmintic activity.	[51,52]
4.	<i>Aloe vera</i>	Aloin, acemannan, polysaccharides	Anti diabetic, anti-cancerous, antiviral, antimicrobial, hepatoprotective, antiulcer, antihyperlipidemic activity	[53,54]
5.	<i>Lawsonia inermis</i> (henna)	Lawsonone, flavonoids, tannins	Anti-bacterial, antifungal, anti-inflammatory, analgesic, anti-tumour and anti-proliferative, antipyretic, antiangiogenic	[55,56]
6.	<i>Ocimum sanctum</i> (holy basil)	Eugenol, ursolic acid, flavonoids	Antioxidant, antimicrobial, hypolipidemic, immunomodulatory, hepato-protective, neuro-protective, anti-stress	[57,58]
7.	<i>Camellia sinensis</i> (tea plant)	Catechins (egcg), polyphenols	Antioxidant, anti-cancerous, anti diabetic, antibacterial, antiviral, neuro-protective,	[59,60]
8.	<i>Allium sativum</i> (garlic)	Allicin, sulphur compounds	Anti diabetic, anti-oxidant, hepato-protective, anti-inflammatory, cardiovascular, antibacterial, antiviral	[61,62]
9.	<i>Zingiber officinale</i> (ginger)	Gingerols, shogaols	Anti-inflammatory, antiviral, radioprotective, anticancer, antioxidant	[63,64]
10.	<i>Trigonella foenum graecum</i> (fenugreek)	Diosgenin, flavonoids	Antioxidant, hypoglycemic, hypocholesterolemic, immunomodulatory, anti-cancer	[65,66]

## 8. Morphological discription:

Plant profile:- *trigonella foenum-graecum l.* (fenugreek)

### Classification

Family: - fabaceae

Scientific name:- *trigonella foenum-graecum l.*

Genus: - trigonella

Phylum(division):- streptophyta

Order:- fabales

Kingdom: - plantae

### 8.1. Description

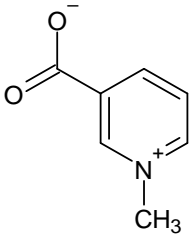
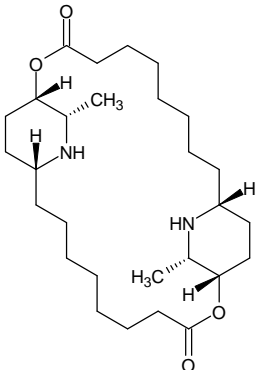
Fenugreek (methi) is a straight, upright herbaceous plant that belongs to the fabaceae family. This plant is mostly found in places like india and south africa that are near the mediterranean sea. It is usually 30 to 60 cm tall. The stem is smooth on the outside and empty on the inside. It might also have branches. There is one leaf on the stem, and each leaf is made up of three smaller leaves (trifoliolate). The leaves are green or bluish green and are 2 to 5 cm long. The leaves of the methi have small, lightyellow flower that grow in group of one or more. Pods form when the flower fall off. Ther care 10 to 20 seeds in each pod, which is 10 to 15 cm long. Seeds are the most important part of methi for medicine. These seeds are hard, a little square or long, and have a deep line that goes across them.<sup>[67,68,69,70]</sup>

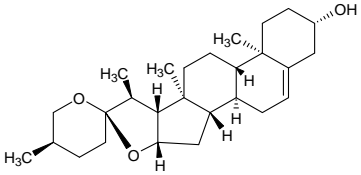
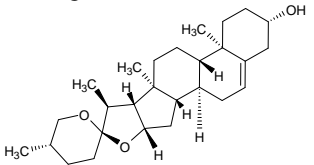
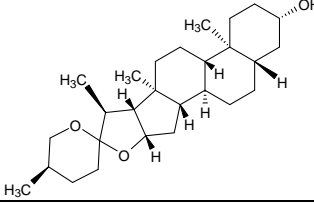
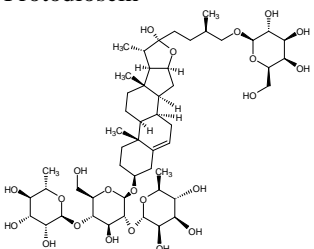
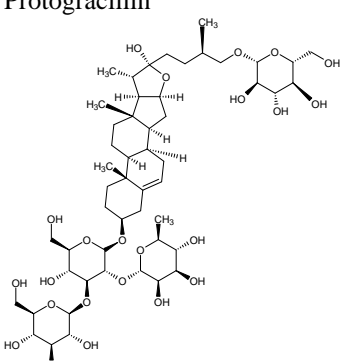
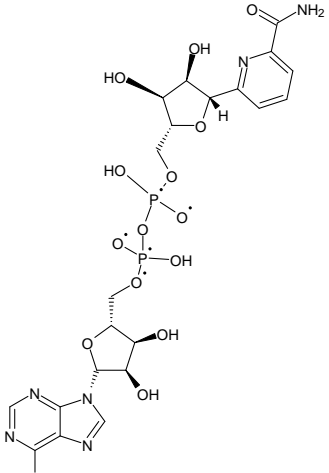
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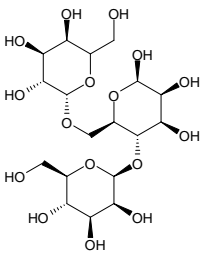
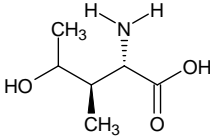
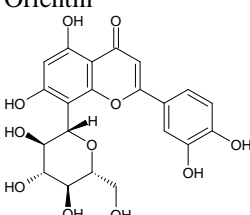
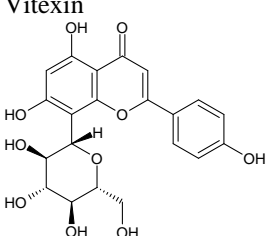
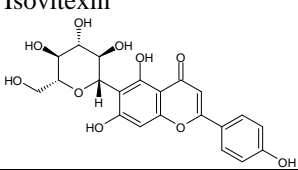
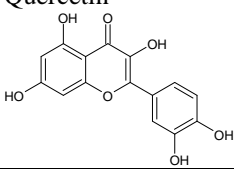
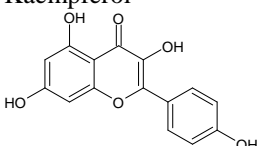
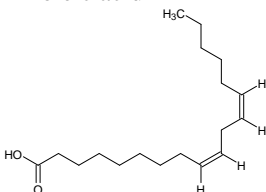
S. No.	Parts	Description	Shape	Size
01.	Roots	Central system bearing nodules for nitrogen fixation	Taproot(branched)	Length 2.5-7.3 cm (varies by genotype)
02.	Stem	Erect, smooth, herbaceous, often hollow, light green to pinkish.	Cylindrical (round and slender)	Length: 30-60 cm Slender
03.	Leaves	Alternate arrangement; compound leaves, oblong leaflets with stipules	Trifoliate (leaflets are obovate to oblong), the leaflets are obscurely dentate (toothed) at the apex.	Leaflet length: 0.7-2.3 cm, width: 0.5-1.8 cm.
04.	Flower	Sessile (stalkless), hermaphroditic, borne singly or in pairs (geminate) in the leaf axils. Colour ranges from white to lemon-yellow	Papilionaceous	~1 cm long (sessile, axillary)
05.	Pod (fruit)	Erect, glabrescent(becoming hairless) and rigid. The surface features longitudinal reticulation; colour ranges from green to straw coloured, brown at maturity.	Sickle-shaped; curved, slender, and pointed	Length: 10-20 cm, contains 10-20 seeds.
06.	Seeds	Hard, smooth and yellowish-brown to golden. It is characterized by a deep, transverse diagonal groove that divides the seeds into two unequal lobes. The seed coat is gummy when wet due to galactomannan	Rhomboidal/cuboid (oblong/rectangular with rounded corners)	Length: 3-6 mm, width: 2-5 mm, thickness: 2 mm.

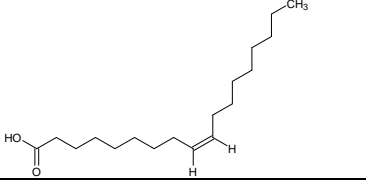
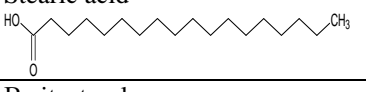
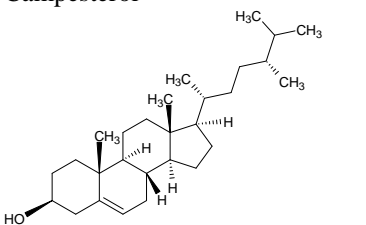
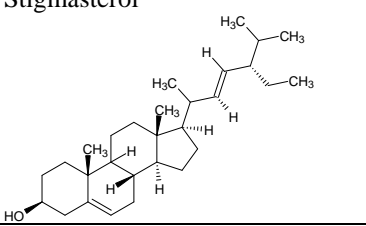
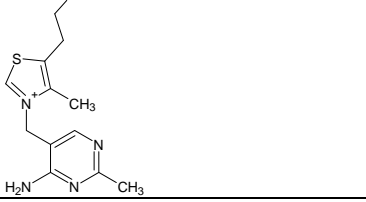
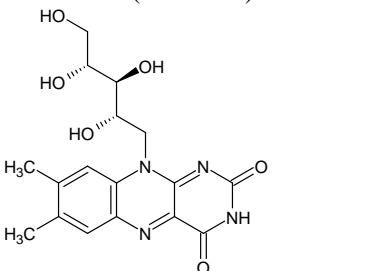
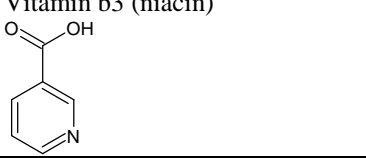
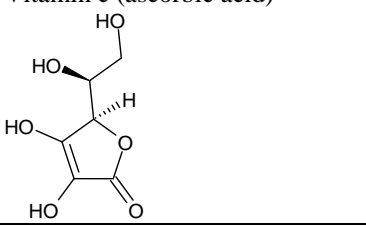
## 9. Chemical constituents

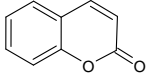
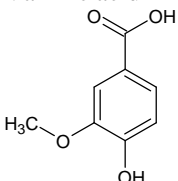
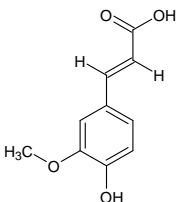
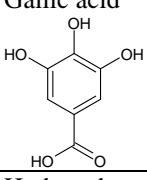
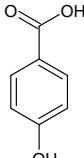
Table 04

Sl. No.	Compound	Nature	Molecular formula	Mol. Weight	Activity
1	Trigonelline 	Alkaloid	$C_7H_7NO_2$	137.13	Antidiabetic, hepatoprotective, cardiovascular effects <sup>[71,2]</sup>
2	Carpaine 		$C_{28}H_{50}N_2O_4$	239.36	

3	<p>Diosgenin</p> 	Steroidal saponin	$C_{27}H_{42}O_3$	414.63	Hypolipidemic, precursor for steroids, anti-inflammatory, cholesterol-lowering <sup>[73]</sup>
4	<p>Yamogenin</p> 		$C_{27}H_{42}O_3$	414.63	
5	<p>Tigogenin</p> 		$C_{27}H_{44}O_3$	414.63	
6	<p>Protodioscin</p> 	Saponin	$C_{51}H_{84}O_{22}$	1049.17	Anabolic-like activity Anticancer potential Antidiabetic <sup>[74,75]</sup>
7	<p>Protogracillin</p> 		$C_{57}H_{90}O_{26}$	1207.27	
8	<p>Fenugreekine</p> 		$C_{21}H_{27}N_7O_{14}P_2$	1079.24	

9	<b>Galactomannan</b> 	Polysaccharide	$C_{18}H_{32}O_{16}$	Variable	Hypoglycemic <sup>[76]</sup>
10	<b>Mucilage</b>		—	—	Demulcent, laxative <sup>[77]</sup>
11	<b>4-hydroxyisoleucine</b> 	Amino acid derivative	$C_6H_{13}NO_3$	147.17	Insulinotropic <sup>[78]</sup>
12	<b>Orientin</b> 	Flavonoid	$C_{21}H_{20}O_{11}$	448.38	Antioxidant Anti-inflammatory Antioxidant Anti-inflammatory, antioxidant <sup>[79]</sup>
13	<b>Vitexin</b> 		$C_{21}H_{20}O_{10}$	432.38	
14	<b>Isovitexin</b> 		$C_{21}H_{20}O_{10}$	432.38	
15	<b>Quercetin</b> 		$C_{15}H_{10}O_7$	302.24	
16	<b>Kaempferol</b> 		$C_{15}H_{10}O_6$	286.24	
17	<b>Linoleic acid</b> 	Fatty acid	$C_{18}H_{32}O_2$	280.45	Antioxidant Hypocholesterolemic energy metabolism <sup>[80]</sup>
18	<b>Oleic acid</b>		$C_{18}H_{34}O_2$	282.47	

					
19	Stearic acid 		$C_{18}H_{36}O_2$	284.48	
20	B-sitosterol	Phytosterol	$C_{29}H_{50}O$	414.71	Hypocholesterolemic Anti-inflammatory Hypoglycemic <sup>[81]</sup>
21	Campesterol 		$C_{28}H_{48}OO$	400.69	
22	Stigmasterol 		$C_{29}H_{48}O$	412.69	
23	Vitamin b1 (thiamine) 	Vitamin	$C_{12}H_{17}N_4OS^+$	265.35	Energy metabolism Antioxidant Lipid metabolism Antioxidant <sup>[82]</sup>
24	Vitamin b2 (riboflavin) 		$C_{17}H_{20}N_4O_6$	376.37	
25	Vitamin b3 (niacin) 		$C_6H_5NO_2$	123.11	
26	Vitamin c (ascorbic acid) 		$C_6H_8O_6$	176.12	
27	Iron		Fe	55.85	Hematopoietic
28	Calcium		Ca	40.08	Bone health

29	Zinc	Mineral	Zn	65.38	Immune function <sup>[82]</sup>
30	Coumarin 	Phenolic compound	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub>	146.14	Anticoagulant-like activity <sup>[83]</sup>
31	Vanillic acid 	Phenolic acid	C <sub>8</sub> H <sub>8</sub> O <sub>4</sub>	168.15	Antioxidant Anti-inflammatory Antimicrobial Antioxidant <sup>[84]</sup>
32	Ferulic acid 		C <sub>10</sub> H <sub>10</sub> O <sub>4</sub>	194.18	
33	Gallic acid 		C <sub>7</sub> H <sub>6</sub> O <sub>5</sub>	170.12	
34	Hydroxybenzoic acid 		C <sub>7</sub> H <sub>6</sub> O <sub>3</sub>	138.12	

## 10. Key outcome of selected medicinal plants

Table 5: selected medicinal plants used in green synthesis of wound healing nanoparticles.

Plant name	Family	Nanoparticle type	Key phytochemicals	Wound healing activity
<i>Aloe vera</i>	Asphodelaceae	Agnpns, aunps	Aloin, polysaccharides	Antimicrobial, anti-inflammatory, moisturizing
<i>Curcuma longa</i>	Zingiberaceae	Agnpns, cuonps	Curcumin, turmerones	Anti-inflammatory, antioxidant, promotes re-epithelialization
<i>Centella asiatica</i>	Apiaceae	Agnpns, znonps	Asiaticoside, madecassoside	Collagen synthesis, angiogenesis
<i>Azadirachta indica</i>	Meliaceae	Agnpns, tio2nps	Nimbin, quercetin	Broad-spectrum antimicrobial, antioxidant
<i>Camellia sinensis</i>	Theaceae	Agnpns, aunps, znonps	Catechins, egcg	Antioxidant, anti-biofilm, anti-inflammatory
<i>Zingiber officinale</i>	Zingiberaceae	Agnpns, znonps	Gingerols, shogaols	Antibacterial, anti-inflammatory
<i>Morinda citrifolia</i>	Rubiaceae	Agnpns	Scopoletin, ursolic acid	Antimicrobial, wound contraction
<i>Ocimum sanctum</i>	Lamiaceae	Agnpns, znonps	Eugenol, ursolic acid	Antibacterial, anti-inflammatory, antifungal

### 10.1. Aloe vera

*Aloe vera* (L.) Brum. F. (asphodelaceae) is one of the medical plants species which has been successfully studied the majority for use in healing wounds. Polysaccharides (acemannan), anthraquinones (aloin, emodin), vitamins (c and e),

enzymes and minerals in the gel work together to speed up the wound healing by reducing inflammation, fighting bacteria, and keeping the skin moist.<sup>[85]</sup> Silver nanoparticles made from aloe vera gel extract show a strong antimicrobial activity against *S. Aureus* and *P. Aeruginosa*, help fibroblasts move via in vivo.<sup>[86]</sup>

### 10.2. Curcuma longa

Curcumin the principal bioactive polyphenol obtained from *Curcuma longa* (Zingiberaceae), is acknowledged as a multi target anti inflammatory and antioxidant agents that modulates NF- $\kappa$ B signalling, suppressor pro inflammatory cytokine production, and promotes collagen synthesis.<sup>[87]</sup> Nanoparticles containing curcumin exhibit superior bioavailability and wound healing properties compared to free curcumin, which suffers from inadequate solubility and rapid degradation. Copper oxide nanoparticles made from curcumin as a reducing agent have been showing to be very effective at killing MDR pathogens and speeding up wound healing in Wistar rats.<sup>[88]</sup>

### 10.3. Centella asiatica

*Centella asiatica* (L.) Urban (Apiaceae), known as Gotu Kola, contains triterpenoid saponins, mainly asiaticoside and madecassoside, which are known to boost collagen biosynthesis and fibroblast proliferation.<sup>[89]</sup> Silver nanoparticles from *Centella asiatica* extract have significant in vivo wound healing properties, such as higher hydroxyproline levels (which show collagen synthesis), faster wound contraction, and better angiogenesis.<sup>[90]</sup>

### 10.4. Azadirachta indica

Neem (*Azadirachta indica* A. Juss., Meliaceae) is a well known plant that kills a wide range of germs. Researches have been able to make silver and titanium dioxide nanoparticles in a green way using its leaf extract, which is high in nimbin, nimbidin, quercetin, and gallic acid. Neem derived AgNPs are effective against multidrug resistant *S. Aureus*, *Klebsiella pneumoniae*, and *Candida albicans*, making them especially useful for treating infected wounds.<sup>[91]</sup>

## 11. Types of herbal-based nanoparticles for wound healing

### 11.1. Silver nanoparticles (AgNPs)

The most studied metallic nanoparticles because they can kill a wide range of germs, such as bacteria (even MDR strains), fungi and viruses. AgNPs can kill bacteria in a number of ways. They can break down cell membranes, make reactive oxygen species, stop bacterial DNA from copying itself, and block respiratory enzymes that are attached to membranes.<sup>[92]</sup> AgNPs work in many ways, so bacteria are much less likely to become resistant to them than to regular antibiotics, which only work on one target. It is now possible to make AgNPs in a way that is good for the environment by using extracts from many medicinal plants such as aloe vera, *Camellia sinensis* from plants help keep the nanoparticles stable after this process. In addition to killing germs they also have stronger anti inflammatory effects. In preclinical wound healing models, topical AgNP formulations have demonstrated accelerated wound contraction, reduced inflammatory infiltrate, increased collagen deposition, and diminished healing duration.<sup>[93]</sup>

### 11.2. Zinc oxide nanoparticles (ZnONPs)

Zinc oxide nanoparticles have attracted considerable interest in wound healing due to their antimicrobial, antioxidant, and pro regenerative properties. Zinc is an important co factor for metalloproteinases that help change the ECM. It is also needed for the activity of antioxidant enzymes like superoxide dismutase. ZnONPs derived from extracts of *Centella asiatica*, *Zingiber officinale*, and *Camellia sinensis* exhibit significant antibacterial efficacy against both gram positive

and gram negative bacteria. They also help keratinocytes move and grow, and they make new blood vessels grow at the wound side.<sup>[94]</sup>

### 11.3. Gold nanoparticles (aunps)

Gold nanoparticles have unique optical properties and work well with living things. Green synthesized aunps from aloe vera and other plant extracts have strong anti-inflammatory effects because they change the way macrophages work by changing them to the pro healing m2 phenotype and stopping nf- $\kappa$ b-mediated inflammatory signalling.<sup>[95]</sup> Aunps have also been added to hydrogels based wound dressing that can kill germs when near infrared light is turned on. This is a way to kill germs without touching them.

### 11.4. Copper oxide nanoparticles (cuonps)

Copper is an important micro nutrient that helps wounds heal by helping new blood vessels grow and connecting collagen fibers. Cuonps made from extracts of curcuma longa and morinda citrifolia have been shown to be very good at fighting bacteria and fungi. They also help by increasing vegf expression and encouraging the growth of new blood vessels at the site of the wound. Cunops are very promising for treating chronic wound because they can kill bacteria and help new blood vessels grown.<sup>[96]</sup>

### 11.5. Titanium dioxide nanoparticles (tio2nps)

Peopke like titanium dioxide nanoparticles because they can kill bacteria when they are i the sun oe in visible light. This is what is known as photocatalytic antimicrobial activity. Tio2nps made from extracts of azadirachta indica and morinda citrifolia have been shown to kill bacteria that cause wounds and lower inflammation. Their photocatalytic mechanism increases the biological activity of the phytochemicals that stick to their surface, which is a complete way to heal wounds.<sup>[97]</sup>

**Table 6: Summary of green-synthesized nanoparticles, herbal sources, and wound healing activities.**

NP type	Plant source	Size (nm)	Synthesis method	Wound healing mechanism
Agnps	<i>Aloe vera</i>	10–50	Aqueous leaf extract	Broad-spectrum antimicrobial, anti-inflammatory, fibroblast migration
Agnps	<i>Camellia sinensis</i>	5–30	Methanolic leaf extract	Anti-biofilm, antioxidant, anti-inflammatory
Znonps	<i>Centella asiatica</i>	20–60	Aqueous extract	Collagen synthesis, angiogenesis, antibacterial
Cuonps	<i>Curcuma longa</i>	25–70	Ethanolic rhizome extract	Anti-inflammatory, vegf stimulation, antifungal
Aunps	<i>Morinda citrifolia</i>	8–25	Aqueous fruit extract	Macrophage m2 polarization, anti-inflammatory
Tio2nps	<i>Azadirachta indica</i>	15–45	Leaf extract	Photocatalytic antimicrobial, anti-inflammatory

## 12. Mechanisms of wound healing by herbal nanoparticles

### 12.1. Antimicrobial activity

Infection is one of the most important things that stops wound from healing. Herbal nanoparticles stops bacteria from growing by using more than one way to do so at the same time, which makes it les likely that bacteria will become resistant. Agnps affect the structure of the bacterial cell walls (lipopolysaccharides, peptidoglycan), the integrity of the cell membranes, electron transport chains, and dna replication.<sup>[92]</sup> Znonps create superior radicals and hydrogen peroxide, which harm bacterial membranes and cell structures. Cuonps generate cupric ions that attach to the thiol

groups of proteins disrupting enzymatic activity.<sup>[96]</sup> Phytochemical molecules that coat the surface of nanoparticles, such as flavonoids, terpenoids, and polyphenols, also help them fight germs.<sup>[98]</sup>

### 12.2. Anti-inflammatory effects

An additional characteristic of chronic wounds is an uncontrolled inflammatory response. The anti-inflammatory properties of herbal nanoparticles encompass various regulatory dimensions. Phytochemicals, including nanoparticles coating like flavonoids found in medicinal herbs for inflammatory treatment,<sup>[10]</sup> obstruct the nf-kb signalling pathway, diminish pro inflammatory cytokine levels (tnf- $\alpha$ , il-1 $\beta$ , il-6), and inhibit cox and lox enzymes.<sup>[99]</sup>

### 12.3. Antioxidant and ros scavenging activity

High levels of ros at the wound site cause structural damage, stop growth factor signalling, and make inflammation worse. Herbal nanoparticles that have plants extracts on them have natural antioxidant properties that help get rid of ros from the wound site. Prior research has demonstrated that plant extracts can effectively scavenge reactive oxygen species owing to their antioxidant properties within the nrf2 antioxidant pathway.<sup>[10,100,101]</sup> Adding either curcumin or green tea extracts to herbal nanoparticles makes them better at picking up ros because they have a larger surface area that is more reactive.<sup>[102]</sup>

### 12.4. Promotion of collagen synthesis and re-epithelialization

The generation of collagen fibres and the proliferation of epithelial cells are the primary features of the proliferative phase in wound healing. Asiaticoside released from centella asiatica nanoparticles promotes collagen fibre synthesis in fibroblast and the generation of tgf- $\beta$ 1.<sup>[89]</sup> moreover, zinc ions generated by znonps serve as a co factor for procollagen prolyl and lysyl oxidases essential for collagen fibre synthesis.<sup>[94]</sup> Some phytochemical nanoparticle complexes have egf like properties, which means they can make keratinocytes move and grow.<sup>[103]</sup>

### 12.5. Angiogenesis

Neovascularisation is a crucial for making sure the regions of an injury that are growing get sufficient nutrients and oxygen. Copper nanoparticles are recognised as effective stimuli of neovascularisation the copper ions emitted via these nanoparticles enhance the expression of vegf, hypoxia inducible factor 1  $\alpha$  (hif-1 $\alpha$ ), and angiopoietins, consequently promoting the proliferation and migration of endothelial cells.<sup>[96]</sup> Gold nanoparticles are additionally believed to promote vascularization by activating heparin binding growth factors.<sup>[95]</sup>

## 13. Integration of herbal nanoparticles into advanced wound delivery systems

To improve the effectiveness of herbal nanoparticles for wound healing, they are being combined more and more with delivery vehicles that provide controlled release, a moist wound environment, and mechanical support.

### 13.1. Hydrogels

Hydrogels are three dimensional, cross linked polymer structures that hold a lot of water molecules and make the environment around a wound similar to the extracellular matrix. This keeps the wound hydrated, absorbs exudates, and allows the cell to move. Hydrogels carriers with herbal nanoparticles made from natural polymers like chitosan, hyaluronic acid, alginate, or gelatin provide a sustained release profile along with support for healing. Curcumin agnps incorporated into chitosan hydrogels demonstrated an exceptional rate of wound clouser, diminished microbial load, and enhanced collagen synthesis via in vivo studies.<sup>[104]</sup>

### 13.2. Electrospin nanofibrous scaffolds

Electrical spinning is a method for making nanofibers that are 50 to 1000 nm in size and look like the framework of native ecm. Adding herbal nanoparticles to nanofibers composed of polymers that are synthetic like poly(lactic co glycolic acid)(plga) or polycaprolactone (plc) can make structures that are very biologically active and can expel their contents in a controlled way. In vitro and in vivo studies show that plc nanofibers scaffolds with aloe vera agnps work really well for cell attachment, growth, and wound healing.<sup>[105]</sup>

### 13.3. Transdermal patches

Nano patches containing phytochemical loaded nanoparticles offer a novel approach for rapid, non invasive, and successful wound healing therapy. The nanoparticles plated with phytochemical are released in a controlled way immediately through the wound with nano patches. Adding nanoparticles to the system makes it easier for hydrophilic phytochemicals to get through the stratum corneum, which is a big problem for transdermal herbal therapy.<sup>[106]</sup>

## 14. Characterization of green-synthesized nanoparticles

A detailed characterization is very important for making sure that synthesised phytochemical nanoparticles are safe and work well. Some of the ways to do physicochemical characterization are:

Uv-vis spectrophotometry to verify nanoparticle formation via lspr peaks of agnps at approximately 400 to 450 nm and aunps at approximately 520 nm.

Use dls and zeta potential to find the hydrodynamic diameter, pdi, and stability of the colloid. Transmission electron microscopy (tem) and scanning electron microscopy (sem) let you see the shape, size, and structure of the nanoparticles.

Xrd for crystallinity for ftir for identifying the functional groups of the phytochemicals used to make nanoparticles.

Exd to look at the nanoparticles elemental makeup and tga to look at their thermal stability.<sup>[107]</sup>

## 15. Safety, toxicological considerations, and regulatory challenges

Even though herbal nanoparticles show great promise in treating wounds, their safety needs to be established strictly before their clinical application. Nanoparticles have the ability to pass through biological barriers and accumulate in organs. Thus, toxicological analysis should include:

In vitro cytotoxicity assessment employing mtt and lactate dehydrogenase release assay in suitable cell cultures, including keratinocytes, fibroblast, and endothelial cells. In vivo testing of acute and subacute toxicity in suitable animal models, accompanied by the assessment of organ histopathology and biochemical tests for toxic effects. Testing for mutagenic and genotoxic effects (ames test, come test). Examination for immunotoxicity to determine if the phytochemicals linked to nanoparticles provoke any detrimental immune responses.<sup>[108]</sup> There are many rules for natural nanoparticles that are used to treat wounds. The fda and ema have rules about pharmaceutical drugs and devices that include control of quality procedures, standardization about the parts in extracts from plants, and standardised clinical studies that show the drugs are safe and effective.<sup>[109]</sup> Plant material are naturally diverse in their compositions, so standardisation needs strict extraction and synthesis conditions.

## 16. Discussion and future perspectives

Bringing together green nanotechnology and herbal medicine is an excellent scientific foundation and practical use for promoting innovative ideas in wound care treatment. The extensive review indicates that plant derived nanoparticles, comprising agnons, cuonps, znonps, aunps and tio<sub>2</sub>nps, exhibit diverse wound healing properties that are directly influence the underlying pathophysiology related to poor wound healing, such as infections, chronic inflammation, oxidative stress, inadequate collagen deposition, and suboptimal angiogenesis. One of the main advantages of herbal nanoparticles is that they can work in a multi target therapeutic mode. Herbal nanoparticles have pharmacological effects on a number of targets, including infection, inflammation, oxidative stress, and tissue repair. That is identical to the way that multi target drugs like ginkgo biloba have effects on a number of biological processes at the same time.<sup>[10]</sup>

The wide range of behaviours is clearly advantageous in the wound micro environment, which includes a number of pathophysiological mechanism. But there are important things to think about nanoparticles are. The initial challenge is that the green synthesis process is hard to scale up because nanoparticles made in a lab may not be able to be used in industrial grade production without changing the quality standards and level of reproducibility. Natural plant extract based nanoparticles exhibit biological variability attributable to their plant origin, geographical location, harvesting season, and extraction methodology, resulting in batch to batch variation that necessitates effective standardisation methods.<sup>[110]</sup> There is a lack of data on long term in vivo toxicology for numerous natural nanoparticles systems, particularly regarding extended use, biodegradability, and potential toxicity resulting from nanoparticles accumulation in tissues. It would be beneficial to perform additional pharmacokinetic and pharmacodynamic studies, supplemented by adequately powered clinical trials to validate therapeutic efficacy for specific wounds. Research priorities encompass the development of natural nanoparticle systems grounded in synergistic phytochemical actions, the application of these nanoparticles to intelligent bandages that release them upon stimulation by infection or inflammation, the employment of nanotechnology for the delivery of genes encoding growth factors to wounds, and the utilisation of computational and system biology techniques to elucidate nanoparticles tissue interactions for the purpose of understanding mechanism and predicting toxicity.

## CONCLUSION

Herbal nanoparticles developed via green nanotechnology are a solid basis in science and a promising platform for the future of healing wounds. By employing the complex combination of biological active compounds that are present in different medicinal plants, such as flavonoids, terpenoids, polyphenols, and alkaloids, to make nanoparticles, it can be achievable to create particles that have their own and multiple wound-healing properties. These capabilities might include strong antimicrobial action against microorganisms that are resistant to drugs, preventing inflammation, eliminating the presence of reactive oxygen species (ros), promoting the formation of collagen and new blood vessels, and making it less difficult for cells to re-epithelialize. Furthermore the efficacy of the nanoparticles can be enhanced significantly by integrating by incorporating them into advanced delivery mechanism such as hydrogels, nanofibrous matrice, and transdermal patches. Wound healing medications produced via herbal nanoparticles possesses plenty of potential, but they need to be standardised, safety tested, and put by means of clinical studies first.

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