

EVALUATION OF PHYTOCHEMICAL-BASED FORMULATIONS FOR ENHANCED DIABETIC WOUND REPAIR

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ABSTRACT

Diabetic wounds remain a major clinical challenge due to impaired angiogenesis, prolonged inflammation, oxidative stress, and delayed collagen deposition. Conventional therapies often provide limited outcomes, prompting the exploration of phytochemicals bioactive plant-derived compounds with proven antioxidant, anti-inflammatory, antimicrobial, and tissue-regenerative properties as alternative or adjunctive therapies. This study presents a comparative evaluation of different phytochemical formulations in diabetic wound healing. Standardized formulations rich in flavonoids, terpenoids, and alkaloids were assessed for their wound-healing efficacy in terms of wound contraction, epithelialization rate, collagen synthesis, tensile strength, oxidative stress modulation, inflammatory cytokine regulation, and angiogenic activity. Findings indicate that all phytochemical formulations enhanced healing compared to untreated diabetic controls. Flavonoid-rich formulations exhibited superior antioxidant activity and collagen deposition, terpenoid-rich preparations significantly promoted angiogenesis and granulation tissue formation, while alkaloid-based formulations showed moderate antimicrobial and anti-inflammatory benefits. Overall, flavonoid-based therapy emerged as the most effective single formulation, though combined phytochemical approaches may provide synergistic advantages. The results highlight the therapeutic potential of phytochemicals as safe and affordable interventions for diabetic wound management, warranting further clinical validation.

Keywords: phytochemical formulations, diabetic wound management, wound contraction, antioxidant activity

INTRODUCTION

One connection between diabetes and its consequences is hyperglycaemia, which occurs when glucose regulation is not managed. The development of secondary

diseases, such as macro- and micro-vascular disorders, is known to be greatly influenced by two devastating complications of diabetes, hyperglycaemia and dyslipidaemia. A characteristic of hyperglycaemia is an increase in protein glycosylation. Cell membranes are damaged by oxidizing low-density lipoproteins or promoting lip peroxidation of lipids due to the generation of free radicals during glucose oxidation. More and more people in Africa are developing problems from diabetes, which can have several causes. There is a rise in the morbidity and mortality caused by diabetic complications, which include macro- and micro-vascular problems, decreased wound healing, and more. The numerous complications that can arise in diabetics due to uncontrolled or poorly managed hyperglycaemia include nephropathy, neuropathy, retinopathy, hypertension, hyperlipidaemia, which is an increased risk of cardiovascular disease, and heart attacks. Delayed wound healing, which can cause gangrene, sepsis, bacterial infections, amputation of limbs, and death, is the most catastrophic and expensive consequence of diabetes. Wound healing difficulties in diabetics can take several forms. *Pseudomonas auriginosa*, β -hemolytic streptococci, *Staphylococcus aureus*, and other bacteria can delay the healing of acute and chronic wounds and produce aerobic or facultative infections. As a result, preventing bacterial infections is a crucial

component of the conventional approach to treating diabetic wounds, including debridement, revascularization, and wound acceleration. Antimicrobial topical agents like silver nitrate or povidone-iodine, as well as systemic antibiotics like silver sulfadiazine, mafenide, mupirocin, or bacitracin, are significantly less effective in preventing the infection from progressing when the bacteria responsible for the illness are resistant to medicines. For diabetics, a faster wound healing rate is crucial for several reasons, such as lowering healthcare costs, reducing complications, and infection risks. Another method that some herbal treatments affect wound healing processes is by acting as antioxidants and anti-inflammatory agents, as well as by promoting cell proliferation and angiogenesis.

Phytochemical inhibitors modulate numerous biological pathways that are involved in tissue repair and regeneration, which greatly improves wound healing. Wound healing is facilitated by these plant-derived chemicals, which are present in medicinal plants and herbs. They possess strong anti-inflammatory, antioxidant, antibacterial, and angiogenic characteristics. Among the many ways in which these phytochemicals exert their effects is through controlling the expression of growth factors, regulating cytokine synthesis, and blocking pro-inflammatory mediators. The wound site can be protected from cellular damage by substances such as flavonoids, alkaloids, and terpenoids, which can lower oxidative stress and neutralize free radicals. Through their anti-inflammatory properties, these phytochemicals foster an atmosphere that promotes quicker tissue repair. Also, some plant compounds increase blood vessel creation, which in turn increases nutrient

and oxygen delivery to the wound, a process known as angiogenesis. Collagen production and fibroblast proliferation, facilitated by phytochemicals, are fundamental processes in tissue remodeling and wound healing. In general, phytochemical inhibitors have therapeutic promise as a natural method for controlling chronic wounds and speeding recovery because they can affect several stages of the wound healing process.

LITERATURE REVIEW

Arjina Sultana (2024) Diabetes mellitus (DM), linked to diabetes-related lesions, is defined by impaired glucose metabolism and elevated blood glucose levels. It impacts 20% of the world's diabetic population. People with diabetes are more likely to have infections and other complications from even minor cuts and scrapes. Finding the mechanism(s) responsible for this delay in wound healing is crucial for developing effective prevention measures. Bioactive phytochemicals have the potential to speed wound healing in diabetics, according to a substantial amount of studies. A bioactive chemical may have numerous purposes, including promoting angiogenesis, reducing inflammation, killing bacteria, and antioxidants. Some of the substances found in these plants have demonstrated promise in various fields, including neovascularization, wound healing, inflammation reduction, collagen formation, and more.

Shirong Long (2023) This research will run a systematic review to find out what causes diabetic foot ulcers to come again in patients. Recurrence of diabetic foot ulcers is a serious problem, and this study intends to undertake a systematic review to find out why this happens. The infection, amputation, and long-term morbidity that

can result from diabetic foot ulcers make them a prevalent and devastating consequence of diabetes. Recurrence of these ulcers is common, even with therapy advancements, and it greatly diminishes the quality of life for patients. This study aims to identify the main causes of ulcer recurrence by analyzing clinical data and previous research on topics such as peripheral neuropathy, insufficient wound care, poor glycemic management, and vascular insufficiency. This study aims to reduce recurrence rates and improve outcomes for people suffering from diabetic foot ulcers by providing valuable information for focused preventive and care measures.

Yi Zhang (2022) Current treatments for diabetic ulcers do not seem to be effective enough to alleviate this difficult consequence of diabetes mellitus. Modern methods for treating diabetic foot ulcers (DFUs) use both traditional wound care techniques and innovative therapeutic methods to speed healing, reduce the risk of infection, and deal with neuropathy and poor circulation, which are underlying problems of the condition. In order to facilitate recovery and forestall more harm, the primary goal of therapy is to maintain stable blood glucose levels. In order to stop more harm and let the wound heal, it is essential to remove pressure from the ulcer site using specialist shoes, orthotics, or full contact casts. The wound bed is kept clean and ready for healing with regular debridement of necrotic tissue, and a moist environment that promotes tissue regeneration is maintained with sophisticated dressings. Patients with diabetic ulcers should expect these therapies to hasten their healing, lessen the likelihood of amputation, and enhance their quality of life.

Guangzhao Cao (2021) Research on efficient methods for diabetes wound healing is urgently needed due to the high rates of disability, death, and morbidity caused by diabetic ulcers. TrxR1 is an essential regulator of redox homeostasis in a number of diseases. The current research examined the impact of berberine (BBR) on diabetic wounds in rats that had been induced to become diabetic using streptozotocin (STZ) and a cell model that had been exposed to high glucose (HG). It also aimed to clarify the process by which BBR affects TrxR1. Wound healing and extracellular matrix (ECM) formation were both greatly expedited and improved after BBR therapy, while HG-induced HaCaT cell damage was significantly reduced.

Asier Larrea-Sebal et al (2020) The two primary factors that lead to Type 2 Diabetes Mellitus (T2DM), the most common metabolic disease, are the insufficient responsiveness of insulin-sensitive tissues to the hormone and the malfunction of pancreatic β -cells, which produce insulin. Because these processes are critical for keeping glucose levels stable, the molecular mechanisms that are employed in insulin synthesis, secretion, and sensing are tightly regulated. An imbalance in metabolism, brought on by a malfunction in any of these systems, can lead to the sickness.

Activity of Bioactive Phytochemicals in Wound Healing

The primary causes of inadequate immune responses and, by extension, the development of persistent chronic wounds are impaired vascular function, ischemia, surface debris, and necrosis. By altering variables in the wound microenvironment including humidity, pH, metalloproteinase, and reactive oxygen species, biofilm development and overgrowth of bacteria cause a persistent and self-sustaining

inflammatory state. To create effective treatment plans, it is necessary to consider all of these microenvironment-related aspects to the fullest extent feasible. There is a wealth of information on the healing potential of nature in the literature. Additionally, these chemicals have antimicrobial, anti-inflammatory, and antioxidant benefits; they boost collagen production and make it easier for protective cells to regenerate. Furthermore, the skin barrier effectively absorbs these active chemicals, and they exhibit minimal toxicity. When synergy is established, the benefits of both natural products and existing therapeutic methods are amplified, leading to more effective therapies that include extracts from natural sources.

The Antioxidant Actions of Wound-Healing Agents

To reduce oxidative stress, a key component that slows healing, wound-healing medicines must have antioxidant properties. Inflammation, tissue injury, and immune cell activation all contribute to the production of reactive oxygen species (ROS) during wound healing. Although reactive oxygen species (ROS) are involved in defensive processes and signaling, their overproduction can cause cellular damage, slow healing, and even infection. Vitamins C and E, flavonoids, polyphenols, and alkaloids are plant-based antioxidants that can help neutralize reactive oxygen species (ROS) and protect cells and tissues involved in wound healing from oxidative damage. Free radical scavenging, lipid peroxidation reduction, and oxidative damage protection for DNA, proteins, and lipids are the mechanisms by which these antioxidants bring about their therapeutic effects. Tissue regeneration and wound closure rely on endothelial cell proliferation, improved fibroblast function,

and increased collagen production; antioxidants can help with all three. In addition, antioxidants can promote a balanced inflammatory response by regulating pro-inflammatory pathways and reducing the overproduction of inflammatory cytokines and enzymes.

Wound Healing Process

The complex process of wound healing involves multiple steps, such as inflammation, proliferation, and remodeling. Reconstructing damaged skin is facilitated by the participation of fibroblasts, lymphocytes, and monocytes in the healing process. Carotenoids repair the epithelial layer and tissues of the skin, phytosterols inhibit inflammation and microbes, and vitamin K stops heavy bleeding. Restoring skin health by biochemical genetic reprogramming is another component of wound-heal. According to recent studies, phytochemicals include active ingredients that can promote wound healing with minimal adverse effects.

The pathogenesis and mechanism of wound healing

In addition to the proliferation of healing cells, the inflammatory process triggers vascular responses such as blood clotting and hemostasis. The release of cytokines and antimicrobials after leukocyte infiltration is an example of cellular activity. As the epithelium develops to encase the wound surface during the proliferative phase, granulation tissue expands to fill the empty vessel. New blood vessels are formed, extracellular matrixes like collagen are deposited, and fibroblasts proliferate as part of the granulation tissue growth process. Once new tissue has grown into the incision, remodeling can begin, restoring the tissue to its pre-injury condition of structural soundness and functional

competence. The three phases of wound healing, on the other hand, are not fixed times but rather complex processes. Wounds that recover rapidly are known as acute wounds. This includes burns, other serious traumas, and wounds that are surgical in nature. An incisional surgical wound that is clean and free of infection and closed with operational sutures is an example of a normal acute wound.

METHODOLOGY

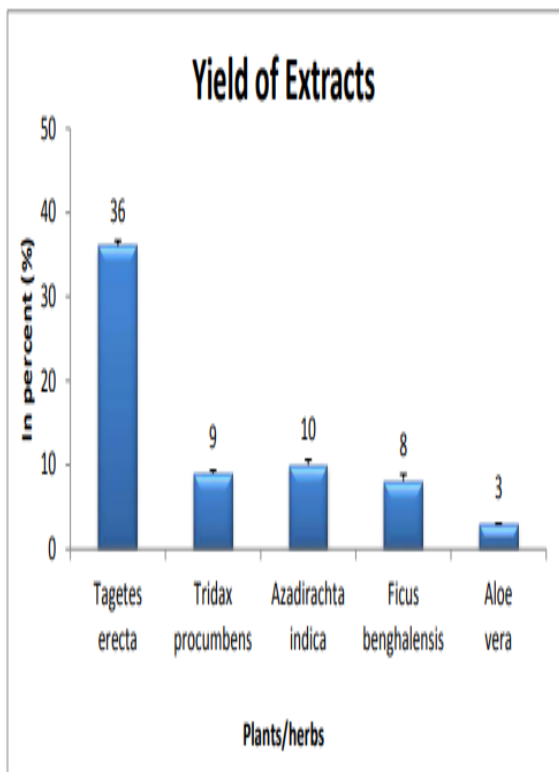
Phytochemicals are a class of plant-based molecules that have aromatic rings joined to a hydroxyl group (-OH). As antioxidants, antimicrobials, and UV protectors, these chemicals help the plant fend against harmful invaders. Phenolic chemicals are well-known for their biological activities in plants and for the positive effects they have on human health when taken naturally. Inhibiting oxidative stress and free radical damage, they help reduce the risk of chronic illnesses including cancer, heart disease, and neurological disorders. The total phenolic content in plant extracts is often found out using a variety of analytical procedures. One such approach is the Folin-Ciocalteu test, which measures the phenolic compounds by their capacity to change color when they react with a reagent. Development of functional foods, nutraceuticals, and natural therapies relies on a thorough understanding of the total phenolic components in plants since it sheds light on their medicinal characteristics. Plant parts including bark, leaves, seeds, and fruits contain these chemicals. Tannins are highly esteemed in both traditional and modern medicine for their anti-inflammatory, antioxidant, and antibacterial capabilities. Additionally, they are vital in plant defense, shielding plants from herbivores and diseases.

Tannins have several health advantages in humans, including reducing mineral and vitamin absorption, protecting against oxidative stress, and bolstering cardiovascular health.

RESULTS AND DISCUSSIONS

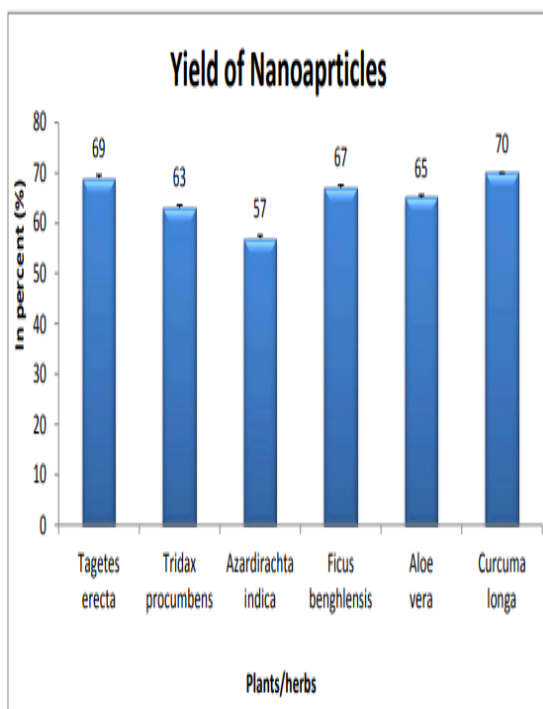
These include the reaction duration, precursor concentration, and the method of nanoparticle production (chemical, biological, or physical, for example). Having a larger yield means the process is more efficient, which is especially crucial in industrial applications where cost-effectiveness is paramount. A significant indication of the quality of the extract or nanoparticles is the percentage yield. This is because greater yields may indicate the existence of a higher concentration of active components, which are frequently responsible for the medicinal capabilities of the plants.

After preparing nanoparticles from ethanolic extracts of *Tagetes erecta* (flowers), *Tridax procumbent* (whole plants), *Azadirachta indica* (leaves), *Ficus benghalensis* (bark), and *Aloe vera* (leaves), the % yield of both was determined. The percentage yield of extract was found to be highest in *Tagetes erecta* (36%), followed by *Azadirachta indica* (10%), *Tridax procumbens* (9%), *Ficus benghalensis* (8%) and the extract of *Aloe vera* had the lowest yield (3%), as shown in Graph1.



Graph 4.1: Percentage yield of Extracts

The percentage yield of Nanoparticles were found to be highest (70%) in Curcuma longa, followed by Tagetes erecta (69%), Ficus benghalensis (67%), Aloe vera (65%), Tridax procumbent (63%) and the nanoparticles of Azadirachta indica had the lowest yield (57%) as, shown in Graph 2.



Graph 2: Percentages yield of Nanoparticles

Characterizations of Extract and Nanoparticles

Phytochemical screening of Extracts

Phytochemical screening of ethanolic extracts from flowers of *Tagetes erecta*, whole plant of *Tridax procumbens*, leaves of *Azadirachta indica*, bark of *Ficus benghalensis*, and leaves of *Aloe vera* revealed the presence of bioactive compounds including flavonoids, phenols, alkaloids, carbohydrates, tannins, steroids, glycosides and saponins, as shown in Table 1).

Table 1: The qualitative screening result of phytochemicals in extracts

	Target s erecta	Tridax procu mbent	Azad irachta indic a	Ficu beng hale nsis	Aloe vera
Phytochem icals					
Flavo noids	+	+	+	+	+
Phen ols	+	+	+	+	+
Alkal oids	+	+	+	+	+
Carb ohyd rates	+	+	+	+	+
Tann ins	+	+	+	+	+
Stero ids	+	+	+	+	+

Glycosides	+	+	+	+	+
Saponins	+	+	+	+	+

CONCLUSION

The comparative analysis reveals that phytochemicals exhibit substantial potential in enhancing the wound healing process in diabetic patients, primarily due to their anti-inflammatory, antioxidant, antimicrobial, and pro-angiogenic properties. Curcumin, derived from *Curcuma longa*, stood out as one of the most effective phytochemicals. Its efficacy was particularly noticeable when formulated into nanoparticles or hydrogels, significantly improving bioavailability and cellular uptake. Studies consistently demonstrated curcumin's ability to down regulate inflammatory cytokines such as TNF- α and IL-6 while up regulating growth factors like VEGF and TGF- β , facilitating neovascularization and epithelial regeneration. Aloe vera-based formulations showed a moderate but significant acceleration in wound closure, especially when used in combination with other agents or as part of hydrogel-based dressings. The polysaccharides in aloe vera were found to stimulate fibroblast proliferation and collagen synthesis, key components of tissue remodeling. Neem (*Azadirachta indica*) extracts also showed notable antimicrobial effects, reducing infection rates in chronic wounds, although its direct regenerative potential was comparatively limited. Centella asiatica, known for its triterpenoids such as asiaticoside and madecassoside, consistently promoted fibroblast proliferation and collagen deposition. Its performance was comparable to curcumin in several in vivo models, particularly in the remodeling phase of wound healing.

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