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Development of a natural nanostructured lipid carrier (NLC)-based delivery system as an antidiabetic and diabetic wound agent: A review

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ABSTRACT

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia due to impaired insulin secretion. Diabetes often causes serious complications such as diabetic wounds, which are characterized by the appearance of ulcers, infections, or tissue damage in the feet. Conventional therapeutic approaches often show less than optimal effectiveness due to limited drug penetration into damaged skin tissue. The use of natural ingredients with antidiabetic and wound healing activities has been widely studied, but their effectiveness is often hampered by low solubility, stability, and bioavailability. One innovative strategy to overcome these problems is the development of nanotechnology-based drug delivery systems, one of which is Nanostructured Lipid Carrier (NLC). NLC is a lipid delivery system that combines solid and liquid lipids to increase stability, drug loading capacity, and control the release of active compounds. Purpose: This article aims to review the development of formulations from natural ingredients that have potential as antidiabetic and diabetic wound healing activities. Methods: This study is a literature review of articles published in the last ten years (2015 – 2025) from the ScienceDirect, PubMed, and Google Scholar databases. Results: Based on several studies, it shows that various active compounds such as curcumin (Curcuma longa), bay leaves (Syzygium polyanthum), and other flavonoid compounds have been formulated in the NLC system with significant improvements in stability, bioavailability, and pharmacological effectiveness. Conclusion: The NLC-based drug delivery system from natural ingredients has proven potential in increasing the effectiveness of antidiabetic therapy and diabetic wound healing. Further research is needed to optimize formulation stability, long-term toxicity testing, and clinical validation to support its therapeutic application.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disease related to disorders of the endocrine system and causes hyperglycemia, namely an increase in blood glucose levels that is uncontrolled and exceeds normal limits.(Herman & Herman, 2023)The prevalence of diabetes mellitus (DM) in Indonesia in 2021 was recorded at 10.8%, or approximately 19.5 million people, and this figure is expected to increase to 28.6 million by 2045 (Federation, 2022)Pathophysiologically, diabetic foot ulcers arise as a result of an ulceration process influenced by various factors, including patient compliance with therapy, smoking habits, and impaired kidney function.(Huang et al., 2021)It is estimated that around 15% of people with diabetes experience diabetic foot ulcers, and around 14–24% of these patients end up having to amputate, with a post-amputation mortality rate of 50–59% (Abidin, 2024),(Zubir, Brisma, Zulkarnaini, & Anissa, 2024).

Conventional therapies to control diabetes and heal diabetic wounds are often less effective or cause side effects, so a new approach is needed that is able to combine glycemic control and improve the wound healing process.(Kambale, Quetin-Leclercq, Memvanga, & Beloqui, 2022)In addition to conventional medicine, the use of natural products as antidiabetic and wound healing agents has shown potential through anti-inflammatory, antioxidant, antimicrobial, and angiogenesis-stimulating effects. However, many natural compounds have low solubility, poor chemical stability, and low bioavailability, which can limit therapeutic effectiveness if not used in an appropriate drug delivery system (Criollo-Mendoza et al., 2023)Therefore, an appropriate nanotechnology-based drug delivery system is needed to overcome these limitations. Nanotechnology is the field of materials engineering at the nanometer scale, approximately 0.1 to 100 nm, which allows for the modification of a material's physical and chemical properties to enhance its therapeutic performance (Jafar & Sutrisno, 2024).

Nanostructured Lipid Carrier (NLC) is the second generation of lipid-based delivery systems developed to overcome the limitations of Solid Lipid Nanoparticle (SLN).(Nugraha, 2024),(Latifah, 2024)This system can increase the stability of active compounds, control the rate of drug release, and improve penetration into skin tissue. The NLC structure consists of a mixture of solid and liquid lipids to contain the active ingredients, thereby increasing encapsulation capacity and reducing the possibility of drug crystallization.(Wathoni et al., 2024).

NLC formulation optimization needs to be carried out for each extract or natural ingredient, including the selection of lipid composition, surfactant type, and manufacturing method, so that stability and drug release profiles can be achieved optimally.(Putra, Pradnyaswari, & Setyawan, 2022),(SURYANI, nd)Understanding the molecular mechanisms by which NLC encapsulation can influence the inflammatory response, angiogenesis, and remodeling processes in diabetic wounds is still limited. Pharmacokinetic evaluation and long-term safety, for both topical and systemic use, are still needed. Therefore, more systematic research is needed, including screening natural ingredients with antidiabetic and diabetic wound healing activity, optimizing NLC formulations, and assessing biological effects through in vitro and in vivo assays.(Shiyan, 2021)(Chiuman, 2024).

Based on the above background, this review article aims to develop an NLC-based drug delivery system containing extracts/bioactives from natural ingredients for antidiabetic applications and diabetic wound therapy, evaluating their physicochemical stability, release profile, and biological activity related to antidiabetic therapy and the ability to accelerate wound closure in relevant in vitro/in vivo models. The expected result is that the NLC formulation can increase the effectiveness of natural ingredients as antidiabetic therapy and diabetic wound healing.

RESEARCH METHOD

This study is a review article that aims to examine and analyze various scientific publications related to the development of a drug delivery system based on Nanostructured Lipid Carrier (NLC) from natural ingredients as an antidiabetic and diabetic wound healing agent. Data sources were obtained from national and international articles indexed by Sinta and Scopus in databases

such as Google Scholar, PubMed, and ScienceDirect with a publication spanning the last 10 years (2015–2025). The search was conducted using the keywords "Nanostructured Lipid Carrier", "Natural Product", "Herbal Extract", "Antidiabetic", "Diabetic Wound", and "Drug Delivery System". The inclusion criteria for this study included articles published in the period 2015–2025, discussing the development or application of natural ingredient-based NLC for antidiabetic therapy or diabetic wounds, available in full text, and originating from reputable journals. The exclusion criteria included articles that were not relevant to the topic of NLC, natural ingredients, or diabetes/diabetic wound therapy, articles with limited access, and publications before 2015. The selection process was carried out by reviewing the title, abstract, and full content of the article to ensure compliance with the criteria, then the data was analyzed descriptively by identifying the type of natural ingredients used, the NLC formulation method, its pharmacological activity as an antidiabetic or wound healer, as well as the advantages, challenges, and prospects for future development.

RESULTS AND DISCUSSIONS

Table 1. Formulation and effectiveness of natural ingredients-based NLC for antidiabetic therapy and diabetic wound healing

Article Title	Active Ingredients / Herbal	NLC Type	Main Effects & Results of the Study	Reference
Zerumbone-Loaded Nanostructured Lipid Carrier Gel Enhances Wound Healing in Diabetic Rats	Zerumbon	NLC Gel	Improves the healing process of diabetic wounds through anti-inflammatory effects and tissue regeneration.	(Albaayit et al., 2022)
An EGF- and Curcumin-Co-Encapsulated Nanostructured Lipid Carrier Accelerates Chronic-Wound Healing in Diabetic Rats	Epidermal growth factor (EGF) & Curcumin	NLC co-encapsulation	Accelerates healing of chronic wounds by increasing cell proliferation and angiogenesis.	(Lee et al., 2020)
Nanostructured Lipid Carriers Loaded with Baicalin: An Efficient Carrier for Enhanced Antidiabetic Effects	Baicalin	NLC Oral	Enhances antidiabetic effects through blood glucose control	(Shie et al., 2016).
Propolis-Based Nanostructured Lipid Carrier of α-Mangostin for Promoting Diabetic Wound Healing in Alloxan-Induced Mice	α-Mangostin	Propolis-based NLC	Promotes wound healing with antioxidant and anti-inflammatory effects	(Suhandi et al., 2025)
The efficacy of carvacrol loaded nanostructured lipid carrier in improving the diabetic wound healing activity: In vitro and in vivo studies	Carvacrol	Oral & topical NLC	Promotes wound healing through anti-inflammatory activity and cell proliferation	(Fauzian et al., 2024).
Selenium-coated nanostructured lipid carriers for oral delivery of berberine to accomplish synergic hypoglycemic effect	Berberine + Selenium	oral NLC	Synergistic hypoglycemic effect is higher than ordinary berberine	(Yin et al., 2017)

The development of a natural nanostructured lipid carrier (NLC)-based drug delivery system for antidiabetic therapy and diabetic wound healing has attracted considerable attention in pharmaceutical and nanomedicine research. NLC is a lipid-based drug delivery system composed of a mixture of solid and liquid lipids, offering advantages in stability, high drug loading capacity, and the ability to control drug release gradually.(Hayati, Sari, & Farm, 2024),(Maslachah, 2024).

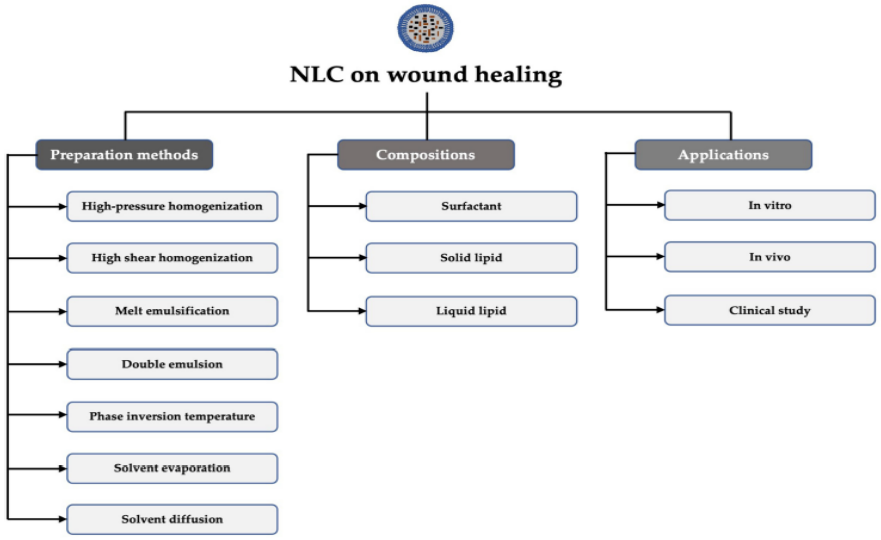

Figure 3. Main component diagram of nanostructured lipid carrier (NLC) in wound healing (Wathoni et al., 2024).

In the context of antidiabetic therapy, NLC has been used to increase the bioavailability of drugs such as metformin and pioglitazone. Based on research(Qushawy et al., 2025)showed that NLC loaded with metformin had high encapsulation efficiency, small particle size, and good in vitro drug release, making NLC potentially useful for the treatment of type 2 diabetes. In addition, research based on(Ilyas et al., 2022). developed NLC loaded with pioglitazone, showing improved solubility and better antidiabetic potency compared to pioglitazone without developing NLC.

Research based on(Fauzian, Garmana, & Mauludin, 2024)developed an NLC loaded with carvacrol, the main component of oregano essential oil, which has antioxidant, anti-inflammatory, and antibacterial activities. This NLC formulation demonstrated increased wound healing activity in diabetic rats and offers a more effective therapeutic alternative for diabetic wounds compared to carvacrol without NLC. Furthermore, the combination of natural ingredients such as curcumin and epidermal growth factor (EGF) in the NLC system has also been explored for diabetic wound healing. Research based on(Lee et al., 2020)showed that NLC loaded with curcumin and EGF can enhance antioxidant activity and accelerate wound healing in diabetes-induced animal models, and demonstrated the synergistic potential of natural products in diabetic wound therapy.(Rismawati, Gondokesumo, & Aryani, 2025),(Evalina & Aryani, nd).

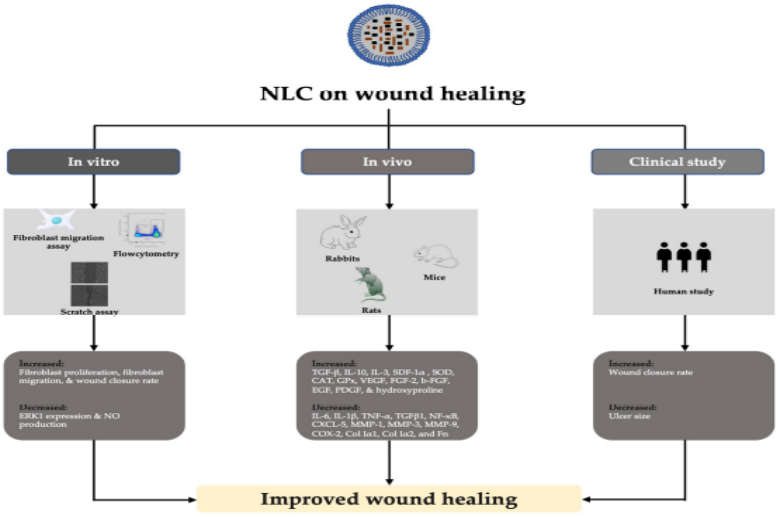

Figure 2. Benefits of using NLC in wound healing

Based on in vitro, in vivo, and clinical studies (Wathoni et al., 2024), the development of NLC-based delivery systems from natural materials offers a promising approach in antidiabetic therapy and diabetic wound healing. The advantages of NLC include improved solubility, stability, and controlled drug release.(Aspadiah, Fristiohady, & Wahyuningrum, 2020),(Hayati et al., 2024).

CONCLUSION

The development of a natural NLC-based drug delivery system shows great promise in antidiabetic therapy and diabetic wound healing. NLC can improve drug solubility, stability, and bioavailability. Furthermore, NLC formulations containing natural ingredients, such as carvacrol and curcumin, exhibit antioxidant, anti-inflammatory, and antibacterial activities that enhance the efficacy of diabetic wound healing. Recent studies (2015–2025) confirm that the combination of NLC with natural bioactive compounds not only increases therapeutic effectiveness but also reduces side effects, thus opening up opportunities for the development of safer and more effective diabetes and diabetic wound therapies.

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