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THEME

Green Synthesis, Characterization, and Biological Evaluation of a Polyherbal-Based Chitosan-Fe_2O_3/ZnO Nanocomposite for Diabetic Wound Healing: In Vitro, In Silico, and In Vivo Study

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الاهـــــــداء

﴿يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ﴾ سورة المجادلة، الآية 11

من قال أنا لها "نالها" وأنا لها إن ابَت رغما عنها اتيت بها.

لم تكن الرحلة قصيرة ولا ينبغي لها أن تكون لم يكن الحلم قريبا ولا الطريق كان محفوفاً بالتسهيلات لكنني فعلتها ونلتها.

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الى التي جعل الله الجنة تحت أقدامها، واحتضنتني قلبًا قبل يدها، وسهّلت لي الشدائد بدعائها...إلى القلب الحنون، وشمعة لياليّ المظلمة، وسرّ قوتي ونجاحي... **أمي**

أتمنى ان يكون هذا العمل المتواضع ثمرة جهودكم التي لاتعد و لا تحصى

إلى أختي الوحيدة... قطعة من قلبي ورفيقة دربي، وجودها أمان وابتسامتها سند في حياتي... **كوثر**

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وإلى أغلاهن وأقربهن إلى قلبي، صديقة الروح ورفيقة الذكريات، شكرًا لوفائها الصادق، ولدعمها الدائم، ولمكانتها الخاصة في حياتي **حنين**

وأتوجه بالشكر أيضًا إلى كل من منحني صداقته في يومٍ من الأيام، وشاركني لحظاتٍ لا تُنسى ستبقى محفورة في قلبي طوال مسيرتي الجامعية، وكانت لي سندًا وذكرى جميلة لا تُقدّر بثمن.

تقدم بخالص الشكر والعرفان إلى **أعمامي وعماتي وخالاتي وأخوالي** على دعمهم المتواصل لي طوال مسيرتي الدراسية، ومشاركتهم فرحة نجاحي، وتشجيعهم الدائم الذي كان سندًا لي في جميع مراحل دراستي.

أهديكم بحث تخرجي هذا، راجيةً من الله عز وجل أن يجعله خالصًا لوجهه الكريم، وأن يتقبله قبولًا حسنًا، ويبارك في أعماركم، ويجزيكم خير الجزاء في الدنيا والآخرة.

الزهرة

الإهـــــداء

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الحمد لله الذي ما تمّ جهدٌ إلا بعونه، ولا اكتمل سعيٌ إلا بفضله، ولا بلغنا نهاية الطريق إلا بلطفه وكرمه.

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ملاك

ا لاهــــــداء

﴿يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ﴾ (سورة المجادلة: آية 11)

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إلى صديقاتي إلى رفيقات العمر والقلوب الصادقة، اللواتي لم يمللن من الاستماع إليّ، وكنّ دائمًا يبعثن في نفسي الأمل والتفاؤل كلما قلّت عزيمتي ،من أفاضني بمشاعره و نصائحه المخلصة **أسماء ، جهان، عبير ونجاح**

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وأسأل الله أن يكون هذا الإنجاز بدايةً لنجاحاتٍ أكبر، وأن يجعل فيما تعلمناه خيرًا ونفعًا وبركة.

فريال

Abstract

Diabetic wound healing is a complex process often delayed by hyperglycemia, oxidative stress, chronic inflammation, impaired angiogenesis, and defective tissue remodeling. This study aimed to evaluate the wound-healing potential of a polyherbal extract prepared from Syzygium aromaticum L. and Boswellia sacra, as well as Ch–Fe_2O_3/ZnO nanocomposite, in diabetic wound healing. The aqueous polyherbal extract was prepared by maceration and analyzed for its phytochemical composition, which revealed the presence of flavonoids, polyphenols, tannins, saponins, free quinones, mucilage, terpenoids, and alkaloids. Quantitative analysis confirmed its richness in total polyphenols and flavonoids. The Fe_2O_3/ZnO nanocomposite was synthesized and coated with chitosan, and its characterization by UV–Visible, FTIR, XRD, and SEM confirmed the structural, functional, and morphological characteristics of the final nanocomposite. In vitro results showed antioxidant, anti-inflammatory, and antibacterial activities against Escherichia coli and Staphylococcus aureus. The in silico study supported these effects through the interaction of Syzygium aromaticum compounds with Keap1 and boswellic derivatives with COX-2, with acceptable ADMET profiles. The in vivo study, performed using an alloxan-induced diabetic wound model in rats, showed that the untreated diabetic group had delayed wound healing, increased oxidative stress, and poor tissue repair. In contrast, treated groups showed improved wound closure, decreased MDA levels, increased GSH levels, and better histological organization. The Ch–Fe_2O_3/ZnO nanocomposite cream showed the best healing progression, with improved re-epithelialization, collagen organization, fibroblast activity, vascularization, and skin regeneration. Overall, the results suggest that the polyherbal extract and Ch–Fe_2O_3/ZnO nanocomposite contributed to improving diabetic wound healing through antioxidant, anti-inflammatory, antibacterial, and tissue-regenerative effects.

Keywords:

Diabetic wound healing; polyherbal extract ; Ch–Fe_2O_3/ZnO nanocomposite ; chitosan ; oxidative stress.

الملخص

يُعدّ التئام الجروح السكرية عملية بيولوجية معقدة، غالبًا ما تتأخر بسبب فرط سكر الدم، والإجهاد التأكسدي، والالتهاب المزمن، وضعف تكوّن الأوعية الدموية، واضطراب إعادة بناء الأنسجة. هدفت هذه الدراسة إلى تقييم قدرة مستخلص نباتي مركب محضّر من القرنفل Syzygium aromaticum ولبان الذكر Boswellia sacra، إضافة إلى المركب النانوي $Ch–Fe_2O_3/ZnO$، على تحسين التئام الجروح السكرية. حُضّر المستخلص النباتي المائي بطريقة النقع، وأظهرت التحاليل الكيميائية النباتية وجود مركبات فعالة مثل الفلافونويدات، والبوليفينولات، والتانينات، والصابونينات، والتربينويدات، والقلويدات، كما أكد التحليل الكمي غناه بالبوليفينولات والفلافونويدات. تم تصنيع المركب النانوي Fe_2O_3/ZnO ثم تغليفه بالكيتوزان للحصول على $Ch–Fe_2O_3/ZnO$، وأكدت تقنيات UV–Visible و FTIR و XRD و SEM خصائصه البنيوية والوظيفية والمورفولوجية. أظهرت الاختبارات المخبرية نشاطًا مضادًا للأكسدة، ومضادًا للالتهاب، ومضادًا للبكتيريا ضد Escherichia coli و_ Staphylococcus aureus_. كما دعمت دراسة المحاكاة الجزيئية هذه النتائج من خلال تفاعل مركبات القرنفل مع Keap1 ومشتقات البوسويليك مع COX–2، مع خصائص ADMET مقبولة. أما الدراسة الحيوية، التي أُجريت على نموذج جروح سكرية مستحدث بالألوكسان عند الجرذان، فقد أظهرت أن المجموعة السكرية غير المعالجة عانت من تأخر واضح في التئام الجروح، وزيادة في الإجهاد التأكسدي، وضعف في الإصلاح النسيجي. بالمقابل، أظهرت المجموعات المعالجة تحسنًا في انغلاق الجروح، وانخفاضًا في مستويات MDA، وارتفاعًا في مستويات GSH، وتحسنًا في التنظيم النسيجي. وقد أظهرت كريمة $Ch–Fe_2O_3/ZnO$ أفضل تطور في الالتئام، من خلال تحسين إعادة تكوين البشرة، وتنظيم الكولاجين، ونشاط الخلايا الليفية، وتكوّن الأوعية الدموية، وتجدد البنى الجلدية. بشكل عام، تشير النتائج إلى أن المستخلص النباتي المركب والمركب النانوي $Ch–Fe_2O_3/ZnO$ ساهما في تحسين التئام الجروح السكرية بفضل خصائصهما المضادة للأكسدة، والمضادة للالتهاب، والمضادة للبكتيريا، والداعمة لتجدد الأنسجة.

الكلمات المفتاحية:

التئام الجروح السكرية؛ المستخلص النباتي المركب؛ المركب النانوي $Ch–Fe_2O_3/ZnO$؛ الكيتوزان؛ الإجهاد التأكسدي.

LIST OF ABBREVIATIONS

2D: Two-dimensional

3D: Three-dimensional

ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity

AKBA: Acetyl-11-keto-β-boswellic acid

$AlCl_3$: Aluminum chloride

ANOVA: Analysis of variance

ATCC: American Type Culture Collection

BA: Boswellic acid

BAs: Boswellic acids

BBB: Blood–brain barrier

BCR: B cell receptor

BSA: Bovine Serum Albumin

CAT: Catalase

CF: Collagen fibers

Ch: Chitosan

Ch - Fe_2O_3/ ZnO: Chitosan-coated iron oxide/zinc oxide nanocomposite

CMC: Carboxymethyl cellulose

COX-2: Cyclooxygenase-2

CRP: C-reactive protein

D: Dermis

DMEM: Dulbecco's Modified Eagle Medium

DPPH: 2,2-diphenyl-1-picrylhydrazyl

DTNB:5,5′-Dithiobis(2-nitrobenzoic acid)

E: Epidermis

EDTA: Ethylenediaminetetraacetic acid

EGF: Epidermal growth factor

ESR: Erythrocyte sedimentation rate

EXT: Polyherbal extract

Fe_2O_3: Iron oxide

$FeCl_3$: Ferric chloride

FGFs: Fibroblast growth factors

FRAP: Ferric reducing antioxidant power

FTIR: Fourier-transform infrared spectroscopy

GAE: Gallic acid equivalent

GEN: Gentamicin

GI: Gastrointestinal

GLP-1: Glucagon-like peptide-1

GLY: Blood glucose

GPx: Glutathione peroxidase

GSH: Reduced glutathione

H&E: Hematoxylin and eosin

HGB: Hemoglobin

HCT: Hematocrit

IC_{50}: Half-maximal inhibitory concentration

IL-1β: Interleukin-1 beta

IL-6: Interleukin-6

IL-10: Interleukin-10

IUPAC: International Union of Pure and Applied Chemistry

KBA: 11-keto-β-boswellic acid

Keap1: Kelch-like ECH-associated protein 1

KGF: Keratinocyte growth factor

Ki: Inhibition constant

LGA: Lamarckian Genetic Algorithm

LD_{50}: Median lethal dose

Lym: Lymphocytes

MDA: Malondialdehyde

MEB: Microscopie électronique à balayage

MMPs: Matrix metalloproteinases

MMFF94: Merck Molecular Force Field 94

MNPs: Metal nanoparticles

NaOH: Sodium hydroxide

Neut: Neutrophils

NF-κB: Nuclear factor kappa B

NH_4OH: Ammonium hydroxide

NI: No inhibition

NPs: Nanoparticles

Nrf2: Nuclear factor erythroid 2-related factor 2

PBS: Phosphate-buffered saline

PDB: Protein Data Bank

PDBQT: Protein Data Bank, Partial Charge and Atom Type format

PDGF: Platelet-derived growth factor

PEG-100: Polyethylene glycol-100

pH: Potential of hydrogen

PLT: Platelets

PMNCs: Polymer matrix nanocomposites

QE: Quercetin equivalent

RBC: Red blood cells

RMSD: Root mean square deviation

ROS: Reactive oxygen species

rpm: Revolutions per minute

SDF: Structure Data File

SEM: Scanning electron microscopy

SOD: Superoxide dismutase

TBA: Thiobarbituric acid

TBARS: Thiobarbituric acid reactive substances

TCA: Trichloroacetic acid

TFC: Total flavonoid content

TGF-β: Transforming growth factor beta

TNF-α: Tumor necrosis factor alpha

TPC: Total phenolic content

TPSA: Topological polar surface area

UV–Vis: Ultraviolet–Visible spectroscopy

VEGF: Vascular endothelial growth factor

VS: Vitesse de sédimentation

WBC: White blood cells

XRD: X-ray diffraction

ZnO: Zinc oxide

$Zn(CH_3COO)_2$: Zinc acetate

ΔG: Binding free energy

Experimental Group Codes

GA: Non-diabetic wounded untreated group

GB: Diabetic wounded untreated group

GC: Diabetic wounded group treated with Douce cream

GD: Diabetic wounded group treated with polyherbal extract cream

GE: Diabetic wounded group treated with Ch–Fe_2O_3/ZnO nanocomposite cream.

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SUMMARY

INTRODUCTION

INTRODUCTION

Diabetic wound healing remains a major biological and therapeutic challenge because diabetes mellitus disrupts the normal sequence of tissue repair. Under physiological conditions, wound healing progresses through coordinated phases, including hemostasis, inflammation, proliferation, and remodeling (Martin & Nunan, 2024). However, persistent hyperglycemia delays this process by increasing oxidative stress, prolonging inflammation, impairing angiogenesis, reducing fibroblast activity, and disturbing collagen deposition (Yadav *et al*., 2024). As a result, diabetic wounds are usually slower to close and more vulnerable to infection, tissue damage, and chronicity (Porel *et al*., 2025).

In recent years, nanotechnology has attracted increasing interest in biomedical applications, particularly in wound healing, because nanoparticles possess unique physicochemical and biological properties related to their small size, large surface area, and high reactivity (Islam *et al*., 2022). Among metal oxide nanoparticles, iron oxide and zinc oxide nanoparticles are especially important. Zinc oxide nanoparticles are widely studied for their antimicrobial, anti-inflammatory, and tissue-repair potential, while iron oxide nanoparticles are known for their functional properties, biocompatibility, and biomedical relevance (Sirelkhatim *et al*., 2015; Skóra *et al*., 2024). The combination of $Fe_2O_3$and ZnO in one nanocomposite system may therefore provide complementary biological and physicochemical properties useful for topical wound-healing applications.

Several methods can be used to synthesize nanoparticles and nanocomposites, including physical, chemical, and biological approaches. Although physical and chemical methods are efficient, they may require high energy, expensive equipment, or toxic reagents (Adeyemi *et al*., 2024). For this reason, green synthesis has become an attractive alternative because it uses plants, microorganisms, or natural biomolecules as reducing and stabilizing agents (Adeyemi *et al*., 2024). Plant-mediated synthesis is particularly interesting because plant extracts contain polyphenols, flavonoids, terpenoids, and other bioactive compounds that can participate in nanoparticle formation and may also improve their biological activity (Fierascu *et al*., 2021).

In this context, medicinal plants represent an important source of natural bioactive molecules. *Syzygium aromaticum L.*, commonly known as clove, is rich in phenolic compounds, flavonoids, and eugenol, which are associated with antioxidant, antimicrobial, and anti-inflammatory activities (Batiha *et al*., 2020). *Boswellia sacra*, commonly known as frankincense, contains resinous compounds, terpenoids, and boswellic acids, which are mainly known for their anti-inflammatory and tissue-protective effects (Miran *et al*., 2022). Therefore, the use of these two plants may be valuable not only for preparing a polyherbal extract with wound-healing potential, but also for contributing to the green synthesis of Fe_2O_3/ ZnO nanoparticles.

Chitosan also plays an important role in the development of nanocomposite systems for wound healing. It is a biocompatible, biodegradable, and bioactive polymer widely used in biomedical and topical applications because of its film-forming ability, antimicrobial activity, and capacity to support tissue regeneration (Dash *et al*., 2011). In nanocomposite formulation, chitosan can act as a coating or polymeric matrix around Fe_2O_3/ ZnO nanoparticles, improving their stability, dispersion, interaction with biological tissues, and suitability for topical application. Thus, coating Fe_2O_3/ ZnO nanoparticles with chitosan may produce a multifunctional Ch–Fe_2O_3/ZnO nanocomposite with potential activity against diabetic wounds.

Despite the availability of several conventional treatments, diabetic wounds remain difficult to manage because many current approaches do not fully correct the main mechanisms responsible for delayed healing, such as oxidative stress, chronic inflammation, microbial contamination, and poor tissue regeneration (Yadav *et al*., 2024; Porel *et al*., 2025). This research gap highlights the need for alternative topical formulations capable of combining antioxidant, anti-inflammatory, antibacterial, and regenerative effects. Based on this need, the present study was designed to evaluate the wound-healing potential of a polyherbal extract prepared from *Syzygium aromaticum L.* and *Boswellia sacra*, and a topical cream containing Ch–Fe_2O_3/ZnO nanocomposite, in an alloxan-induced diabetic wound model in rats.

This dissertation is divided into two main parts. The first part presents the bibliographic synthesis, including general information about medicinal plants, diabetes and wound healing, and nanocomposites. The second part presents the experimental study, including the preparation of the polyherbal extract, synthesis and chitosan coating of Fe_2O_3/ ZnO nanoparticles, characterization of the Ch–Fe_2O_3/ZnO nanocomposite, in vitro antioxidant, anti-inflammatory, and antibacterial assays, in silico molecular docking and ADMET prediction, formulation of topical creams, and In Vivo evaluation of wound healing through wound contraction, biochemical and hematological parameters, oxidative stress markers, and histopathological examination.

First Part:

Bibliographic Synthesis

CHAPTER 01

MEDICINAL PLANTS

General Overview

Medicinal plants are recognized as vital sources of bioactive chemicals, especially secondary metabolites like phenolics and terpenes, which demonstrate considerable chemical diversity and biological significance (Fierascu *et al*., 2021). Recent investigations have shown that these plant-derived chemicals form a foundation for a great deal of research in the fields of biochemistry and pharmaceutical sciences because of their potential uses (Marrelli, 2021). Additionally, medicinal plants continue to be extensively employed, and there is a persistent scientific pursuit of understanding their biological mechanisms and properties (Krishnaprabu, 2020). In this case, aromatic plants like frankincense (*Boswellia sacra*) and clove (*Syzygium aromaticum L.*) are thought to have a lot of beneficial compounds, which makes them good models for more research (Fierascu *et al*., 2021).

I. *Boswellia sacra*

I. 1. Taxonomy and botanical description of *Boswellia sacra*

Frankincense *(Boswellia sacra)* is a highly aromatic terpenoid oleogum resin produced by species of the genus Boswellia and obtained from incisions made in the trunks of these trees (Vang *et al*., 2024; Miran *et al*., 2022). It is secreted when the bark is damaged naturally by animals or insects or intentionally cut by humans for resin extraction (Miran *et al*., 2022). Taxonomically, the frankincense tree belongs to the family Burseraceae, and its genus is identified as Boswellia (Siddiqui, 2011). Species of this genus are distributed in Africa, the Middle East, and India (Singh *et al*., 2024), particularly in the arid regions of Africa, the Arabian Peninsula, and South Asia (Vang *et al*., 2024).

The genus Boswellia was named in honor of Johan Boswell, who discovered some of its species (Singh *et al*., 2024). Frankincense is mainly obtained from *B. frereana*, *B. sacra, B. papyrifera*, and *B. serrata*, which are indigenous to Somalia, Yemen, Oman, and parts of India and Pakistan (Vang *et al*., 2024). In traditional medicine, Frankincense (*Boswellia sacra*) resin has been used for millennia because of its anti-inflammatory, antibacterial, and wound-healing properties (Al-Saban *et al*., 2025), and recent research has highlighted its medicinal potential, particularly against resistant bacterial strains and oxidative stress (Al-Saban *et al*., 2025).

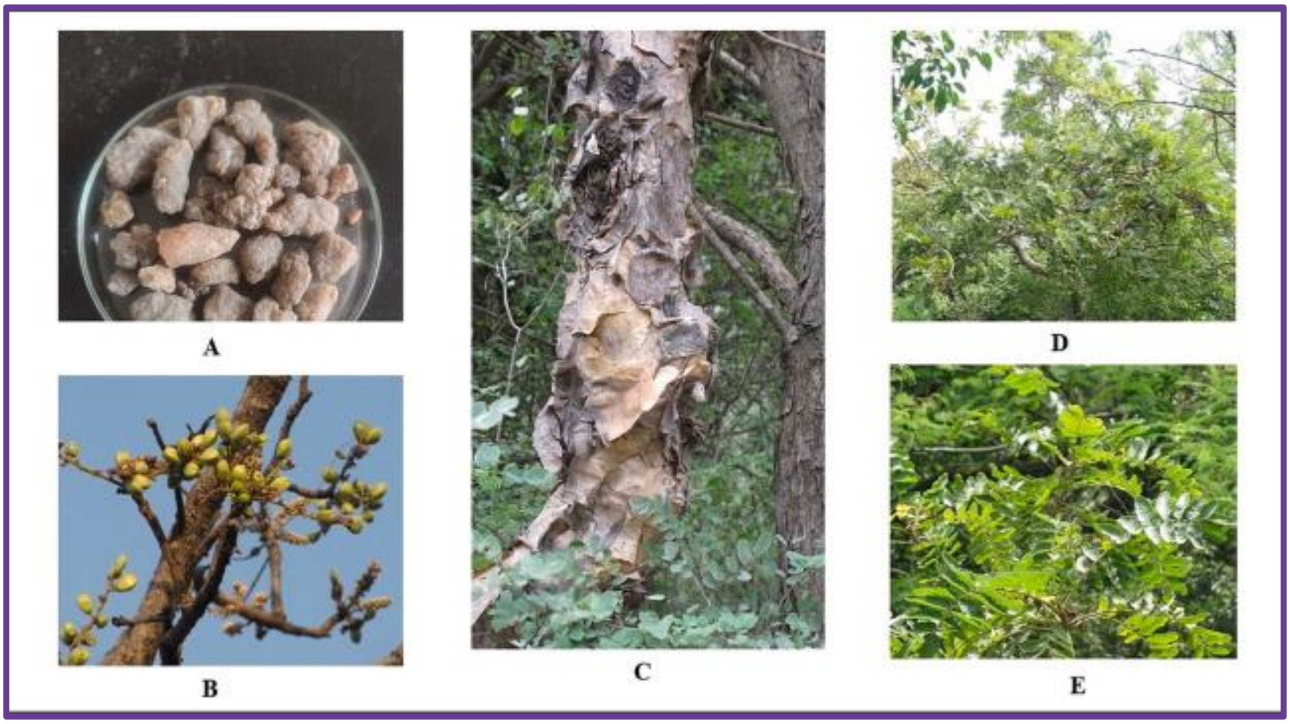

Figure 01: Frankincense Plant & its different parts- A: Oleo-gum resin; B: Fruits; C: Bark of tree; D: Whole plant; E: Leaves. (Mishra *et al*., 2025).

Table 01: The taxonomy of frankincense tree (Al-Shanfari & Al-Yafi, 2025).

Taxonomy	
Kingdom	Plantae
Division	Angiosperms (Flowering plants)
Class	Eudicots (A group of dicotyledonous plants)
Order	Sapindales (Consists of various flowering plant families)
Family	Burseraceae (known for its resin-producing species)
Genus	*Boswellia*
Species	*Boswellia sacra*

I. 2. Chemical composition of frankincense (*Boswellia sacra*)

Boswellia sacra frankincense gum resin has a complex phytochemical composition. It comprises 5-9% oil, a 60-70% alcohol-soluble fraction, and a 25-30% water-soluble fraction. The lipophilic fraction serves as a substantial source of terpenoids, especially boswellic acids, which are considered biologically active and pharmacologically significant constituents (Miran *et al*., 2022; Khan & Rashan, 2025).

The phytochemistry of *Boswellia sacra* predominantly centers on the resin, which comprises various terpenoids, essential oils, and polysaccharides, with many bioactive substances that contribute to its therapeutic and aromatic properties. The essential oil comprises several monoterpenes, diterpenes, and sesquiterpenes, which provide the resin with its distinctive fragrance, alongside other triterpenoid derivatives, such as ursane and oleanane, as well as smaller amounts of phenolic compounds and plant sterols, including β-sitosterol. (Al Shahry & Sivamani, 2024).

Boswellic acids (BAs), isolated from the oleogum resin of the Boswellia genus, represent a general term for a series of pentacyclic triterpenoid compounds and are considered unique constituents of Boswellia species. (Cui *et al*., 2024) (Al Shahry & Sivamani, 2024) According to their parent nucleus structure, most bosacid components obtained from Boswellia can be classified into ursane, oleanane, or lupane families. Representative compounds within this group include α-boswellic acid (α-BA), β-boswellic acid (β-BA), acetyl-α-boswellic acid (acetyl-α-BA), acetyl-β-boswellic acid (acetyl-β-BA), 11-keto-β-boswellic acid (KBA), and acetyl-11-keto-β-boswellic acid (AKBA). (Cui *et al*., 2024).

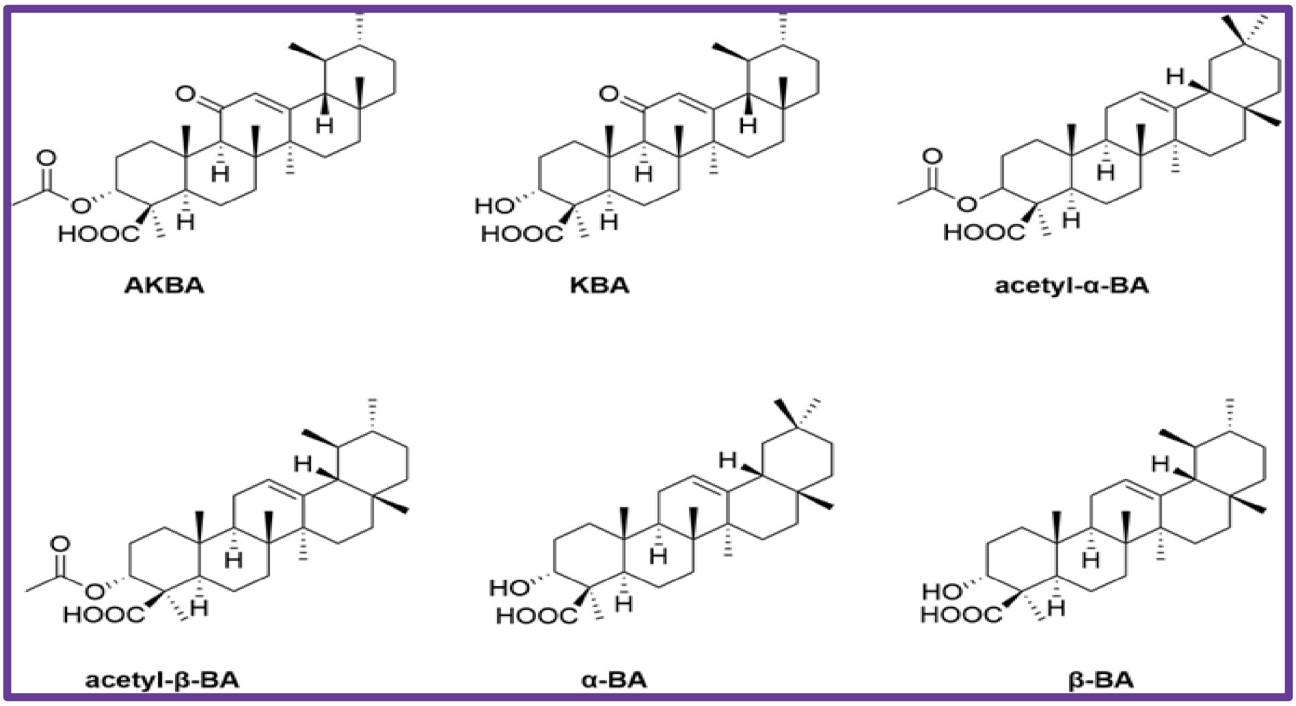

Figure 02: The six representative components of BA (Cui *et al*., 2024).

I. 3. Applications of *Boswellia*:

I. 3.1. Traditional and Ethnobotanical Applications:

Frankincense has occupied an important place in traditional medicine and cultural practice for more than 5,000 years, and its use is extensively described in the Vedic literature (Al-Saban *et al*., 2025). Over millennia, frankincense resin has been harvested and traded and has been used in cultural and religious rituals, in traditional medical systems such as Ayurveda and Traditional Chinese Medicine, and as a component of perfumes and aromatic substances (Sun *et al*., 2025). Its oleo-gum resin has been burned for fragrance and as incense, while its essential oil has been used in aromatherapy and perfumery since antiquity (Al-Kharousi *et al*., 2023; Almeida-da-Silva *et al*., 2022). In Oman, *Boswellia sacra* is also used in religious ceremonies, traditional celebrations, and customary practices, and its essential oil is incorporated into perfumery, cosmetics, and aftershaves (Al-Shanfari & Al-Yafi, 2025). In Middle Eastern countries, *Boswellia sacra* has additionally been used as a home remedy, while frankincense has also been employed in cosmetic, perfume, beverage, food, detergent, and pharmaceutical industries (Miran *et al*., 2022). More generally, *Boswellia sacra* has been recognized for centuries as an aromatic resin used in traditional medicine, religious rituals, and perfumery, and ethnomedicine has made use of different parts of the plant, including the bark, fruit, leaves, stem, and roots (Al Shahry & Sivamani, 2024; Al-Saban *et al*., 2025).

I. 3.2 Therapeutic Applications:

Frankincense has long been recognized for its medicinal value, particularly as an anti-inflammatory agent, and has also been used in the treatment of back pain, chronic cough, leukemia, and liver and colon cancers (Al-Kharousi *et al*., 2023). It has further been described as possessing anti-inflammatory, antimicrobial, and antioxidant properties and has been employed in the treatment of arthritis, asthma, and skin infections, as well as in cancer prevention (Al-Saban *et al*., 2025). In traditional medical systems, frankincense has been used to treat digestive, skin, ear, and throat infections, to relieve menstrual pain, and to address cardiovascular and neurological problems (Sun *et al*., 2025). In addition, *Boswellia sacra* resin has been associated with anti-inflammatory, analgesic, and potential anticancer properties (Al Shahry & Sivamani, 2024). Frankincense resin and gum extracts have also been used to improve digestion and to treat dental infections, colds, cough, fever, muscle pain, asthma, and arthritis, while supportive therapy for certain cancers, as well as cardioprotective and hepatoprotective effects, has also been reported (Al-Shanfari & Al-Yafi, 2025).

I. 4. Previous studies on the biological properties of *Boswellia*

I.4.1 Antioxidant and Antimicrobial Activities

Frankincense, the oleo-gum-resin obtained from Boswellia species, is rich in bioactive compounds such as boswellic acids, terpenoids, and phenolic constituents, which are responsible for its wide range of pharmacological activities. Boswellia extracts have demonstrated significant antioxidant activity through the scavenging of free radicals and the reduction of oxidative stress, which plays an important role in tissue protection and wound repair. In addition, frankincense exhibits notable antimicrobial properties against several pathogenic microorganisms, including Gram-positive and Gram-negative bacteria commonly associated with wound infections (Al-Saban *et al*., 2025; Ragab *et al*., 2024). Boswellic acids are considered the principal active constituents contributing to these biological effects due to their anti-inflammatory, antimicrobial, and antioxidant mechanisms (Ragab *et al.*, 2024).

I.4.2 Anti-inflammatory Activity

The anti-inflammatory activity of frankincense has been extensively documented and is mainly attributed to boswellic acids, particularly acetyl-11-keto-β-boswellic acid (AKBA). These compounds inhibit inflammatory mediators such as 5-lipoxygenase (5-LOX), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines, thereby reducing inflammation and tissue damage (Hussain *et al.*, 2024). Through modulation of inflammatory pathways, frankincense may create a favorable microenvironment for tissue regeneration and wound healing.

I.4.3 Wound Healing Activity

Frankincense (Boswellia spp.) has been widely recognized for its role in wound healing, as its topical application has been shown to influence several stages of the healing process, particularly collagen synthesis and wound contraction, thereby contributing to improved recovery outcomes (Badr *et al.*, 2023). Experimental studies further demonstrated that frankincense-based treatments enhance wound contraction, stimulate epithelialization, support collagen deposition, and improve tissue remodeling while reducing inflammatory cell infiltration (Venkatesan *et al.*, 2025). Moreover, frankincense promotes the transition of wounds from the inflammatory phase to the proliferative phase, ultimately facilitating effective tissue repair and regeneration (Venkatesan *et al.*, 2025).

II. *Syzygium aromaticum L.*:

II. 1 Taxonomy and botanical description of *Syzygium aromaticum L.*:

The aromatic plant *Syzygium aromaticum L.,* also called Eugenia caryophyllata Thunb., is native to Indonesia and grows to a height of approximately 10 to 20 meters. It is an evergreen tree with gray smooth bark, large opposite leaves, leathery ovate-long elliptic leaf blades that are heavily covered in oil glands, red or pink flowers, and white buds that turn green and then red when they reach a length of 1.5 to 2 cm (Xue *et al.*, 2022). The different parts of S aromaticum are shown in Figure 1.

Syzygium aromaticum is classified as a member of the Kingdom Plantae, Sub Kingdom Tracheobionta, Super Division Spermatophyta, Division Magnoliophyta, Class Magnoliopsida, Subclass Rosidae, Order Myrtales, Family Myrtaceae, Genus Syzygium, and Species aromaticum (L) (Kaur & Kaushal, 2019).This is a medicinal plant utilized in Asia for therapeutic and culinary purposes, with the flowering buds referred to as cloves, which are desiccated and extensively commercialized (Tariq *et al.*, 2025).

Syzygium aromaticum, commonly referred to as clove, is cultivated for economic purposes in Sri Lanka, India, Madagascar, southern China, and Indonesia, with the flower buds being the commercially valuable portion of the tree (Pandey *et al*., 2024).

Figure 03. Various S. aromaticum sections. (A) entire plant; (B) dried flower buds; (C) fruit; (D) leaf. (Cortés-Rojas *et al*., 2014).

Syzygium aromaticum is classified as a member of the Kingdom Plantae, Sub Kingdom Tracheobionta, Super Division Spermatophyta, Division Magnoliophyta, Class Magnoliopsida, Subclass Rosidae, Order Myrtales, Family Myrtaceae, Genus Syzygium, and Species aromaticum (L) (Kaur & Kaushal, 2019).

This is a notable medicinal plant utilized in Asia for therapeutic and culinary purposes, with the flowering buds referred to as cloves, which are desiccated and extensively commercialized (Tariq *et al*., 2025). Syzygium aromaticum, commonly referred to as clove, is cultivated for economic purposes in Sri Lanka, India, Madagascar, southern China, and Indonesia, with the flower buds being the commercially valuable portion of the tree (Pandey *et al*., 2024).

Table 02: The taxonomy of *Syzygium aromaticum* (Suparman *et al*., 2020).

Taxonomy	
Kingdom	Plantae
Division	Angiosperms
Class	Magnoliopsida
Order	Myrtales
Family	Myrtaceae
Genus	*Syzygium*
Species	*Syzygium aromaticum*

II. 2 Chemical composition of *Syzygium aromaticum*

The phytochemical makeup of *Syzygium aromaticum* is classified into two primary classes, namely volatile and non-volatile components, which notably contain aromatics, sesquiterpenoids, monoterpenoids, flavonoids, triterpenoids, and organic acids (Xue *et al*., 2022) .One of the main plant sources of phenolic compounds, such as flavonoids, hydroxybenzoic acids, hydroxycinnamic acids, and hydroxyphenyl propens, is clove. Other phenolic acids found in cloves include caffeic, ferulic, ellagic, and salicylic acids, with gallic acid being the most concentrated. Flavonoids, including kaempferol, quercetin, and its derivatives, are also found in diminished amounts (Cortés-Rojas *et al*., 2014).

In addition, phytochemical research of clove has showed the presence of saponins, alkaloids, flavonoids, glycosides, tannins, and steroids (Kaur & Kaushal, 2019).

Table 03. The chemical formula and name of the bioactive compounds separated from S. aromaticum according to the International Union of Pure and Applied Chemistry (IUPAC) (Batiha *et al*., 2020).

Compd.	IUPAC Name	Chemical Formula	Compd.	IUPAC Name	Chemical Formula
Eugenol	2-Methoxy-4-(prop-2-en-1-yl)phenol	$C_{10}H_{12}O_2$	Gallic acid	3,4,5-Trihydroxybenzoic acid	$C_7H_6O_5$
β-Caryophyllene	(1*R*,4*E*,9*S*)-4,11,11-Trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene	$C_{15}H_{24}$	Biflorin	5,7-dihydroxy-2-methyl-6-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	$C_{16}H_{18}O_9$
Vanillin	4-Hydroxy-3-methoxybenzaldehyde	$C_8H_8O_3$	Myricetin	3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-4-chromenone	$C_{15}H_{10}O_8$
Crategolic acid (Maslinic acid)	(4a*S*,6a*R*,6a*S*,6b*R*,8a*R*,10*R*,11*R*,12a*R*,14b*S*)-10,11-dihydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid	$C_{30}H_{48}O_4$	Campesterol	(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*R*)-5,6-dimethylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol	$C_{28}H_{48}O$
Kaempferol	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4*H*-chromen-4-one	$C_{15}H_{10}O_6$	Stigmasterol	3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(*E*,2*R*,5*S*)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*] phenanthren-3-ol	$C_{29}H_{48}O$
Rhamnetin	2-(3,4-dihydroxyphenyl)-3,5-dihydroxy-7-methoxychromen-4-one	$C_{16}H_{12}O_7$	Oleanolic acid	(4aS,6a*R*,6a*S*,6b*R*,8aR,10*S*,12a*R*,14b*S*)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid	$C_{30}H_{48}O_3$
Eugenitin	5-Hydroxy-7-methoxy-2,6-dimethylchromen-4-one	$C_{12}H_{12}O_4$	Bicornin	[(12R,14S,15R,16R,17R)-4,5,6,22,23,29,30-heptahydroxy-9,19,26-trioxo-14,15-bis[(3,4,5-trihydroxybenzoyl)oxy]-2,10,13,18,25-pentaoxahexacyclo[18.9.3.03,8.012,17.024,32.027,31]dotriaconta-1(29),3,5,7,20,22,24(32),27,30-nonaen-16-yl] 3,4,5-trihydroxybenzoate	$C_{48}H_{32}O_{30}$
Eugenin	5-Hydroxy-7-methoxy-2-methylchromen-4-one	$C_{11}H_{10}O_4$	Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	$C_{15}H_{10}O_7$
Ellagic acid	2,3,7,8-Tetrahydroxy-chromeno [5,4,3-cde]chromene-5,10-dione	$C_{14}H_6O_8$	Carvacrol	2-methyl-5-propan-2-ylphenol	$C_{10}H_{14}O$

II. 3. Applications of *Syzygium aromaticum*

People from many countries have valued clove in traditional medicine for its many health benefits and everyday uses. It has long been used in Asian traditional medicine to treat a variety of illnesses, such as arthritis, colds and coughs, digestive issues, nausea, vomiting, diarrhea, toothaches, burns, wounds, scabies, malaria, tuberculosis, and other common problems (Tomasa *et al*., 2022). In traditional Indian and Chinese medicine, cloves are considered a warming and stimulating agent, historically utilized for vomiting, flatulence, nausea, and illnesses of the liver, intestine, and stomach. Additionally, clove formulations have been employed in the treatment of burns, wounds, and dental care (Batiha *et al*., 2020). In Moroccan folk medicine, cloves are used as cardiotonic agents, diuretics, carminatives, analgesics, and stimulants, and are also applied in the management of dental issues, inflammation, diabetes, hypertension, stomach disorders, diarrhea, rheumatism, and hair care (Zouhri *et al*., 2022).

II. 4. Previous studies on the biological properties of *Syzygium aromaticum*

II.4.1 Antioxidant Activity

Clove has phenolic chemicals, notably eugenol, which significantly contribute to the plant's antioxidant properties. Research indicates that clove efficiently neutralises free radicals, aiding in the prevention of degenerative diseases such as Alzheimer's and cancer (Hussain *et al*., 2017). Additional research indicates that the antioxidant properties of clove may aid in mitigating oxidative stress damage and enhancing cardiovascular health (Gülçin *et al*., 2012).

II. 4.2 Antibacterial Activity

Clove possesses a potent capacity to combat pathogenic germs owing to its phenolic constituents, particularly eugenol. Studies indicate that clove extracts can efficiently eradicate microorganisms responsible for diseases including *Staphylococcus aureus* and *Escherichia coli* (Jaiswal *et al*., 2021). Moreover, research has demonstrated that clove extracts are efficacious against antibiotic-resistant bacteria, hence augmenting their therapeutic potential (Bhowmik *et al*., 2012).

II.4.3 Anti-inflammatory Activity

Clove is conventionally employed to mitigate inflammation owing to its potent influence on immunological pathways. Research indicates that chemicals in clove, particularly eugenol, mitigate swelling and erythema associated with inflammation (Abdul Aziz *et al*., 2023). Researchers assert that these activities render clove an efficacious remedy for numerous inflammatory conditions, such as arthritis and cardiovascular disorders (Batiha *et al*., 2020).

II.4.4 Wound Healing Activity

Cloves positively influence the acceleration of wound healing owing to its antibacterial and anti-inflammatory properties. Studies indicate that clove enhances collagen synthesis and tissue regeneration, hence accelerating wound healing (Bhowmik *et al*., 2012). Moreover, cloves have demonstrated efficacy in accelerating wound healing and tissue regeneration owing to its therapeutic properties (El-Shouny *et al*., 2019).

CHAPTER 02

DIABETES & WOUNDS

General Overview

One of the most common chronic illnesses in the world, diabetes mellitus, is caused by either insufficient insulin secretion or decreased cellular sensitivity to insulin, which impairs blood glucose homeostasis. The utilisation of natural chemicals and medicinal plants is an important field of current study for diabetes prevention and treatment because modern lifestyle factors, such as bad eating habits and physical inactivity, have contributed to its rising prevalence (Forouhi & Wareham, 2019).

A significant complication of diabetes is decreased wound healing, especially in chronic wounds that do not advance through the typical healing stages, leading to extended difficulties in diabetic patients (Levy *et al*., 2024; Falanga *et al*., 2022). Chronic diabetes wounds detrimentally impact patients' health-related quality of life due to pain, reduced mobility, heightened infection risk, and potential amputation, resulting in significant physical, psychological, and social consequences (Reinboldt-Jockenöllfer *et al*., 2021).

I. Diabetes

Diabetes mellitus is a chronic metabolic disease caused by impaired insulin secretion or action. It is typified by persistent hyperglycemia, which causes abnormalities in the metabolism of proteins, fats, and carbohydrates as well as negative effects on a number of organs, including the kidneys, blood vessels, nerves, and eyes (Ueki, 2024; Lu *et al*., 2024). The World Health Organization states that fasting blood glucose levels of 1.26 g/L (7 mmol/L) or higher, blood glucose levels of 2 g/L or higher (11.1 mmol/L) two hours after an oral glucose tolerance test, or glycated haemoglobin (HbA1c) levels of 6.5% or higher are indicative of diabetes (Pleus *et al*., 2024).

I. 1. Types of diabetes

I.1.1. Type 1 diabetes

Insulin-dependent diabetes, or type 1 diabetes mellitus, is a chronic autoimmune disease that requires lifelong insulin therapy due to severe insulin deficiency and elevated blood glucose levels caused by immune-mediated destruction of pancreatic beta cells that produce insulin (Herold & Walker, 2023; James *et al*., 2023). This disease usually appears in childhood or adolescence and is becoming more widespread over the world (Gregory *et al*., 2022). Despite recent breakthroughs in detection and treatment, type 1 diabetes still causes clinically substantial acute complications (Subramanian *et al*., 2024).

Severe or chronic insulin shortage combined with hyperglycemia can cause diabetic ketoacidosis by utilising lipids as an alternate energy source and accumulating ketone bodies, which can escalate to coma or death if not treated (Umpierrez *et al*., 2024). Furthermore, insulin therapy may cause hypoglycemia, which can lead to neurological symptoms such as confusion, loss of consciousness, and seizures, and in severe cases, coma or death (Sherr *et al*., 2024).

I.1.2 Type 2 diabetes

Type 2 diabetes mellitus, or non-insulin-dependent diabetes, is the predominant variant of diabetes, largely impacting adults and the elderly, while its incidence among younger demographics has risen in recent years (Saeedi *et al*., 2024). This condition mostly arises from insulin resistance coupled with compromised pancreatic beta-cell functionality, resulting in hyperglycemia and metabolic dysregulation (Accili *et al*., 2025). It is frequently linked to additional metabolic problems, such as hypertension and dyslipidaemia, which elevate the risk of cardiovascular illnesses (Tanaka & Node, 2024).

Obesity, especially the buildup of visceral fat, is regarded as a significant contributor in the development of insulin resistance and decreased glucose tolerance (Gupta *et al*., 2024). Hormonal imbalances, particularly diminished incretin actions like GLP-1, also lead to sustained hyperglycemia (Nauck & Müller, 2024). Recent genetic studies demonstrate that genetic predisposition significantly influences susceptibility to type 2 diabetes and the heterogeneity of its clinical symptoms among individuals (Suzuki *et al*., 2024).

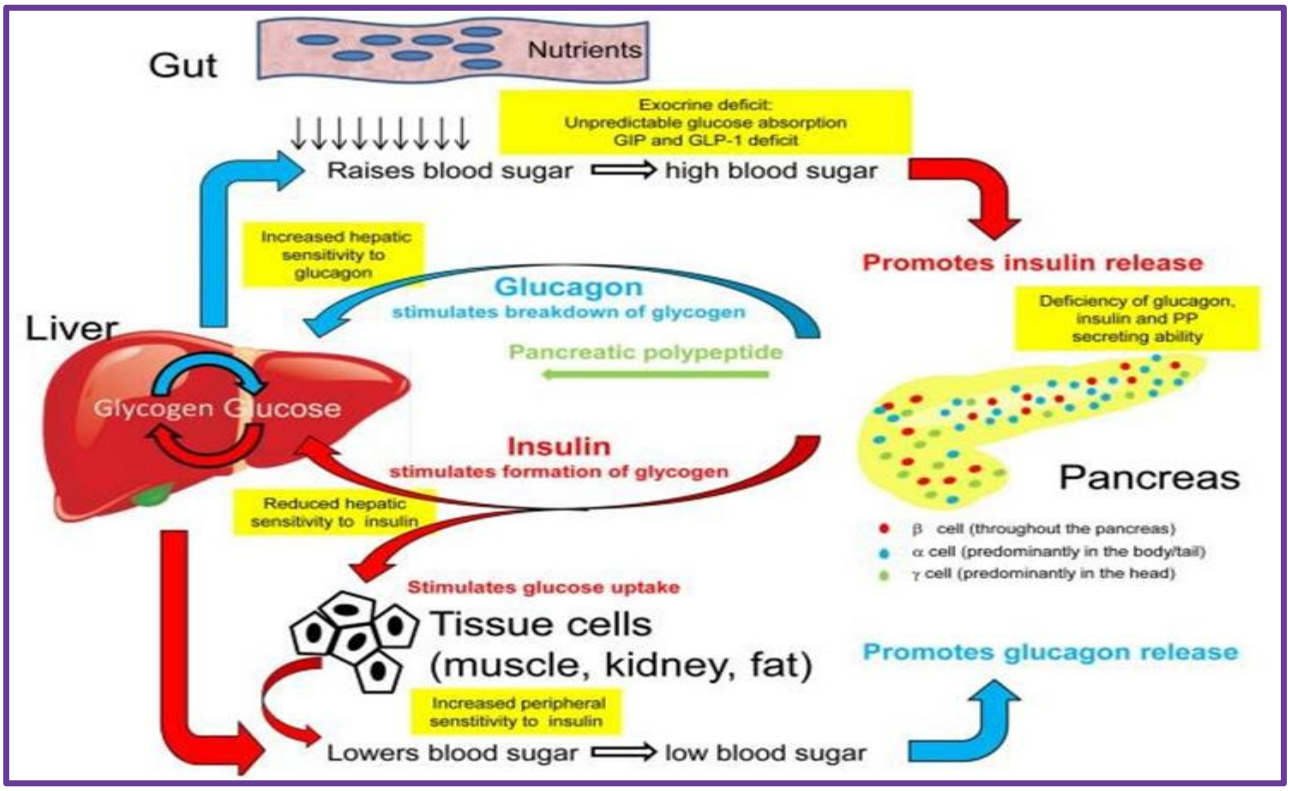

Figure 04: Pathophysiology of pancreatogenic diabetes (Balzano & Piemonti, 2014).

I.2. Symptoms

The clinical signs of diabetes mellitus include prominent symptoms such as polyuria, polydipsia, and weight reduction, and may also be linked to visual impairments, weariness, and asthenia (El Sayed *et al*., 2024). Diabetes heightens vulnerability to infections due to related immunological and metabolic impairments (Holt *et al*., 2024). Without suitable treatment, the illness may advance to serious metabolic consequences, including diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome, both of which pose significant life-threatening risks (Morey-Vargas, 2025). Additionally, type 1 diabetes in adults may have unusual signs, potentially leading to delayed or erroneous diagnoses in certain instances (Aamodt & Powers, 2025).

I.3. Treatment

The management of type 1 diabetes mellitus predominantly relies on insulin therapy via daily injections or insulin pumps, complemented by adherence to a suitable diet and the adjustment of insulin dosages based on physical activity and nutritional intake to sustain stable blood glucose levels (Janež *et al*., 2020; AlBabtain *et al*., 2023). The care of type 2 diabetes mostly depends on lifestyle modifications, such as dietary adjustments, weight loss, and enhanced physical activity, alongside the use of glucose-lowering medicines or insulin if necessary (Bajaj *et al*., 2024; Basu *et al*., 2023). The care of diabetic wounds, especially diabetic foot wounds, involves wound cleansing, debridement of necrotic tissue, infection management, enhancement of blood circulation, consistent monitoring, and application of suitable bandages (Jeffcoate *et al*., 2024). Effective glycemic regulation and enhancement of nutritional status are critical for expediting wound healing and minimizing the risk of infection or amputation (Ogbeide *et al*., 2024). Oral hypoglycemic medicines encompass various types, including biguanides, thiazolidinediones, sulfonylureas, glinides, and alpha-glucosidase inhibitors, as well as newer therapeutic drugs such as DPP-4 inhibitors and GLP-1 receptor agonists (Basu *et al*., 2023; Drucker, 2024; Zheng *et al*., 2024).

II. Wounds

II. 1. Normal Wounds Healing

Normal wound healing is a multifaceted biological process designed to restore tissue integrity and function, often progressing through four interrelated phases: haemostasis, inflammation, proliferation, and remodelling or maturation. The process commences with blood clot formation and vasoconstriction, succeeded by an inflammatory response to eliminate debris and avert infection. The proliferative phase include angiogenesis, granulation tissue development, fibroblast proliferation, and re-epithelialization, while the remodelling phase is defined by collagen reorganisation and a steady enhancement of tissue strength (Martin & Nunan, 2024). Effective wound healing relies on a precise equilibrium of inflammatory cells, the extracellular matrix, cytokines, and growth factors; any disruption in these phases may lead to delayed healing or the development of a chronic wound (Jin *et al*., 2025).

II. 1.1 Phases of Wounds Healing

II.1.1.1 Hemostasis

The immediate response to tissue injury is to activate the haemostatic system to prevent blood loss and the creation of a fibrin-rich clot via platelet adhesion and aggregation (Smith *et al*., 2015; Golebiewska & Poole, 2015). Activated platelets release bioactive mediators like PDGF, VEGF, and TGF-β, attracting immune cells and fibroblasts to the injury site (Palta *et al*., 2014). In addition to their haemostatic activity, platelets help to regulate wound healing by acting as a scaffold for cell migration and commencing the inflammatory phase (Swieringa *et al*., 2018).

II.1.1.2 Inflammation

Neutrophils are the first cells to reach the site of injury during the inflammatory phase, which is marked by the recruitment and activation of innate immune cells. In addition to their function in removing cellular waste, these cells emit reactive oxygen species, proteolytic enzymes, and neutrophil extracellular traps that have antibacterial effects (Raziyeva *et al*., 2021; Yang *et al*., 2025; Glennon-Alty *et al*., 2018; Zhu *et al*., 2021). Monocytes then move into the wound and develop into macrophages, which control the change from inflammation to healing. While subsequent polarisation toward the reparative M2-like phenotype encourages the production of IL-10, growth factors, and extracellular matrix-remodeling enzymes, M1-like macrophages generate pro-inflammatory cytokines such TNF-α, IL-1β, and IL-6 (Chen *et al*., 2023; Hassanshahi *et al*., 2022).

II.1.1.3 Proliferation

In the proliferative phase, new tissue is created to replace injured tissue. Growth hormones such as PDGF and TGF-β stimulate fibroblasts to produce components of extracellular matrix such as collagen and fibronectin (Chitturi *et al*., 2015). Also, the extracellular matrix provides structural support and helps with cell migration (Darby *et al*., 2014). Moreover, growth factors like EGF and KGF encourage keratinocyte migration and proliferation to restore epithelial continuity, while VEGF and FGFs increase angiogenesis to deliver oxygen and nutrients to the regenerated tissue (Santoro & Gaudino, 2005; Singh *et al*., 2017).

II.1.1.4 Remodeling (Maturation)

The concluding phase of wound healing entails the maturation and reorganisation of granulation tissue into a more stable scar, wherein myofibroblasts facilitate wound contraction and diminish wound size (Shin & Minn, 2004). Collagen fibres undergo gradual reorganisation, with type III collagen being supplanted by the more robust type I collagen, hence enhancing tissue tensile strength (Mayorca-Guiliani *et al*., 2025). Matrix metalloproteinases (MMPs) and their inhibitors modulate extracellular matrix remodelling and limit fibrosis, whereas blood vessels progressively diminish, leading to a comparatively avascular scar (Kremastiotis *et al*., 2021; Korntner *et al*., 2019).

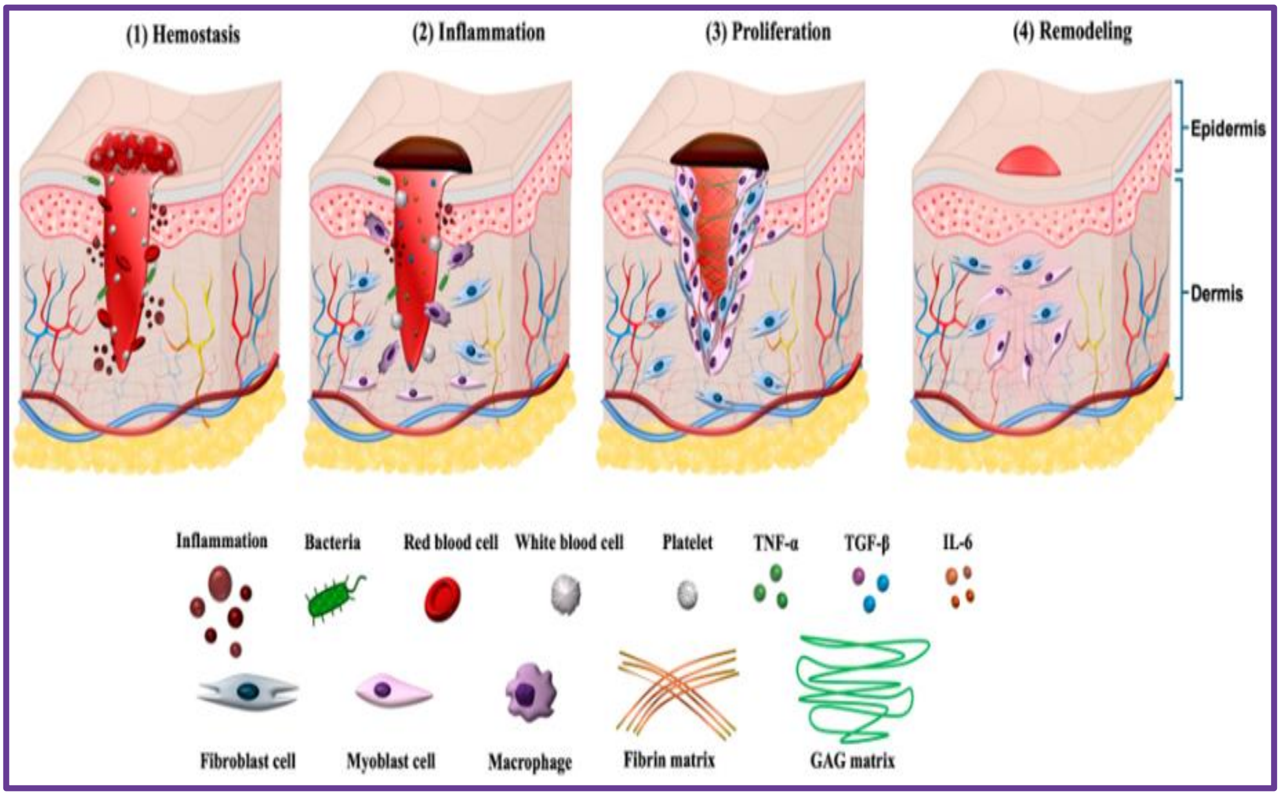

Figure 05. Illustration of the Four Phases of Wound Healing (Trinh *et al*., 2022).

II.2. Diabetic Wounds

Diabetic wounds differ from normal wounds due to metabolic, vascular, and immunological abnormalities caused by diabetes mellitus. Hyperglycemia, decreased blood perfusion, peripheral neuropathy, and immunological dysfunction all contribute to delayed wound healing and the maintenance of a chronic inflammatory state, while also inhibiting fibroblast proliferation, angiogenesis, and tissue repair (Yadav *et al*., 2024). Furthermore, loss of protective sensibility and vascular insufficiency heighten the danger of recurring injuries and infections, resulting in chronic and difficult-to-heal wounds (Porel *et al*., 2025).

II.2.1 Factors Contributing to Delayed Healing in Diabetic Wounds

II.2.1.1 Mechanisms of Delayed Wound Healing in Diabetes

Hyperglycemia hinders wound healing and promotes diabetic wounds by disrupting the cellular and inflammatory milieu, causing vascular insufficiency, and diminishing the supply of oxygen and nutrients to the injury site, consequently delaying tissue repair (Yadav *et al*., 2024; Sun *et al*., 2025). Diabetes mellitus is linked to endothelial cell dysfunction and compromised angiogenesis (Liu *et al*., 2024). Additionally, peripheral neuropathy leads to a loss of protective sensibility, heightening the chance of recurrent undiscovered injuries and facilitating the onset and duration of chronic wounds (Porel *et al*., 2025).

II.2.1.2 Role of Oxidative Stress in Impaired Wound Healing in Diabetes:

When levels of reactive oxygen species (ROS) are low, they play a crucial function in wound healing regulation (Dunnill *et al*., 2017). However, increased oxidative stress mixed with decreased antioxidant activity causes redox imbalance, which is regarded as a primary contributor to defective diabetic wound healing and delayed tissue repair (Sanchez *et al*., 2018). Hyperglycemia and tissue hypoxia are also linked to an enhanced oxidative environment in diabetic wounds, whereas oxidative stress causes skin damage, neuropathy, and local infections (Dworzanski *et al*., 2020).

II.2.1.3 Chronic Inflammation and Its Role in Delayed Healing in Diabetes:

Chronic wounds in diabetes individuals exhibit sustained inflammation and a protracted shift to the proliferative phase, leading to compromised wound healing. This disease is linked to heightened inflammatory cytokines, polymicrobial infections, alteration of the extracellular matrix, increased reactive oxygen species, and diminished levels of growth factors essential for wound closure (Porel *et al*., 2025). Moreover, immunological dysfunction and compromised angiogenesis contribute to protracted wound healing in diabetes patients (Dawi *et al*., 2025).

II.2.1.4 Bacterial Infection and Its Role in the Progression of Diabetic Wounds:

Bacterial infection is regarded as one of the most serious consequences of diabetic wounds, owing to poor skin barrier function and weakened local defence systems, which enhance wound susceptibility to microbial colonisation. Pathogenic bacteria such Pseudomonas aeruginosa and *Staphylococcus aureus* are frequently found in diabetic wounds, contributing to increased inflammation and delayed wound healing (Lou *et al*., 2025). Furthermore, biofilm formation increases bacterial antibiotic resistance and promotes chronic infection, delaying healing and complicating wound regeneration (Almuhanna, 2025).

CHAPTER 03

NANOCOMPOSITES

I. Nanotechnology

Nanotechnology, which focuses on the production and usage of materials smaller than 100 nanometre, is regarded as one of the most significant modern scientific accomplishments. Wastewater treatment, environmental monitoring, functional food additives, and antimicrobial agents are just a few of the many applications of nanoparticles in environmental science, food, biotechnology, and medicine (Zahra *et al*., 2020; Rassaei *et al*., 2011; Chen *et al*., 2023; Islam *et al*., 2022).

The use of nanoparticles in biomedical and biotechnological disciplines has expanded due to their special qualities, which include biocompatibility, antibacterial and anti-inflammatory characteristics, and effective drug delivery. Furthermore, because of their tiny size and huge surface area in comparison to bulk materials, nanoparticles display unique physical and chemical properties (Guo *et al*., 2013; Hasan, 2015).

II. Nanocomposites

Nanocomposites represent an innovative class of materials created by amalgamating one or more heterogeneous substances at the nanoscale to manipulate and enhance shapes and properties. The term nanocomposite refers to a diverse array of materials, including three-dimensional metal matrix composites, two-dimensional lamellar composites, one-dimensional nanowires, and zero-dimensional core-shell structures, all of which exemplify various forms of nanomixed and layered materials (Sahay *et al*., 2014).

III. Classification of nanocomposites

III.1. Metal Matrix Nanocomposites

Nanocomposites with a metallic continuous phase are covered in this section. These materials are appropriate for aerospace, biomedical, automotive, and technical applications due to their high mechanical strength, thermal stability, corrosion resistance, and enhanced durability. In order to increase mechanical strength, corrosion resistance, thermal conductivity, and durability, metal matrix nanocomposites (MMNCs) are made of metallic matrices reinforced with nanoscale materials. These nanocomposites are very helpful in engineering and biomedical applications because they combine the remarkable qualities of nanomaterials with the ductility of metals (Kumar *et al*., 2020; Tjong, 2007).

III .1.1 Iron/Zinc Oxide Nanocomposite

Because of their magnetic, antibacterial, antioxidant, and catalytic qualities, iron and zinc oxide nanoparticles are frequently utilized in the creation of metal-based nanocomposites. Zinc oxide nanoparticles have exceptional antibacterial and photocatalytic properties, while iron nanoparticles, especially iron oxide nanoparticles, have strong magnetic behavior and biocompatibility. In wound healing, drug delivery, tissue engineering, and antibacterial biomedical systems, iron/ZnO nanocomposites have garnered a lot of interest (Sirelkhatim *et al*., 2015).

III.1.2 Silver-Based Nanocomposites

Silver-based nanocomposites are significant metallic nanocomposites because to their exceptional antibacterial, antifungal, and anti-inflammatory properties. Silver nanoparticles are extensively integrated into nanocomposite systems to enhance biological efficacy and physicochemical stability. These nanocomposites have been thoroughly examined for applications in wound dressings, medical coatings, water treatment, and drug administration, owing to their robust antibacterial efficacy against a wide range of microbes (Rai *et al*., 2009).

III.2. Organic Matrix Nanocomposites

This category encompasses nanocomposites utilizing organic or polymeric matrices augmented with nanoscale fillers. Polymer matrix nanocomposites are lightweight, flexible, biodegradable, and biocompatible materials extensively utilized in biomedical engineering, packaging systems, wound healing, and pharmaceutical applications..Organic matrix nanocomposites, or polymer matrix nanocomposites (PMNCs), comprise organic polymer matrices augmented with nanoscale constituents. These nanocomposites are often utilized materials due to their lightweight composition, flexibility, ease of production, and superior biological and mechanical capabilities (Ray & Okamoto, 2003).

III.2.1 Polyester/ TiO_2Nanocomposite

Polyester/TiO_2 nanocomposites are polymeric materials reinforced with titanium dioxide nanoparticles. The incorporation of TiO_2 nanoparticles improves UV resistance, thermal stability, and mechanical performance. These nanocomposites are extensively used in coatings, packaging materials, and biomedical fields because of their durability and protective properties (Fischer, 2003).

III.2.2 Chitosan-Based Nanocomposites

Chitosan-based nanocomposites are essential biopolymer nanocomposites because they are biodegradable, biocompatible, and antibacterial. In these systems, chitosan serves as the polymeric matrix, with nanoparticles like zinc oxide and iron oxide acting as reinforcing agents. Because of their superior physicochemical and biological properties, chitosan nanocomposites have shown promise in wound healing, tissue engineering, drug delivery, and antibacterial systems (Dash *et al*., 2011).

III.3 Ceramic Matrix Nanocomposites

Ceramic matrix nanocomposites (CMCs) are inorganic materials that enhance toughness, hardness, thermal stability, and resistance to wear and corrosion by reinforcing ceramic matrices with nanoscale particles, fibers, or whiskers. These nanocomposites are extensively used in high-temperature industrial systems, medicinal implants, and aeronautical engineering (Sharma *et al*., 2020).

III.3.1 Al_2O_3/TiO_2 Nanocomposite

Al_2O_3/TiO_2 nanocomposites are among the most studied ceramic nanocomposites due to their high hardness, heat resistance, and photocatalytic activity. The incorporation of TiO_2 nanoparticles into the alumina matrix increases fracture toughness and mechanical strength, making these materials appropriate for coatings, biomedical devices, and environmental purification (Atmakuri *et al*., 2020).

III.3.2 Al_2O_3/SiC Nanocomposite

Al_2O_3/SiC nanocomposites are ceramic composites reinforced with silicon carbide nanoparticles. The addition of SiC enhances the crack resistance, thermal conductivity, and wear resistance. Thus, these nanocomposites are widely employed in cutting tools, turbine components, and aerospace constructions that are exposed to high temperatures (Sun *et al*., 2022).

IV. Synthesis Methods of Nanocomposites

IV.1 Physical Methods

Using physical procedures like milling, laser ablation, evaporation-condensation, and sputtering techniques, nanocomposites are produced. These techniques are frequently employed to produce extremely pure nanomaterials with regulated size distribution (Rane *et al*., 2024).

IV.2. Chemical Methods

Chemical synthesis techniques encompass sol–gel, co-precipitation, hydrothermal synthesis, chemical vapour deposition, and microemulsion processes. These methods are frequently favoured because to their effective regulation of particle form, composition, and crystallinity (Kumar *et al*., 2024).

IV.3. Biological or Green Synthesis Methods

Biological synthesis, commonly referred to as green synthesis, uses microorganisms, plant extracts, or biomolecules for the creation of nanocomposites. This methodology is deemed eco-friendly, economical, and less harmful than standard chemical methods (Adeyemi *et al*., 2024).

V. Characterization Techniques of Nanocomposites

V.1. X-ray Diffraction (XRD)

The crystalline structure, phase composition, and crystallite size of nanocomposites are frequently ascertained by X-ray diffraction (XRD) (Ogbezode *et al*., 2023).

V.2. Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) is used to detect functional groups to study the surface chemistry and chemical interactions of nanocomposites (Altammar, 2023).

V.3. Scanning Electron Microscopy (SEM)

SEM is utilised to investigate the surface morphology, particle dispersion, and topographical properties of nanocomposite materials (Kim & Lee, 2023).

V.4. Transmission Electron Microscopy (TEM)

High-resolution images of nanoparticles' size, shape, dispersion, and internal nanostructure can be obtained using transmission electron microscopy (TEM) (Altammar, 2023).

V.5. UV–Visible Spectroscopy (UV–Vis)

UV–Visible spectroscopy is frequently employed to assess the optical characteristics of nanoparticles and to verify their generation during synthesis (Borowska & Jankowski, 2023).

V.6. Energy Dispersive X-ray Analysis (EDX)

Energy dispersive X-ray analysis (EDX) is utilised for the investigation of elemental composition and the verification of specific elements in nanocomposites (Altammar, 2023).

VI. Toxicity and safety of nanocomposites

One of the key factors that determines the scope of nano systems' potential use in biological and medical applications is their toxicity and biosafety, include those for topical use in wound treatment, as a high level of functional efficiency is insufficient for these systems to be considered biosafe. Research on zinc- and iron-based systems has yielded promising findings concerning biosafety, and recent reviews emphasize the necessity of assessing toxicity, biocompatibility, and the biosafety profile of these systems based on their composition and physicochemical characteristics(Asif *et al*., 2023; Skóra *et al*., 2024).Iron-doped zinc oxide nanoparticles, for instance, have been investigated as a biodegradable and biocompatible system and have demonstrated decreased toxicity in in vitro experiments, Together with the monitoring of hematological and histological markers that supported the biosafety evaluation, there were no obvious negative effects noted in the animal model utilized (Kiełbik *et al*., 2021).

SECOND PART

EXPERIMENTAL STUDY

CHAPTER 01

MATERIALS & METHODS

CHAPTER 02

RESULTS AND DISCUSSION

Results and Discussion

CONCLUSION

Conclusion

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Bibliographic

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ANNEXES

Annexe I

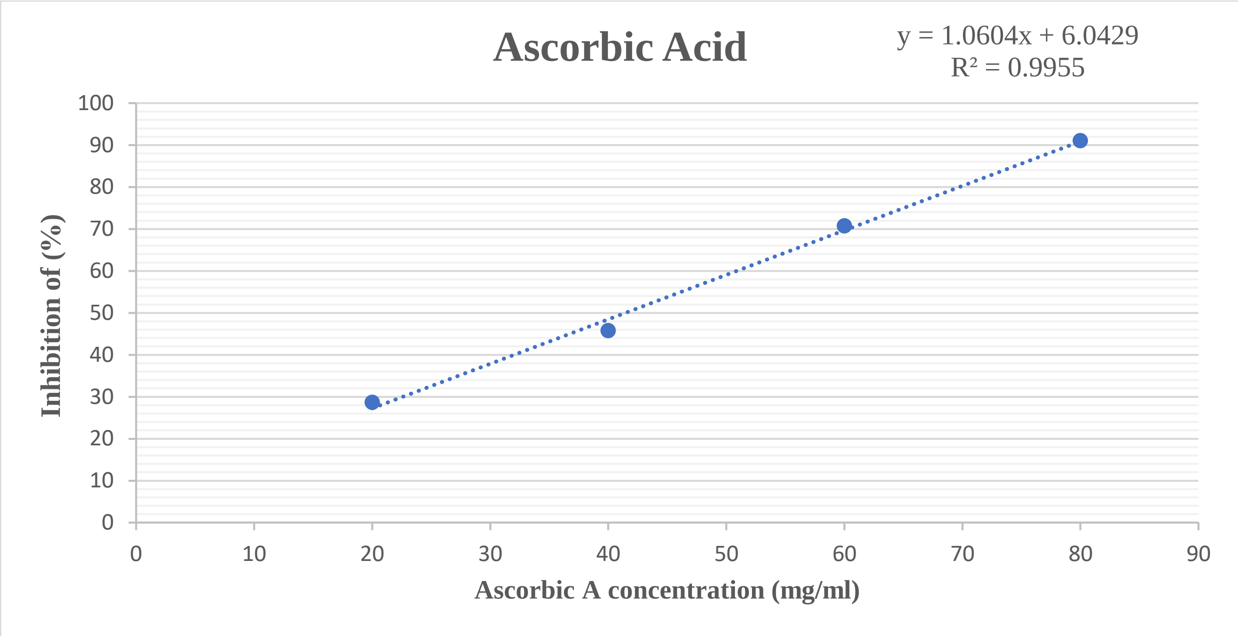

Figure 01: Percentage inhibition of the DPPH radical by ascorbic acid

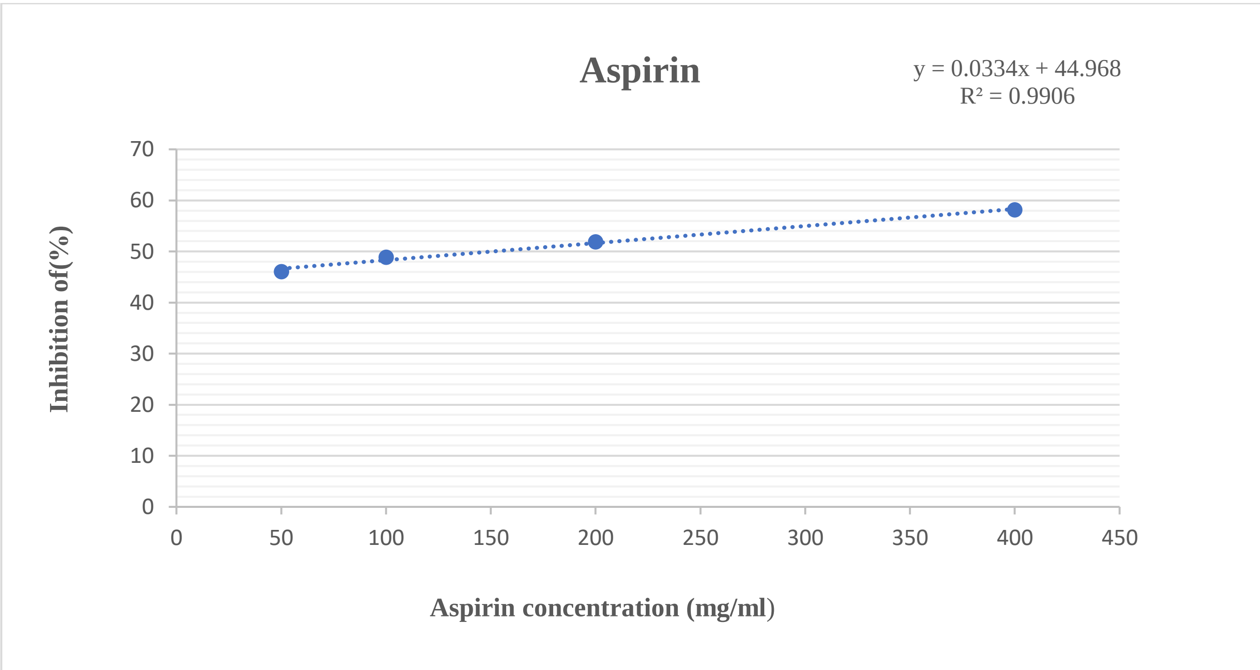

Figure 02: Percentage inhibition of albumin denaturation by Aspirin

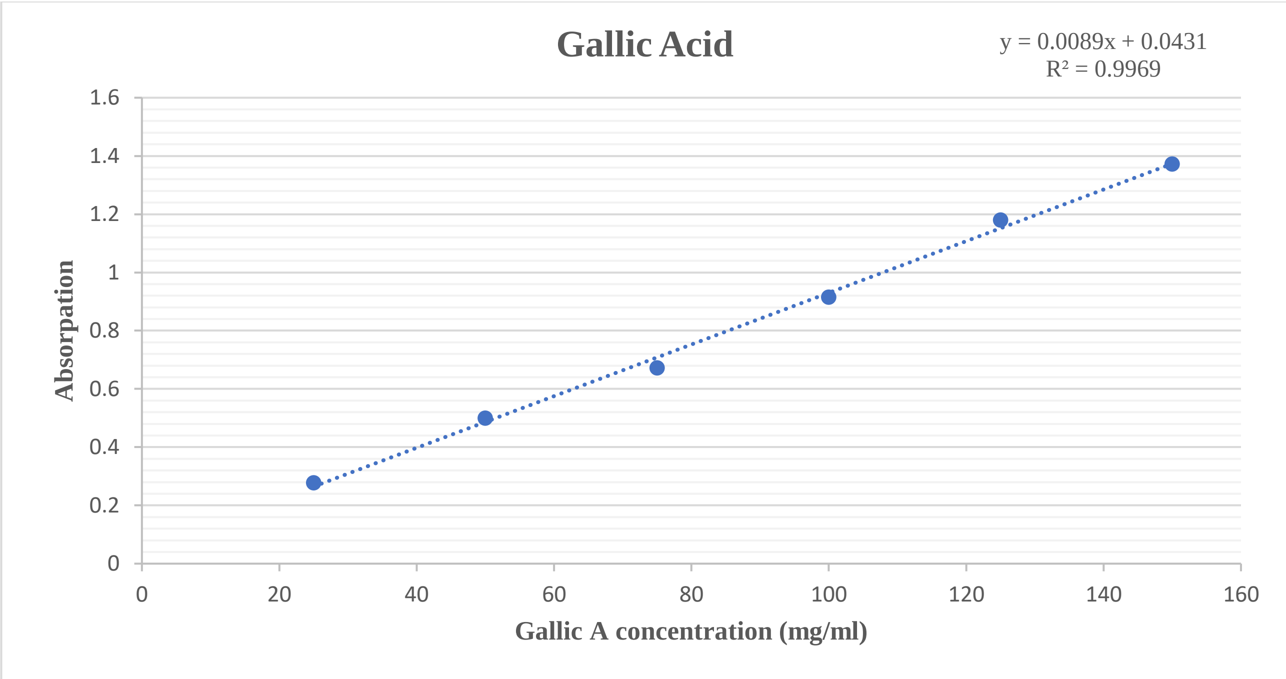

Figure 03. Calibration curve of gallic acid used for the determination of total polyphenol content in the plant extract.

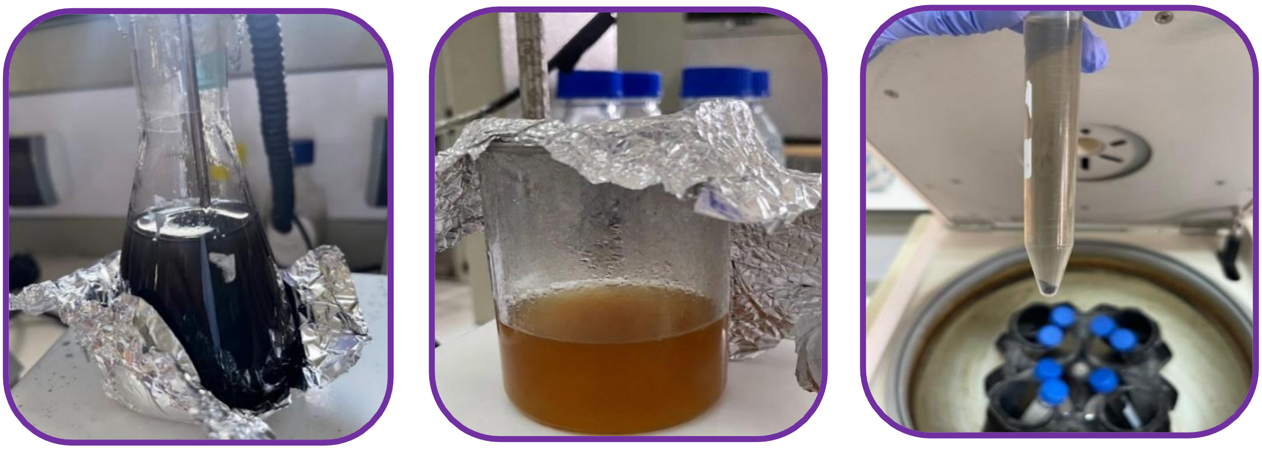

Figure 04: Experimental steps for the preparation of the Ch–Fe_2O_3/ZnO nanocomposite.

Figure 05. Blood Glucose Monitoring in Experimental Rats Using a Glucometer.

Figure 06. Wound induction and topical cream application in the experimental rats.

Figure 07. Sacrifice procedure and collection of blood and organ samples.

Figure 08. Histological tissue processing and slide preparation.

Figure 09. Preparation steps for the antibacterial activity assay.