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THEME

Multifunctional Prickly Pear (*Opuntia ficus-indica*) Leaf Extract Cream: A Natural Remedy for Burns, Anti-Inflammatory Action, and UV Protection.

Presented by:

Miss: BOUTRAA Douaa Tourkia

Miss: DOUDI Rania

Miss: LEGHDEMSI Djihane

Jury Members:

President: Dr.	**MCA**	**El-Oued University**
Examiner: Dr.	**MCA**	**El-Oued University**
Supervisor: Dr. LAIB Ibtissam	**MCB**	**El-Oued University**

University year: 2024/2025

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دعاء

Abstract

This study aimed to evaluate the therapeutic efficacy of *Opuntia ficus-indica* (prickly pear) leaf extract in accelerating burn wound healing, with a focus on its biological activities, including antioxidant, antibacterial, Photoprotective and anti-inflammatory properties. The leaves were collected from northern and eastern regions of Algeria, and active compounds were extracted using hot water extraction at 50°C for two hours, yielding 1.30 % of crude extract. Phytochemical analysis revealed a high content of total phenolic compounds (111.895 ± 1.39796 mg gallic acid equivalent/g) and flavonoids (9.44 ± 1.02 mg quercetin equivalent/g). Chemical screening confirmed the presence of saponins, cardiac glycosides, and alkaloids, while terpenoids, tannins, anthocyanins, and steroids were absent.

Regarding biological activities, the extract demonstrated strong antioxidant capacity (71.56 ± 3.46 mg ascorbic acid equivalent/g), moderate antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, and anti-inflammatory properties with an IC_{50} of 629.71 ± 0.080 µg/mL in albumin denaturation inhibition, comparable to the standard drug aspirin (IC_{50} = 646.11 ± 0.1646 µg/mL). Hemolytic activity results showed that the extract was safe for topical application, with a maximum hemolysis rate of 8.11% at 175 µg/mL, compared to 44.33% for SDS.

In vivo study, thirty rats were divided into six groups, receiving topical creams containing the extract at concentrations of 5%, 10%, and 20%. The 10% formulation achieved almost complete burns healing by day 21, significantly superior to the control groups. Histological analysis confirmed enhanced tissue regeneration and reduced inflammation.

These findings suggest that *Opuntia ficus-indica* leaf extract has promising therapeutic potential as a natural, safe, and effective alternative for burn wound treatment.

Keywords: *Opuntia ficus-indica*, Phytochemical analysis, Burn wound healing, Antioxidant activity, Anti-inflammatory, Antibacterial, analysis, Haematological marker, Histopathology analysis, Wistar rats.

Résumé

Cette étude visait à évaluer l'efficacité thérapeutique de l'extrait de feuilles d'*Opuntia ficus-indica* (figuier de Barbarie) dans l'accélération de la cicatrisation des plaies de brûlures, en se concentrant sur ses activités biologiques, notamment ses propriétés antioxydantes, antibactériennes et anti-inflammatoires. Les feuilles ont été collectées dans les régions nord et est de l'Algérie, et les composés actifs ont été extraits par extraction à l'eau chaude à 50°C pendant deux heures, avec un rendement de 1.30 % d'extrait brut.

L'analyse phytochimique a révélé une teneur élevée en composés phénoliques totaux (111,895 ± 1,39796 mg équivalent acide gallique/g) et en flavonoïdes (9,44 ± 1,02 mg équivalent quercétine/g). Le criblage chimique a confirmé la présence de saponines, de glycosides cardiaques et d'alcaloïdes, tandis que les terpènes, les tanins, les anthocyanines et les stéroïdes étaient absents.

En ce qui concerne les activités biologiques, l'extrait a démontré une capacité antioxydante élevée (71,56 ± 3,46 mg équivalent acide ascorbique/g), une activité antibactérienne modérée contre *Staphylococcus aureus* et *Escherichia coli*, et des propriétés anti-inflammatoires avec une IC50 de 629,71 ± 0,080 µg/mL pour l'inhibition de la dénaturation de l'albumine, comparable au médicament standard aspirine (IC50 = 646,11 ± 0,1646 µg/mL). Les résultats de l'activité hémolytique ont montré que l'extrait était sûr pour une application topique, avec un taux maximal d'hémolyse de 8,11 % à 175 µg/mL, comparé à 44,33 % pour le SDS.

Dans l'étude animale, trente rats ont été divisés en six groupes, recevant des crèmes topiques contenant l'extrait à des concentrations de 5%, 10% et 20%. La formulation à 10% a permis une cicatrisation quasi complète des brûlures dès le 21e jour, surpassant significativement les groupes témoins. L'analyse histologique a confirmé une régénération tissulaire améliorée et une réduction de l'inflammation.

Ces résultats suggèrent que l'extrait de feuilles d'*Opuntia ficus-indica* possède un potentiel thérapeutique prometteur, en tant qu'alternative naturelle, sûre et efficace pour le traitement des brûlures.

Mots-clés : *Opuntia ficus-indica*, Figuier de Barbarie, Cicatrisation des brûlures, Activité antioxydante, Anti-inflammatoire, Antibactérien, Analyse phytochimique, Marqueur hématologique, Analyse histopathologique, Modèle animal.

الملخص

هدفت هذه الدراسة إلى تقييم الفعالية العلاجية لمستخلص أوراق *Opuntia ficus-indica*(التين الشوكي) في تسريع التئام الجروح الناتجة عن الحروق، مع التركيز على نشاطه البيولوجي، بما في ذلك مضادات الأكسدة، المضادات الحيوية، والخصائص المضادة للالتهاب. جُمعت الأوراق من مناطق شمال وشرق الجزائر، وتم استخراج المركبات الفعالة باستخدام طريقة الاستخلاص بالماء الساخن عند درجة حرارة 50 درجة مئوية لمدة ساعتين، مع تحقيق عائد استخلاص قدره 1.30 %من المستخلص الخام. أظهر التحليل الكيميائي للمستخلص احتواءه على نسبة عالية من المركبات الفينولية الكلية (111.895 ± 1.39796 ملغ مكافئ حمض الغاليك/غرام) والفلافونويدات (9.44 ± 1.02 ملغ مكافئ كيرسيتين/غرام). وأكدت الفحوصات الكيميائية وجود السابونينات والجليكوزيدات القلبية والقلويدات، بينما غابت التيربينويدات، العفص، الأنثوسيانينات، والستيرولات.

فيما يتعلق بالنشاط البيولوجي، أظهر المستخلص قدرة عالية كمضاد للأكسدة، مع سعة مضادة للأكسدة بلغت 71.56 ± 3.46 مكافئ حمض الأسكوربيك/غرام، وفعالية معتدلة كمضاد للبكتيريا ضد *Staphylococcus aureus* و .*Escherichia coli*كما أظهر المستخلص تأثيرًا مضادًا للالتهاب، حيث بلغت قيمة IC50 لتثبيط تحلل الألبومين 629.71 ± 0.080 ميكروغرام/مل، مقارنةً بالدواء القياسي أسبيجيك 0.1646 ± 646.11 = IC50) ميكروغرام/مل .(وبيّنت نتائج السمية الخلوية أن المستخلص آمن للاستخدام الموضعي، مع نسبة تحلل كريات الدم الحمراء بلغت 8.11% عند أعلى تركيز (175 ميكروغرام/مل)، مقارنة بـ 44.33% لمادة SDS القياسية.

أما في الدراسة الحيوانية، فقد تم تقسيم ثلاثين جرذًا إلى ست مجموعات، حيث تلقت المجموعات كريمات موضعية تحتوي على المستخلص بنسب 5%، 10%، 20%. أظهرت النتائج أن التركيبة بنسبة 10% حققت تقريبًا شفاءً كاملًا للحروق بحلول اليوم 21من العلاج، وهو ما أكدته الفحوصات النسيجية التي أظهرت تجديدًا محسّنًا للأنسجة وتقليلًا واضحًا للالتهاب.

تشير هذه النتائج إلى أن مستخلص أوراق *Opuntia ficus-indica* يمتلك خصائص علاجية واعدة، مما يجعله بديلاً طبيعيًا فعالًا وآمنًا في علاج الجروح الناجمة عن الحروق.

الكلمات المفتاحية: الصبار الشائك، التئام جروح الحروق، النشاط المضاد للأكسدة، مضاد للالتهابات، مضاد للبكتيريا، التحليل الكيميائي النباتي، تحليل الأنسجة المرضية , العلامة الدموية , نموذج الفئران.

List of abbreviations

Abs: Absorbance

DMSO: dimethyl sulfoxyl

PP: Prickly Pear

OFI: Opuntia ficus-indica

TSS: Total Soluble Solids

FAO: Food and Agriculture Organization

DPPH: 2,2-diphenyl-1-picrylhydrazyl

EC50: Median effective concentration

EDTA: Ethylenediaminetetraacetic acid

FRAP: Ferric reducing antioxidant power

HPLC: High-performance liquid chromatography

IC_{50}: Inhibitory concentration 50

NB: N-butanol

PBS: Phosphate-buffered saline

P.aeruginosa: Pseudomonas aeruginosa

S.aureus: *Staphylococcus aureus*

B.subtilis: Bacillus subtilis

K.pneumoniae: Klebsiella pneumoniae

E.coli : *Escherichia coli*

SDS: Sodium dodecyl sulfate

SPF: Sun protection factor

TAC: Total Antioxidant Capacity

UV-VIS: Ultraviolet Visible

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Summary

Introduction

Introduction

For millennia, humans have relied on nature's pharmacopoeia to treat a wide range of diseases and injuries. Medicinal plants have consistently formed the backbone of traditional medicine systems across diverse cultures. Even in the modern era of synthetic pharmaceuticals, medicinal herbs continue to play a crucial role in drug discovery and therapeutic research *(Turarug, 2023).* According to the World Health Organization (WHO), over 21,000 plant species hold potential for medicinal use *(Bouopda Tamo & Mundene-Timothee, 2023).* These plants often harbor bioactive compounds with a broad spectrum of pharmacological activities, including antimicrobial, anticancer, antidiabetic, antihypertensive, antifungal, and hepatoprotective properties *(Uttpal et al., 2022).* Traditional uses, such as employing Capparis sepiaria bark for stomachaches, Saxifraga jacquemontiana leaves for wound healing, or Chromolaena odorata leaf decoctions for Escherichia coli-induced diarrhea, exemplify the empirical basis for their continued scientific validation (Mahwasane et al., 2013).

Among the botanical treasures, few are as pharmacologically versatile as the prickly pear (Opuntia ficus-indica, OFI), a cactus species celebrated in both traditional medicine and modern research. Its name originates from the Greek city of Opus and the term "kaktos," meaning thorny plant *(Schweizer, 1997; DeFelice, 2004).* Belonging to the Cactaceae family—comprising over 1,500 species across 130 genera *(Griffith, 2004; Pareek et al., 2003) Opuntia ficus-indica* thrives in arid and semi-arid regions including Mexico, South Africa, and Mediterranean countries (Butera et al., 2002). The plant is nutritionally rich, containing high levels of vitamin C, potassium, calcium, magnesium, and a wide array of phenolic and flavonoid compounds *(Barba et al., 2020; Aruwa et al., 2019; Bakar et al., 2020).* These phytochemicals are known for their potent antioxidant, anti-inflammatory, hypolipidemic, hypoglycemic, and even anti-cancer activities *(Medina et al., 2007; Silva et al., 2021; Çakmak et al., 2020; Baba et al., 2020; Aksay et al., 2010).*

Recent studies have extended the therapeutic potential of O. ficus-indica. For example, *(El-Hawary et al.,2020)* demonstrated neuroprotective effects of its extract in a rat model of aluminum-induced neurotoxicity. *(Ali et al .,2022)* reported strong antimicrobial and anticancer activities from its peel extract. *(Zeghbib et al.,2024)* identified 18 phenolic compounds in *O. ficus-indica* and O. stricta fruits, linking them to robust antioxidant and anti-inflammatory effects. Additionally, *(Berraaouan et al.,2015)* found that its seed oil helped regulate blood glucose levels and protected pancreatic β-cells in diabetic mice. More recently, *(Nascimento et al. 2025)* showed that a betanin-rich extract from O. ficus-indica inhibited over 75% of tumor

cell growth in vitro and suppressed tumor progression in vivo, without affecting normal hematological parameters.

Despite its extensive pharmacological profile, the therapeutic potential of *Opuntia ficus-indica* leaf extract, particularly in the context of burn injuries, remains largely unexplored. Considering that oxidative stress and inflammation are key contributors to the pathophysiology of burns, the high flavonoid, tannin, and polyphenol content of the leaves positions them as a promising natural remedy for promoting wound healing and preventing tissue damage.

This study aimed to develop and characterize a topical cream formulated from *Opuntia ficus-indica* leaf extract and to evaluate its biological activities through both in vitro and in vivo approaches. Specifically, the objectives were:

The present thesis aims to explore the therapeutic potential of *Opuntia ficus-indica* leaves through a comprehensive scientific investigation. The study begins with the extraction and characterization of the plant's phytochemical constituents, followed by an in-depth evaluation of its biological properties through a series of **in vitro** assays. These include assessments of antioxidant, anti-inflammatory, hemolytic, and antibacterial activities. Subsequently, the research extends to **in vivo** experimentation, where a cream formulated with the plant extract is tested on rats with burn-induced skin injuries. The therapeutic efficacy of the formulation is evaluated based on hematological parameters and histopathological analysis, providing insights into both local and systemic responses to treatment.

The thesis is divided into two main sections. The **first part**, constituting the theoretical framework, includes a critical review of the literature. Chapter one outlines the botanical, chemical, and pharmacological features of *Opuntia ficus-indica*, while chapter two delves into its documented biological activities and therapeutic applications. The **second part**, dedicated to the experimental work, is structured into two components: the first detailing the methodologies and findings of the *in vitro* studies, and the second presenting the results of the *in vivo* investigations, thereby offering a holistic assessment of the plant's potential in burn wound management.

PART I Bibliographic

CHAPTER I
Opuntia ficus-indica

Introduction

1. Generality:

Prickly pear is a succulent cactus plant of the Opuntia genus and is primarily cultivated for fruit production. It thrives in hot temperatures and full sun, for instance, in the Mediterranean and Central America.

The semi-arid regions of Mexico have the most diversity of cacti on earth. The genus *Opuntia* comprises some 300 species, many of which have edible, succulent stems and fruits. In fact, prickly pear is also farmed for the production of nopals or nopalitos (young cladodes consumed as vegetables in Mexico) or, less commonly, for the breeding of the cochineal insect (Dactylopius coccus), employed to produce a red pigment, primarily in the Canary Islands.

Globally, *Opuntia* species are cultivated in various regions, covering approximately 100,000 hectares, mainly in South America, the Mediterranean area, the Middle East, and India.

The yield of prickly pear cladodes *(Opuntia ficus-indica)* ranges from 30 to 80 tons per hectare annually, based on geographical location, climate, and crop variety *(Stintzing et al., 2005).*

It is also cultivated in Tunisia, mainly in the Kasserine area, particularly in Tala, and is widely enjoyed during the summer months. With irrigation, the production can range from 250 to 300 quintals of fruit per hectare *(Dubeux et al., 2006).*

2. Botanical description :

Cacti belong to the botanical family Cactaceae, which comprises some 1,600 species distributed across 130 genera. The genera are further grouped into three subfamilies: Pereskioideae, Opuntioideae, and Cactoideae. Among the order Caryophyllales, the most widespread genus is Opuntia, with more than 300 species, for example, *Opuntia ficus-indica (L.) Mill. (O. ficus-indica).* The plant was named thus in 1700 by French botanist Joseph Pitton de Tournefort due to the fact that its morphology was like that of Opuntia species that occur in thorny plants in the city of Opus in ancient Greece. *O. ficus-indica* regional common names are prickly pear, agave, devil's fig tree, and tabaio or tabaibo in the Madeira Archipelago.

Due to rigorous domestication, *O. ficus-indica* has significant genetic variation, with ensuing complex taxonomy. Its environmental conditions significantly determine its phenotypic traits, which enhance its variability in adaptation responses. The plant is polyploid

and also reproduces through sexual and asexual modes, with interspecific hybrids existing in a variety of forms. All these complicate taxonomy and necessitate intensive research to tax the species, varieties, and adaptation traits expressed through their morphological traits.

Morphological and Structural Adaptations

Cacti are dicotyledonous angiosperms that possess a perennial growth habit. They are typically shrub or tree-like in appearance with succulent stems, photosynthetic tissues, and lacking or small leaves. Flowers are large, hermaphrodite, and typically red, according to *(Schweizer ,1997).*

Opuntia ficus-indica is a sturdy, tree-like cactus measuring 3 to 5 meters in height. It has a woody, fleshy trunk and produces flat, ovate to elliptical cladodes (pads or bats) 30–50 cm long, 15–30 cm wide, and 1.5–3 cm thick. These cladodes are modified branches that are capable of photosynthesis and are covered with a waxy cuticle that suppresses transpiration and offers protection against herbivores *(Wallace & Gileson, 2002).*

Cacti possess areoles, which are modified structures 2 mm beneath the epidermal surface. Under favorable environmental conditions, these areoles give rise to new cladodes, flowers, or roots from their meristematic tissue. In O. ficus-indica, the areoles are spirally arranged on the cladodes and give rise to spines instead of conventional leaves *(Powell & Weedin, 2004).* These spines are one of the primary taxonomic features, as their morphology varies between species. Two forms of spines are distinguished:

- Glochids – Small, barbed, and easily shed spines.
- Primary spines – Stiffer and more persistent structures.

Both forms of spines are morphological homologs of leaves, which have evolved from modified leaf primordia, as stated by the Food and Agriculture Organization *(FAO, 2018).*

O. ficus-indica flowers arise from areolar meristems, most often at the tip of the cladodes. They are 4–10 cm in diameter and range from yellow and orange to red in color *(Boutakiout, 2017).* Fruits are fleshy berries, typically oval-shaped, with yellow-green rind bearing tiny spines.

- Root System and Adaptations to Drought

The root system of *O. ficus-indica* is shallow and highly specialized, with the majority of the roots concentrated in the upper 30 cm of the soil *(Mulas & Mulas, 2004).* The roots of O. ficus-indica are heteromorphic in nature, unlike the majority of other plants, which enables

them to live for extended periods under very dry conditions. The heteromorphic features include:

Reduction of root surface area to minimize water permeability and lower water loss.

Abrupt development of rain-induced roots ("rain roots"), which emerge within hours of rain, for efficient water absorption prior to drying up when the soil dries out.

Negative root potential regulation of transpiration, which reduces transpiration loss via the cladodes.

These physiological features are responsible for the plant's high drought tolerance, allowing *O. ficus-indica* to live in arid and semi-arid environments.

2.1. Morphology of Prickly Pear Cladodes :

In botanical literature, the term "prickly pear leaves" is often used to describe the flattened stem segments of the plant that functionally replace true leaves. However, the accurate terminology for these structures includes "cactus stems," "cactus pads," or "cladodes," which are collectively referred to as "nopales." Structurally, the cladodes consist of an inner white parenchyma (ground tissue) and an outer chlorophyll-containing chlorenchyma (cortical tissue) .The surface of the chlorenchyma is equipped with spines, which are modified leaves, as well as multicellular trichomes, both of which originate from specialized structures known as areoles, a defining characteristic of the Cactaceae family *(Anderson, 2001).*

Glochids, which are small, barbed bristles emerging from the areoles, are composed entirely of crystalline cellulose (*Waldron et al., 1996).* The cellulose microfibrils measure approximately 0.4 mm in length and 6–10 μm in diameter and are embedded in a matrix primarily composed of arabinose. This arabinose matrix exists in a gel-like solid state, intricately interwoven with cellulose fibers. The spines, which contribute to the plant’s defensive and adaptive strategies, are composed of 96% polysaccharides, with their composition further divided into 49.7% cellulose and 50.3% arabinose, along with minor components including ash, lipids, waxes, and lignin *(Malainine et al., 2003).* The spines typically range from 1 to 3 cm in length and account for approximately 8.4% of the total cladode mass. Their primary functions include mechanical deterrence against herbivory, light reflection, shading of the stem to minimize water loss, and enhancement of fog condensation, which contributes to the plant’s water acquisition strategy *(Anderson, 2001; Maritime, 2010).*(Figure 1-2)

2.2. Distribution of mucilage

The mucilage is a hetero-polysaccharide of high molecular weight produced in specialized cells in plants. According to different studies, the main composition of this polysaccharide consists of six neutral sugars: arabinose, galactose, rhamnose, xylose, uronic acid, and gal- acturonic acid *(Trachtenberg & Mayer, 1982).* The mucilage is an interesting compound of these kinds of plants. It has remarkable prop- erties such as a high capacity for water holding, ion binding, and its gel- formation ability that contributes to considering mucilage as a func- tional additive that can be used in several industries *(McGarvie, & Parolis, 1979; Saenz, Sepulveda & Matsuhiro, 2004).* The nopal mucilage has some applications in the food industry. These macromol- ecules are used as an edible coating in fruits *(Del-Valle, Hernandez- Mun˜oz, Guarda, & Galotto, 2005);* as a stabilizer of emulsions and foam *(Garti & Leser, 2001)*; to control the crystallization; as a suspension stabilizer; to inhibit the syneresis, and to form gels *(Dziezak, 1991). (Missaoui et al., 2020)*

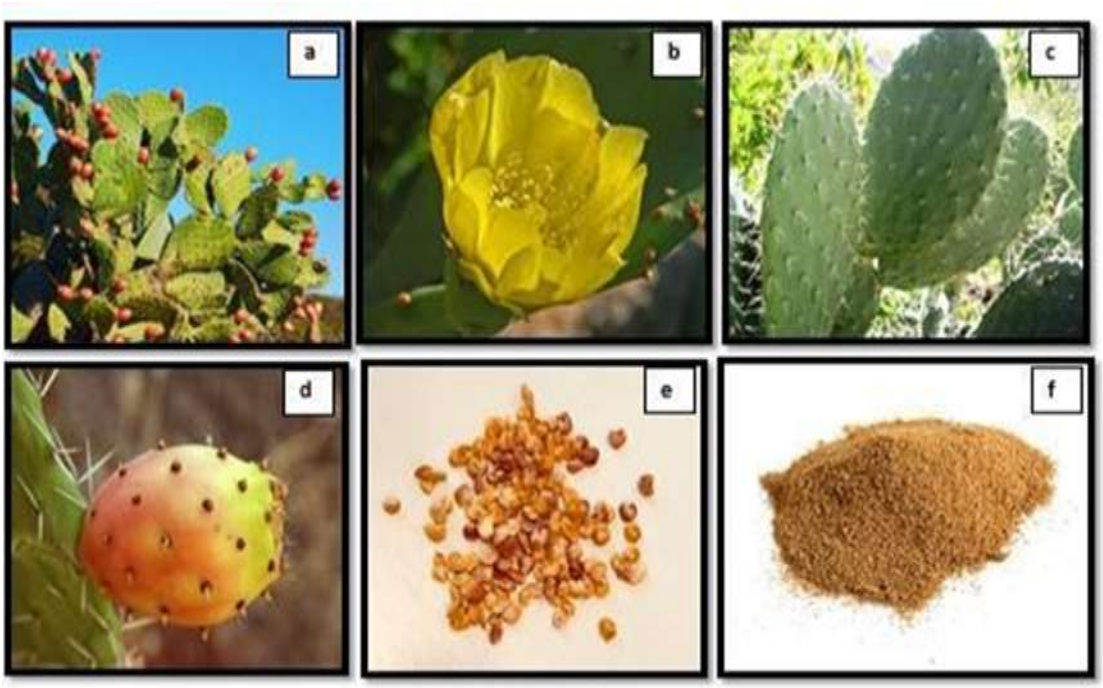

Figure 01: Botanical description of the prickly pear ((a) The prickly pear: b) flower, c) cladode, d) fruits, e) seeds, f) seed powder) (Aknouche, 2018).

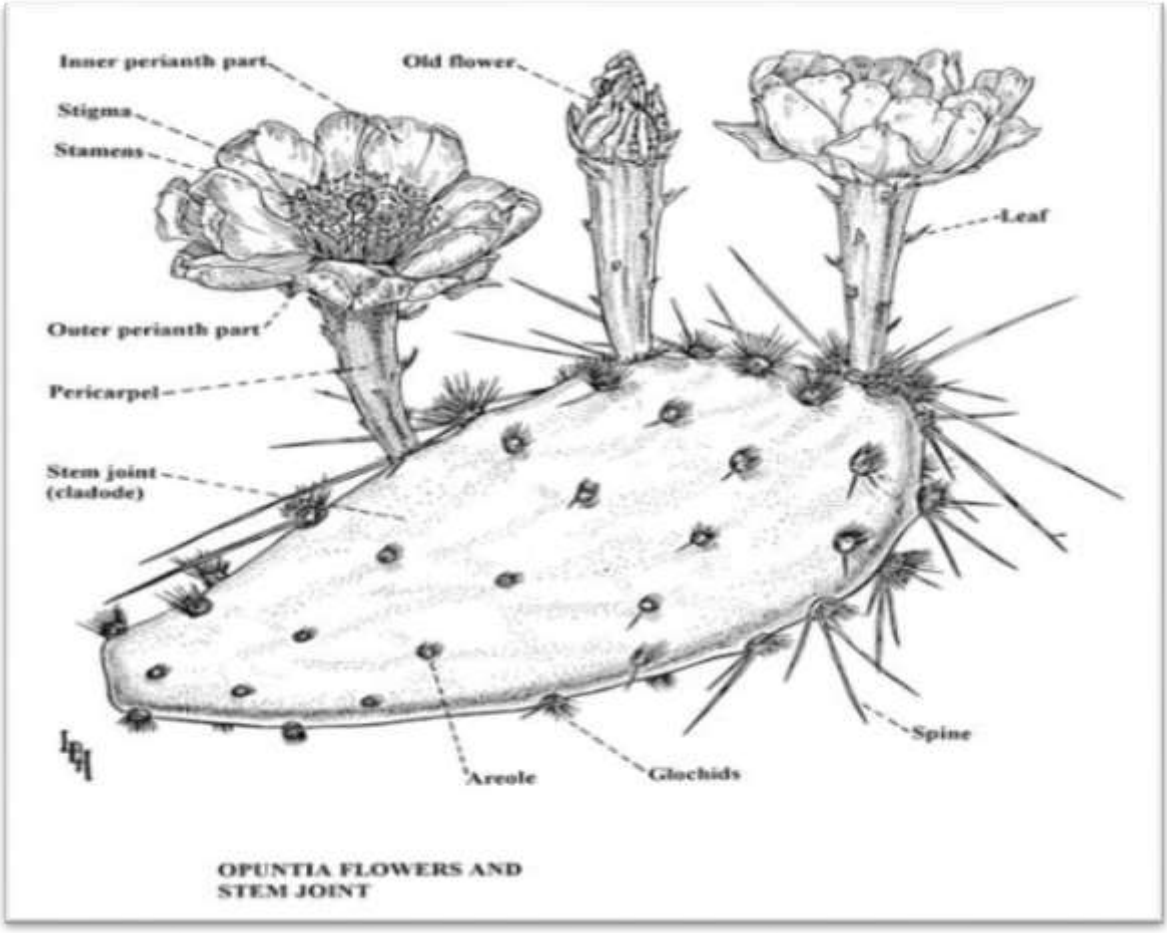

Figure 02: Diagram illustrating the different parts of the prickly pear.

3. Taxonomy and Classification of *Opuntia ficus-indica*

The genus *Opuntia* belongs to the family *Cactaceae*, order *Caryophyllales*, and is classified under the subgenus *Platyopuntia*. The most widely accepted taxonomic system is that proposed by *(Britton and Rose .1963),* which classifies *Opuntia ficus-indica* as follows:

- **Kingdom**: Plantae
- **Order**: Caryophyllales
- **Subclass**: Caryophyllidae
- **Family**: Cactaceae
- **Tribe**: Opuntieae
- **Genus**: *Opuntia*
- **Subgenus**: *Platyopuntia*
- **Species**: *Opuntia ficus-indica*

Opuntia ficus-indica is one of the most economically significant cacti due to its edible fruits and cladodes (also called pads or "rackets"), which are used as food, fodder, or vegetables *(Mulas et al., 2004).*

The *Cactaceae* family is taxonomically diverse and has been subdivided into eight major groups based on morphological and genetic characteristics: the *Pereskia*, *Opuntia*, *Cereus*, *Echinopsis*, *Hylocereus*, *Neoporteria*, *Melocactus*, and *Echinocactus* groups *(Lamb, 1991).*

4. Cultivation System

The *Cactaceae* family is a diverse botanical group comprising approximately 1,600 species distributed across 130 genera, divided into three subfamilies: *Pereskioideae*, *Opuntioideae*, and *Cactoideae*. Among these, the genus *Opuntia* is the most widely distributed, including over 300 species, notably *Opuntia ficus-indica* (L.) Mill., commonly known as prickly pear. First named in the 18th century by Joseph Pitton de Tournefort, *O. ficus-indica* exhibits significant genetic and phenotypic diversity influenced by environmental conditions, polyploidy, and both sexual and asexual reproduction, contributing to ongoing taxonomic challenges and highlighting the need for further morphological and genetic studies (*Ingeles et al., 2017; Sáenz et al., 2013; Ferreira et al., 2016; Alves et al., 2008; Potgieter & D'Aquino, 2017; Louhaichi et al., 2019; Khalafalla et al., 2007; Codex Alimentarius Commission, 2013*).

- **Structural and Physiological Adaptations**

O. ficus-indica is a perennial, woody cactus that grows between 3 and 5 meters in height, featuring flattened, fleshy cladodes (30–50 cm long, 15–30 cm wide) that function as photosynthetic organs and are covered with a protective waxy cuticle. The plant's areoles, which are modified meristematic structures, produce flowers, roots, or spines. Two types of spines are present: *glochids* (small and barbed) and primary spines (rigid and persistent), both of which are modified leaf structures.

The flowers, ranging in diameter from 4 to 10 cm, emerge from the terminal areoles of the cladodes and vary in color from yellow to red, while the fruit is a fleshy berry with a spiny rind that varies in shape and color (*Ingeles et al., 2017; Sáenz et al., 2013; Ferreira et al., 2016; Alves et al., 2008*).

- **Root System and Drought Tolerance**

The root system of *O. ficus-indica* is shallow, with most roots concentrated within the top 30 cm of soil. It exhibits heteromorphic adaptations that enhance drought resistance, including a reduced root surface area to minimize water loss, the rapid emergence of "rain roots" for quick water uptake, and a unique root signaling mechanism that downregulates transpiration. These characteristics enable the plant to survive in arid and semi-arid climates with limited water availability (*Potgieter & D'Aquino, 2017; Louhaichi et al., 2019; Khalafalla et al., 2007; Codex Alimentarius Commission, 2013*).

5. Origin and geographical diffusion:

Prickly pears originated in Mexico and were propagated across the globe, thriving in arid conditions *(Griffith, 2004).* Aside from Mexico being the world's top producer and consumer of prickly pear, it is also documented that Christopher Columbus, with his discovery of the New World, introduced the fruit to Spain, which then spread to other Mediterranean countries *(Fernández-López et al., 2002; Messina et al., 2021).* Sicily and Calabria, for instance, are home to the majority of the *Opuntia ficus-indica* plant in Italy *(Maniaci et al., 2024).* More than thirty countries, including those in Africa, Asia, and southern Europe, now cultivate the plant.

Historical records show that the Spanish introduced the cactus pear to North Africa in the 16th century *(Diguet, 1928).* Land devoted to this species is currently in perpetual expansion in Algeria, Morocco, and Tunisia, with the overall surface area exceeding 30,000, 120,000, and 600,000 hectares, respectively *(Inglese et al., 2017).*

In northern Algeria, the entire plant is used to fence in towns and homes, and the fruits produced by the same plants used for fencing are meant for human consumption. In contrast, in the south, cladodes are used to feed small animals *(Griffith, 2004).* (Figure 03)

Figure 03: Global distribution of *Opuntia ficus-indica* (Bennatia F, 2017)

6. Local name of prickly pear

In North Africa, particularly in Algeria, Morocco, and Tunisia, the coexistence of both Arab and Berber cultures has contributed to a rich linguistic diversity, reflected in the varied local names assigned to *Opuntia ficus-indica*. In Algeria, the species is commonly referred to as "El Hendi" *(Sarri et al., 2015).* In Morocco, multiple vernacular names have been documented, including Sabbar, Handiya, and Karmouss n'sara *(Ouhaddou et al., 2014),* as well as Nawwar and Al'Handiyya *(Merzouki et al., 2000).* This linguistic variation underscores the cultural significance and widespread recognition of *O. ficus-indica* across the Maghreb region.

7. Bioactive compound

Opuntia ficus-indica is recognized as a rich source of bioactive and nutritional phytochemicals, including ascorbic acid, flavonoids, carotenoids, betacyanins, and betaxanthins *(Osorio-Esquivel et al., 2011; Paiz et al., 2010; Schaffer et al., 2005; Stintzing et al., 2003).* Seeds and cactus peel are notably used for producing cactus oil, which is rich in essential fatty acids and liposoluble antioxidants *(Ramadan & Mörsel, 2003).* Vitamins, antioxidants, and various flavonoids are abundant in the cladodes *(Lee et al., 2002; Stintzing & Carle, 2005),* while the fruits and skin exhibit higher concentrations of betacyanins and betaxanthins *(Stintzing et al., 2002; Impillizzeri & Piattelli, 1972).*

7.1.Polyphenols:

Polyphenols in *Opuntia ficus-indica* are primarily composed of flavonoids and phenolic acids. These compounds are well-known for their antioxidant activities *(Cartea et al., 2011).* Flavonoids protect against oxidative damage by directly scavenging free radicals *(Jakobek, 2015),* inhibiting xanthine oxidase and cytochrome activities *(Chang et al., 1993; Iio et al., 1986),* and chelating iron to prevent lipid peroxidation *(Ferrali et al., 1997).* Additionally, they demonstrate anti-inflammatory and anti-thrombogenic effects through the inhibition of arachidonic acid metabolism *(Ferrandiz & Alcaraz, 1991).*

7.2.Carotenoids:

Carotenoids in *O. ficus-indica* include lutein, β-carotene, and α-cryptoxanthin *(Eldahshan & Singab, 2013).* These compounds are efficient quenchers of singlet oxygen and peroxyl radicals (Goodwin, 1980). Notably, the carotenoid content in fruits varies by color, with orange cultivars showing the highest concentrations *(Jaramillo-Flores et al., 2003).*

7.3.Betalains:

Betalains, comprising betacyanins and betaxanthins, are responsible for the vivid pigmentation of Opuntia fruits. Their antioxidant properties are attributed to their phenolic hydroxyl groups and a stable electronic resonance system *(Minale & Piattelli, 1965; Piattelli & Minale, 1964; Yeddes et al., 2013).* Betanin and indicaxanthin, two primary pigments in *O. ficus-indica*, have been demonstrated to effectively scavenge free radicals, with betanin showing the strongest antioxidant activity *(Taira et al., 2015).* Moreover, their synergistic interactions with other antioxidants like α-tocopherol enhance their protective effects *(Tesoriere et al., 2009; Tesoriere et al., 2007).*

8. Traditional and Medicinal Uses of Cactus Pear *(Opuntia ficus-indica) :*

Cactus pear *(Opuntia ficus-indica)* has been widely used in traditional medicine across various cultures for the treatment of burns, wounds, edema, and indigestion. Studies have demonstrated that its alcoholic extracts exhibit anti-inflammatory, hypoglycemic, and antibacterial properties. Additionally, the stem (cladodes) of Opuntia ficus-indica has been traditionally utilized for managing diabetes *(Saenz, 2000).*

In Mexican traditional medicine, nopal cladodes are empirically used to lower serum cholesterol levels, regulate blood pressure, and control gastric acidity. They are also employed in the treatment of various ailments, including ulcers, fatigue, dyspnea, glaucoma, capillary fragility, liver conditions, rheumatic pain, and wounds *(Muñoz de Chávez et al., 1995; Domínguez-López, 1995).* More recent research supports potential applications in treating gastritis, hyperglycemia, arteriosclerosis, diabetes, and prostatic hypertrophy *(Hegwood, 1990; Frati et al., 1990; Palevitch et al., 1993).*

Chapter II
Biological Activities of Prickly Pear
(Opuntia ficus-indica)

1. Anti-inflammatory activity :

Opuntia ficus-indica, commonly known as prickly pear, has garnered significant attention for its potential anti-inflammatory properties, which have been extensively studied through various extracts, including those from its fruit, lyophilized cladodes, and stem. Numerous studies have demonstrated the anti-inflammatory and analgesic activities of *Opuntia*, thanks to its rich content of bioactive compounds such as betalains, flavonoids, polyphenols, and phytosterols, notably β-sitosterol, found in both the fruit and stem extracts *(Allegra et al., 2014; Kemi et al., 2006; Panico et al., 2007; Tesoriere et al., 2014).* These compounds are known to play crucial roles in modulating inflammatory pathways.

One of the primary mechanisms through which *Opuntia* exerts its anti-inflammatory effects is by inhibiting the release of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) *(Lee et al., 2002).* The suppression of these cytokines is crucial, as they are involved in the initiation and perpetuation of the inflammatory process in various chronic diseases.

In an animal model, *(Park et al.,2001)* observed that prickly pear extract effectively reduced inflammatory markers and inhibited the activation of nuclear factor-kappa B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory genes. Furthermore, *Opuntia*'s ability to suppress cyclooxygenase-2 (COX-2) expression—an enzyme responsible for the production of inflammatory mediators—further corroborates its role as a natural anti-inflammatory agent *(Kim et al., 2013).*

Opuntia ficus-indica's anti-inflammatory properties have been linked to its potential benefits in treating various inflammatory conditions. For instance, it has been shown to alleviate symptoms associated with arthritis, a common inflammatory joint disorder, and gastrointestinal disturbances such as gastritis and irritable bowel syndrome *(Zou et al., 2005).* Its ability to reduce inflammation in these contexts positions *Opuntia* as a promising therapeutic agent for conditions characterized by chronic inflammation.

Additionally, β-sitosterol, a phytosterol found in the cactus stem, is recognized for its own anti-inflammatory properties. While its effects have been demonstrated in several studies *(Allegra et al., 2014),* it is worth noting that the anti-inflammatory activity of β-sitosterol from the lyophilized aqueous extract of the fruit of *Opuntia ficus-indica* is being reported for the first time, adding a novel dimension to the plant's therapeutic potential.

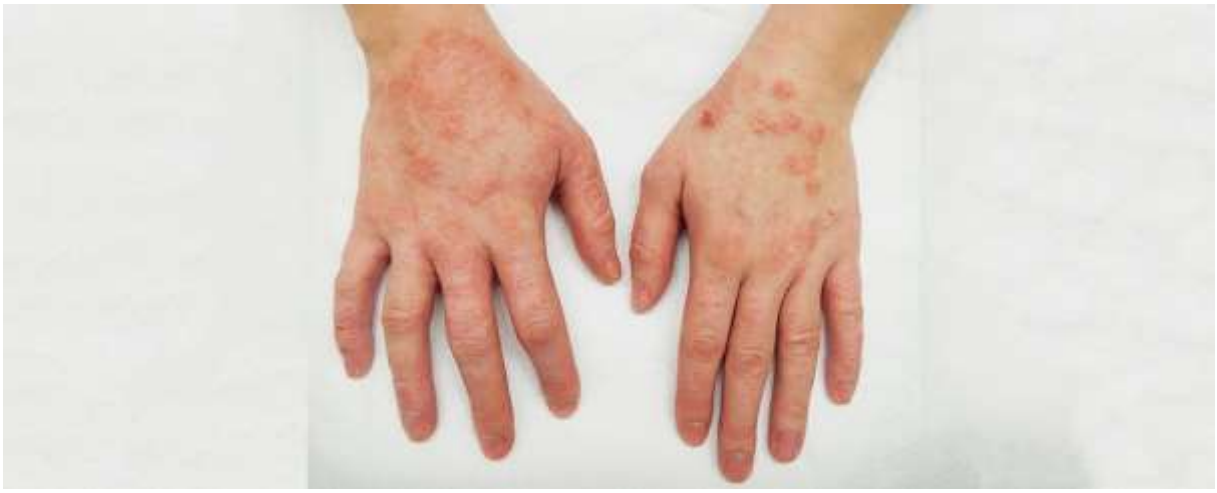

Figure 04: Skin infections*(Basirclinc .2019)*

2. Antioxidant activity :

Opuntia ficus indica, commonly known as prickly pear, has been extensively studied for its potent antioxidant properties, which are primarily attributed to its rich composition of polyphenols, flavonoids, betalains, vitamin C, and carotenoids. These bioactive compounds work synergistically to combat oxidative stress, protect against cellular damage, and maintain overall health.

2.1.Mechanism of Antioxidant Action

Research on the ethanol extract of Opuntia ficus indica stem has demonstrated its ability to inhibit oxidative processes in vitro. One notable study revealed a concentration-dependent inhibition of linoleic acid oxidation using the thiocyanate assay system, highlighting the extract's capacity to neutralize oxidative damage *(Butera et al., 2002).* Additionally, the ethanol extract exhibited dose-dependent free radical scavenging activity, which was shown to protect plasmid DNA from strand breakage induced by hydroxyl radicals—further emphasizing its ability to mitigate oxidative stress at the molecular level.

These effects are largely due to the presence of phenolic compounds in the extract, which are known for their potent antioxidant activity. These compounds act as free radical scavengers, reducing oxidative stress and preventing cellular damage. The ability to neutralize harmful radicals, such as superoxide anions and hydroxyl radicals, underpins the antioxidant potential of prickly pear.

Enhanced Antioxidant Potential Through Nutrients

In addition to phenolic compounds, prickly pear is rich in vitamin C and carotenoids, both of which further enhance its antioxidant activity. Vitamin C is a well-known antioxidant that not only scavenges free radicals but also regenerates other antioxidants, supporting the body's natural defense systems. Carotenoids, including beta-carotene, contribute to the neutralization of free radicals, thereby reducing oxidative stress. Collectively, these compounds contribute to the fruit's ability to protect cells from damage and support overall cellular homeostasis.

2.2.Supporting Evidence from In Vitro and In Vivo Studies

In vitro studies have shown that prickly pear extracts exhibit significant free radical scavenging activity. For instance, Butera et al. (2002) demonstrated strong radical scavenging effects, particularly against superoxide anions and hydroxyl radicals, which are some of the most harmful reactive oxygen species (ROS) that contribute to oxidative damage.

In vivo studies also support the antioxidant benefits of prickly pear. (Galati et al.,2003) observed that prickly pear juice significantly increased the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), which are critical in protecting cells from oxidative damage. These enzymes play a pivotal role in detoxifying harmful ROS and reducing lipid peroxidation, thereby preventing cellular damage.

2.3.Health Benefits and Therapeutic Potential

The antioxidant properties of prickly pear have extended beyond basic cellular protection, showing promise in the management of metabolic disorders. For example, in diabetic patients, prickly pear consumption has been linked to reduced oxidative damage, making it a potential adjunctive therapy in managing oxidative stress-related diseases such as diabetes *(Sanchez-Machado et al., 2006).* The increase in antioxidant enzyme activity further supports its therapeutic potential, offering a natural means to combat oxidative stress and prevent the development of chronic conditions associated with oxidative damage.

2.4.Sun protection factor (SPF)

Different photoprotection factors (PPFs) of the 200 µl°C extract of PPSP were analyzed by an accredited Malaga, Spain laboratory(IBYDA, Málaga University). Sun protection factor (SPF) was determined against the erythematic action spectrum; UV-A radiation

protection factor (UVAPF) according to ISO 24442:2022 was determined against the action spectrum of pigmentation Persistent Pigment Darkening -PPD and protection factors against other biological effects related to UV radiation (BEPFs- Biological Effective Protection Factors), were performed relative to the following action spectra:

photocarcinogenesis (UV-B associated), immunosuppression (UV-B associated), elastosis (UV-A associated), photoaging (UV-A associated) and singlet oxygen formation (associated UV-A) according to (Coba et al., 2019).

The critical k value (kkc), wavelength at which 90 % of the incident radiation is absorbed, and the SPF were calculated based on the ISO:24442, 2022. For BEPFs, PMMA plates (Polymethylmethacrylate; 25 25 mm; roughness 6 lm; Schönberg, Hamburg, Germany), whose roughness mimics human skin were employed to spread the body lotion. The spread cream at a concentration of 1.3 mg cm-2 (=32.5 mg plate-1) was incubated in the PMMA for 15 min in the dark at room temperature and measure the transmittance across the plate in a spectrophotometer (UV-2600, Shimadzu, Duisburg, Germany) with integrating sphere (ISR 2600 Plus, Shimadzu, Duisburg, Germany). 2 plates per sample and two readings of each plate were made (Yéssica .A et al.,2023). (Figure 5).

Figurr05: Skin pigmentation due to sun rays*(Healthshots.2021)*

3. Antibacterial activity:

Recent scientific research has confirmed the notable antibacterial potential of *Opuntia ficus-indica* (prickly pear), underscoring its value as a natural source of antimicrobial agents. Extracts obtained from various parts of the plant including cladodes and fruit peels using solvents such as ethanol, methanol, chloroform, and ethyl acetate, have demonstrated considerable antibacterial activity against both Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhimurium*, *Bacillus subtilis*, and *Pseudomonas fluorescens (El-Rahman et al., 2013; Ramadan & Mörsel, 2007).*

Moreover, ethanol, methanol, and chloroform extracts from the cladodes and fruit skins have shown strong antibacterial effects *(El-Rahman et al., 2013)*, while antifungal activity—though mild has also been reported against *Aspergillus niger (Benattia et al., 2014; Ammar et al., 2015).* In addition, extracts of *O. ficus-indica* have exhibited bactericidal activity against *Campylobacter coli* and *Campylobacter jejuni*, two of the most common causes of foodborne gastroenteritis, along with a significant reduction in their adhesion to Vero cells *(El-Mostafa et al., 2014).*

Antimicrobial properties have also been observed against *Vibrio cholerae*, with methanolic extracts displaying superior efficacy compared to ethanolic and aqueous ones *(Geng et al., 2013). (Blando et al., 2020)* demonstrated that polyphenolic extracts from *O. ficus-indica* cladodes at different maturity stages were capable of inhibiting biofilm formation by *S. aureus* and suppressing the growth of enteric bacteria such as *E. coli*, *S. typhimurium*, and *Enterobacter aerogenes*, with juvenile cladodes being more effective at 1500 µg/mL and mature ones at 2000 µg/mL.

Furthermore, aqueous and alcoholic extracts of the cladodes have shown significant antibacterial activity against *Proteus mirabilis* and *Vibrio cholerae*, likely through mechanisms involving membrane damage, increased permeability, and disruptions in pH and ATP balance. The minimum bactericidal concentration (MBC) of these extracts was found to be 4 mg/mL against *E. coli* and 1 mg/mL against *S. aureus (Sánchez et al., 2017).*

These antimicrobial effects are largely attributed to the plant's bioactive compounds, including flavonoids, phenolics, alkaloids, and particularly polyphenols such as isorhamnetin *(Galati et al., 2003).* Additionally, the high mucilage content of *O. ficus-indica* may enhance its defense mechanisms by forming a physical barrier that hinders microbial invasion *(Bensadón*

et al., 2010). Recent studies have also highlighted the antibacterial activity of discarded fruit peels, especially against pneumonia-causing bacteria *(Tesoriere et al., 2004).*(Figure 6).

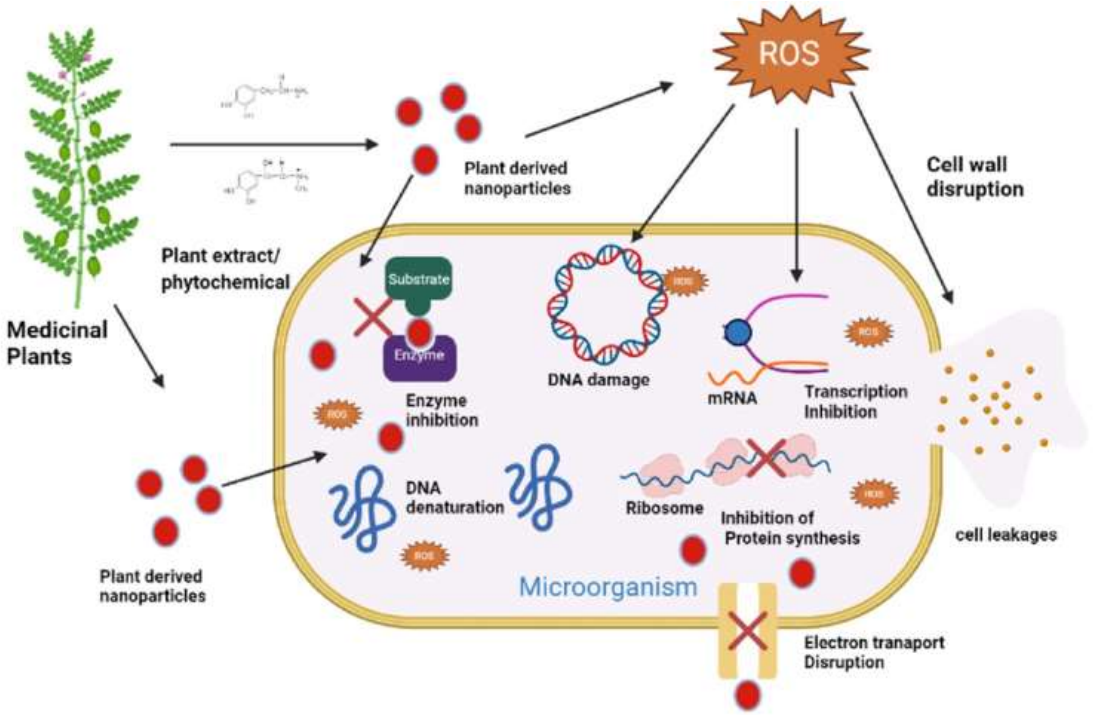

Figure 06: Mechanisms of antimicrobial activities of plant *(Okeke, E et al.,2023)*

4.Anti-burn effect :

Prickly pear *(Opuntia spp.)* has long been utilized in traditional medicine for its effectiveness in promoting wound healing, including the treatment of burns. The plant's therapeutic potential can be attributed to its high mucilage content, along with a range of bioactive compounds such as flavonoids, polyphenols, essential oils, and polysaccharides. These components are known to exert antimicrobial, anti-inflammatory, antioxidant, and tissue-repairing effects, all of which are crucial in the various phases of burn wound healing. (Figure 7,8,9)

4.1. Mechanism of Action in Burn Treatment

4.1.1. Inflammatory Phase:

During the inflammatory phase of wound healing, the initial response is focused on reducing infection and inflammation. Prickly pear's antimicrobial properties are essential in preventing microbial colonization and infection, which is a critical concern in burn wounds. Flavonoids and polyphenols present in prickly pear are known for their antibacterial activities, which help reduce the risk of secondary infections.

Furthermore, the plant's anti-inflammatory compounds modulate the immune response. They can influence the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-8 (IL-8), and tumor necrosis factor α (TNF-α), which are pivotal in regulating the body's inflammatory reaction. By modulating these cytokines, prickly pear helps mitigate excessive inflammation, thus preventing tissue damage and promoting a balanced healing environment.

4.1.2. Proliferative Phase:

In the proliferative phase, the focus shifts to tissue regeneration and the formation of new cellular structures. Prickly pear's polysaccharides play a vital role in enhancing skin hydration and forming a protective film over the wound. This protective layer not only prevents microbial entry but also reduces the risk of dehydration, which can slow down the healing process.

Additionally, prickly pear has been shown to stimulate cell proliferation, which is essential for re-epithelialization—the process by which new skin cells regenerate to cover the wound. It encourages the formation of granulation tissue, a key component in wound healing that provides the foundation for the formation of new blood vessels. The stimulation of angiogenesis (formation of new blood vessels) is further supported by the plant's ability to enhance the expression of vascular endothelial growth factor (VEGF), a key mediator in blood vessel formation.

Collagen synthesis, which is vital for the structural integrity of the wound site, is also supported by prickly pear. The plant's amino acids and vitamins, such as vitamin C, play a crucial role in collagen formation, helping to strengthen the newly formed tissue and accelerate wound contraction. This action significantly reduces the overall time required for healing, as evidenced in animal model studies *(González-Reyes et al., 2014).*

4.1.3. Remodeling Phase:

The final phase of wound healing, the remodeling phase, involves the maturation and strengthening of the extracellular matrix (ECM), with the goal of restoring the skin's original structure and function. Prickly pear aids in this process by promoting the formation of collagen and elastin fibers, which are essential for the tensile strength and elasticity of the healed skin. The presence of compounds like transforming growth factor β (TGF-β), which is involved in collagen production, and other growth factors further supports the remodeling of the ECM, ensuring that the wound heals with minimal scarring and optimal function.

Figure 07: first degree burns *(Webteb.2021)*

Figure 08: First degree burn hand *(altibi.2024)*

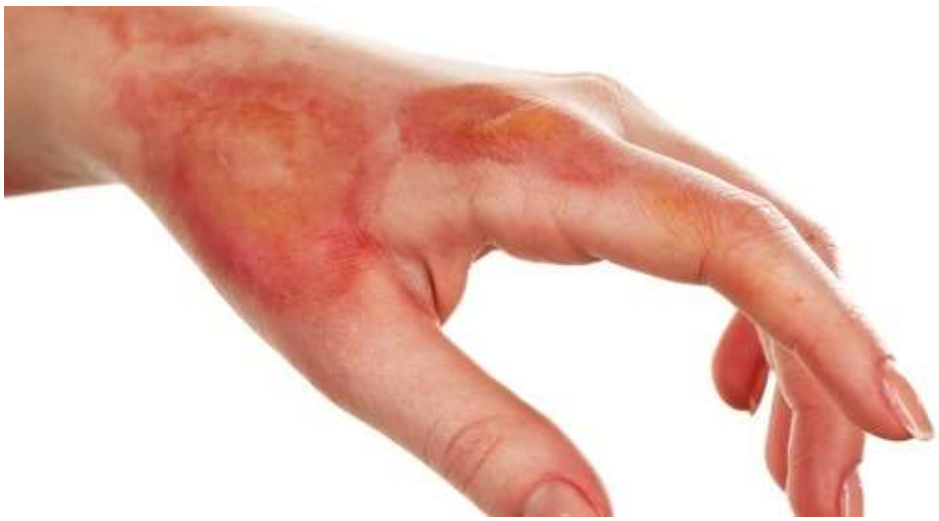

Figure 09: First degree burn. *(Webteb.2019)*

Part II

EXPERIMENTAL STUDY

CHAPTER I: MATERIALS AND METHODS

Experimental:

I. Materials:

1. Chemicals and Reagents:

Dilute ammonia (NH4 OH , ~25%), aluminum chloride (AlCl3, ≥ 98%),quercitin , SDS (Sodium dodecyl sulfate) ($C_{12}H_{25}NaO_4S$, ≥ 99%):, dimethyl sulfoxide (DMSO, C_2H_6OS, 99.9%), DPPH($C_{18}H_{12}N_5O_6$,≥ 95%) and ascorbic acid (Vit C) ($C_6H_8O_6$,≥ 99%). Gallic acid($C_7H_6O_5$,≥ 98%) , (CHCl3, ≥ 99%), mayer's, Wanger's reagent ,chloroform ,ferric chloride (FeCl3, ≥ 98%) , sulfuric acid (H2 SO4, ~98%) and folin-Ciocalteu reagent ($H_3PW_{12}O_{40}$ + $H_3PMo_{12}O$). hydrochloric acid (HCl, ≥ 37%) , ammonium molybdate Trichloroacetic acid(CCl_3COOH, ≥ 99%), potassium ferricyanide(K_3[Fe(CN), ≥ 99%) ,blood , sodium carbonate(Na_2CO_3,≥ 99%), methanol (CH_3OH, ≥ 99.9%) , sodium phosphate(Na_3PO_4,≥ 98%) and phosphate buffer(NaH_2PO_4,) and ethylenediaminetetraacetic acid (EDTA, 99.0%). All chemicals and reagents utilized in this study were of analytical grade and procured from Sigma-Aldrich (St. Louis, MO, USA).

2. Bacterial Strains:

The bacterial strains used in this study work, including *Pseudomonas aeruginosa (*ATCC 27853), *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 25973), *Klebsiella pneumoniae* (ATCC 13885), and *Escherichia coli* (ATCC 25922), were all sourced from the Pasteur Institute laboratory center in Algiers, Algeria.

3. Collection and Preparation of *O.Ficus Indica* :

The cladodes of *Opuntia ficus-indica* were picked during summer (August 2024) and again in December 2024 from the northern and northeastern parts of Algeria, specifically the Skikda (Collo) (6°56'05"E 36°52'22"N). To eliminate spines, dust, and other impurities, the cladodes were washed thoroughly under running tap water. The spines were carefully removed, and the outer epidermal layer was peeled off to ensure total elimination of impurities. The decontaminated cladodes were then extracted, dried, and kept for future use (Figure 10).

Figure 10: Images of cladodes of *Opuntia ficus-indica* (Original photos)

4. Animals:

Thirty (30) adult male albino rats (**185.64** ±**27.9** g) were obtained from the animal facility of the Pasteur Institute, Algeria. The animals were housed in the Molecular and Cellular Biology Department's animal facility at the University of El Oued, Faculty of Natural and Life Sciences. They were maintained under controlled laboratory conditions and allowed a two-week acclimatization period. During both the acclimatization and experimental phases, the rats had continuous access to standard feed and drinking water. This study was reviewed and approved by the Institutional Review Board of El Oued University (Approval No. 03/2025; Ethical Reference N°: 03/S.C/F.L.N.S/E.U/2025; Scientific Council Meeting No. 02/2025, held on 22/04/2025), confirming full compliance with local ethical guidelines.

II. Methods

1. Phytochemical analysis of *O.Ficus Indica*

1.1. Extraction of *O.Ficus Indica* Aqueous extract

To prepare the aqueous extract, 10 g of Fresh leaf parts of *O. Ficus Indica* were accurately weighed and mixed with 100 mL of distilled water. The mixture was heated at 50°C for 2 hours to enhance the extraction of bioactive compounds, followed by maceration at room temperature for 24 hours to ensure maximum phytochemical yield. After the maceration period, the extract was filtered through Whatman No. 1 filter paper to remove plant debris. The filtrate was then concentrated using a rotary evaporator under reduced pressure, and the resulting semi-solid extract was weighed and stored at 4°C for further phytochemical *(Murugan and Parimelazhagan,2014).* (Figure11)

1.2. Extraction yield

Extraction yield was calculated by the following equation (1):

$$\text{Yield (\%)} = W1/W2 \times 100 \qquad (1)$$

Where W1 = weight of the extract and W2 = weight of plant material dried powder *(Boutennoun et al., 2017).*

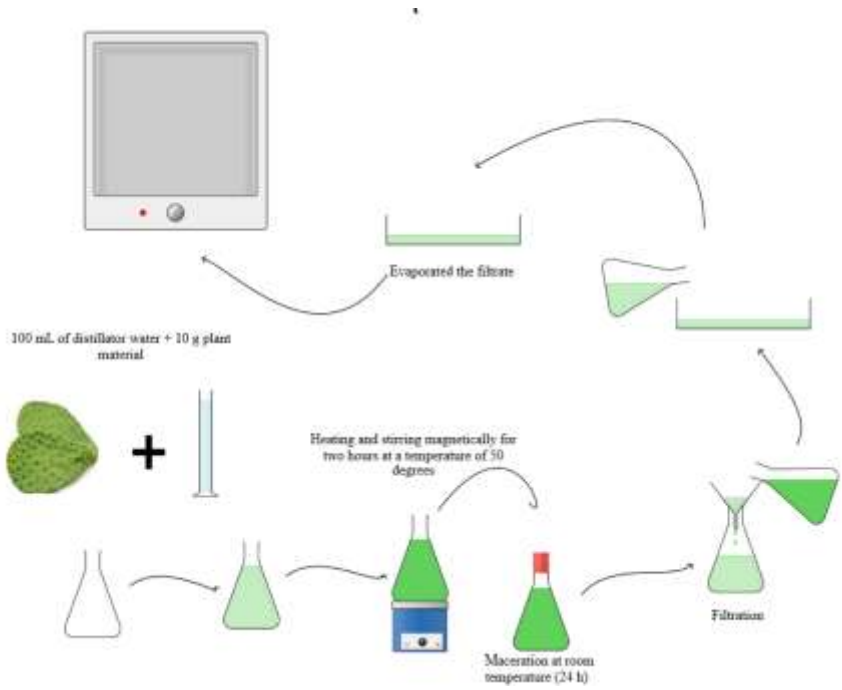

Figure 11: *Opuntia ficus-indica* aqueous extract preparation

2. Phytochemical Screening:

2.1.Alkaloids

Put 1 mL of test extract in two test tubes. Acidify the medium with a few drops of HCl and add drops of Mayer's reagent to one tube and a few drops of Wagner's reagent to the second tube. Appearance of a white or brown precipitate respectively is a sign of the presence of alkaloids *(Gontijo et al., 2017)*

2.2. Flavonoids

We add 2.5 mL of the test extract, 2.5mL of diluted ammonia, and 0.5mL of H_2SO_4 into the test tube, and the presence of flavonoids is indicated by the formation of yellow color *(Ibtissam et al., 2021).*

2.3.Terpenoids

We add 2.5 mL of plant extract, 1 mL of chloroform, and 1.5 mL of concentrated sulfuric acid into a test tube. Reddish-brown color is yielded by the terpenoids *(Harborne, 1998).*

2.4. Saponins

10 mL of the aqueous extract is contained in a test tube. The tube was shaken for 15 seconds and left to settle for a further 15 minutes. A clear indication of the presence of saponins was seen with more than 1 cm of foam stand *((Edeoga et al., 2005).*

2.5.Search for tannins

In a test tube, we combine 2.5 mL of the extract with 0.5 mL of an aqueous ferric chloride solution ($FeCl_3$) of 2%. A greenish or bluish-blackish tinge was an indication of the presence of tannins*(Evans, 2009).*

2.6.Steroids

1mL of the extract received 5 drops of concentrated H_2SO_4. The presence of steroids is indicated by the color red *(Trease and Evans, 1989).*

2.7.Cardiac glycosides

2 mL of chloroform were mixed with 1mL of the extract. The inner part of the test tube was then slowly filled with H2SO4. A reddish-brown coloration *(Yam et al., 2009)* indicates the presence of a glycone component of a cardiac glycoside.

3. Quantification of phytochemicals compound :

3.1. Estimation of total phenolics :

The total amount of phenolics was determined using the Folin-Ciocalteu method. To 1 mL of 10% Folin-Ciocalteu reagent, 0.2mL of the aqueous extract of OFI leaf was included. 800 µL saturated sodium carbonate (75 g/L) was added at 4 minutes. The absorbance was read at 765 nm after incubation for 30 minutes at room temperature. For being able to replicate the results, the tests were done three times (Slinkard and Singleton, 1977). From the standard gallic acid linear calibration equation, the total phenolic content was calculated in terms of mg of gallic acid equivalent per g extract. *(Oracz et al., 2023)*

3.2. Quantitative determination of the total flavonoids :

We used aluminum chloride ($AlCl_3$) colorimetry for the quantification of OFI leaf extract total flavonoid content (Ahn et al., 2007) as given below;1mL of the $AlCl_3$ solution is mixed with 1mL of the sample, and on the other side with 1mL of the standard. At 430 nm, absorbance was measured, after 30 minutes against the reagent blank prepared.

For the calculation of the results, a linear calibration equation using quercetin as the standard was employed. The results were presented as milligrams of quercetin per gram of extract. *(Sultana et al., 2024)*

4.In Vitro Activity of the aqueous extract of *O. Ficus Indica*

4.1. Antioxidant activity:

4.1.1. DPPH free-radical scavenging activity (DPPH) *:*

1 mL of DPPH• solution is mixed with 1 mL of every extract (or ascorbic acid as a control). To finish the reaction, the reaction mixture is agitated and, afterwards, left at room temperature for 30 minutes in the dark. The reaction medium's absorbance at 517 nm is measuredb (Equation 04)(Mansouri et al., 2005).

Percent inhibition (PI) = [(Abs control - Abs sample) / Abs control) × 100] (4)

Where Abs control is the absorbance of the control (which has all reagents but not the sample) and Abs sample is the absorbance of the control. *(Gulcin & Alwasel, 2023)*

4.1.2. Reducing Power Assay (RP):

Oyaizu's method was used to determine the reducing power of the extract. The sample was blended with phosphate buffer (1.25 mL, 0.2 M, pH 6.6) and 1% potassium ferricyanide water solution (1.25 mL, K3 [Fe (CN) 6]) in various concentrations (mg/mL) in distilled water. After the addition of aliquots of trichloracetic acid (1.25mL, 10% aqueous solution), the mixture was incubated at 50°C for 20 minutes and then centrifuged for 10 minutes at 3000 rpm. The supernatant (1.25mL) and filtered water were mixed with freshly prepared FeCl3 (0.25mL, 0.1%) solution (1.25mL) the absorbance was read at 700 nm wavelength. Ascorbic acid as a positive control was used *(Oraiza, 1986).*

4.1.3. Phosphomolybdate assay (Total Antioxidant Capacity) :

The assay is based on the extract's capacity to reduce Mo (VI)-Mo (V) and further form a green phosphate/Mo (V) complex under acidic pH. An aliquot of 0.2 mL of extract was combined with 2 mL of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate). The reaction mixture was incubated for 90 minutes at 95°C in tubes. When the samples became room temperature, spectrophotometry was conducted measuring the absorbance of the solution at 695 nm relative to a blank. A blank consists of 0.2mL of distilled water in place of extract *(Islam et al., 2013).* A standard AA graph was used to calculate ascorbic acid equivalents. The experiment was conducted in triplicate, and the results are expressed as mg per g of extract equivalent to ascorbic acid.

4.2. Anti-inflammatory activity :

Denaturation inhibition of egg albumin was used to investigate the anti-inflammatory effect of aqueous extract of OFI cladode . Reaction mixture (5 mL) contained 100 µL of fresh hen's egg albumin and 1.4 mL of phosphate buffer (pH 6.4) and was spiked with 1 mL of various concentrations of our standard sample drug diclofenac sodium, and 1 mL of distilled water was also used in lieu of extract or diclofenac to get the control. The reaction mixtures were incubated for 15 min at 37°C in a water bath and then subjected to a heating time for 5 min at 70°C. Reaction mixtures absorbance at 660 nm was measured through UV-visible spectrophotometry after cooling with the help of blank buffer *(Dharmadeva et al., 2018).* In order to find the inhibition percentage of egg albumin denaturation, the following formula was utilized (equation 02):

$$\text{Inhibition percentage} = \frac{A\ Control - A\ sample}{A\ control} \times 100 \qquad (2)$$

4.3. Hemolytic activity:

Hemolysis experiment is conducted as outlined below, according to *(Vinjamuri et al.,2015);* 5mL of blood was centrifuged at 1000 rpm for 10 minutes at 40°C in tubes containing 5.4 mg of EDTA to avoid coagulation.

The hemolytic assay was conducted on washed erythrocytes that were kept at 40°C for 6 hours. 200 µL of sample tests (containing an OFI leaf component) and 100 µL of erythrocyte suspension in 07 dilutions were utilized. Positive controls, 200 µL each of 1XPBS, and negative controls, 100 µL each of 1% SDS, were utilized. Then incubate for 60 minutes in a 37 °C water bath *(Vinjamuri et al., 2015).* 1.7mL of XPB were added to the reaction mixture to make it 2 mL. The mixture was centrifuged for 3 minutes at 300 rpm. The concentration of hemoglobin was determined by measuring the resulting quantity of hemoglobin in the supernatant with a spectrophotometer at 540 nm. The following formula was used to compute the hemolysis percent (equation 03):

$$\%\ \boldsymbol{Hemolysis\ Inhibition} = \mathbf{100} - \frac{\boldsymbol{OD\ Sample}}{\boldsymbol{OD\ Control}} \times 100 \quad (3)$$

4.4. Antibacterial activity assays

As previously described, the antibacterial activity of the tested materials was evaluated using the agar diffusion method. Bacterial cultures were grown in nutrient agar for 24 hours at 37 °C to reach the stationary growth phase before application. A standardized bacterial suspension (approximately 10^6 colony-forming units per mL) was uniformly spread onto Mueller-Hinton agar plates using sterile swabs. Sterile discs (6 mm diameter) were impregnated with 10 µL of the respective plant extracts, which were dissolved in 5% (v/v) dimethyl sulfoxide (DMSO) at various concentrations. Discs containing 5% DMSO served as the negative control, while appropriate antibiotics were used as positive controls. All plates were incubated at 37 °C for 24 hours prior to measuring the inhibition zones *(Goanar, Tafesse, & Fereja, 2024).*

5. *In vivo* activity of aqueous extract *of O. Ficus Indica*

5.1. Preparation of Formulation creams

The burn-healing creams were meticulously formulated according to protocols adapted from *(Saratha et al., 2010; Patil et al.,2012; Goyal et al., 2012), and (Nagar et al. ,2016)* .Two topical preparations were developed using classical Galenic pharmaceutical techniques, incorporating *Opuntia ficus-indica* extract at concentrations of 5% , 10% and 20% into a simple cream base (Vaseline®). The formulation process involved gently heating the Vaseline® base

in a water bath precisely maintained at 45 °C, followed by the gradual incorporation of the plant extract under continuous stirring. This ensured the formation of a uniform and homogenous mixture with optimal consistency. The resulting formulations were designated as OFI-I (1% *Opuntia ficus-indica*) and OFI-II (2% *Opuntia ficus-indica*). Upon preparation, the ointments underwent initial physicochemical evaluation. The pH of each formulation was measured using a calibrated digital pH meter to ensure compatibility with skin application. To maintain their stability and preserve the therapeutic bioactivity of the phytoconstituents, the ointments were stored at 4 °C until further use. For comparative purposes, MEBO® ointment containing 0.25% β-sitosterol and manufactured by Gulf Pharmaceutical Industries, Ras Al Khaimah, UAE was used as a standard reference. This allowed for a comprehensive evaluation of the burn-healing efficacy of the *Opuntia ficus-indica* formulations against an established commercial product with proven clinical effectiveness. *(Martins et al., 2023)*

5.2. Acute toxicity study

Ankomah et al. in 2022 and Liu et al. in 2024 conducted pre skin irritation research based on OECD guidelines which included work with Wistar male rats. Two male Wistar rats were kept in a separate room, put on a standard diet with free access to water, and monitored for ad lib access to water. The fur from the dorsal area of the rats was shaved cleanly. *Opuntia ficus-indica* cladodes were formulated into a topical cream and was spread on the skin at a dosage of 50 mgs. First group was given the 5% creams while second group got 10% and 20% at different locations on the skin. The rats were monitored for signs of potential toxicity for a 48 hours period post intervention. The animal study was done as per the regulations set by IAEC of University of El Oued in Algeria. *(Ankomah et al., 2022 ; Liu et al., 2024)*

5.3. Experimental Design and Burn Wound Induction:

After two weeks of acclimatization, the adult Wistar albino rats were randomly divided into six groups, each containing six rats (n=5) as follow:

- **Group A**: burned untreated rats.
- **Group B:** burned rats treated with the cream base only.
- **Group C**: burned rats treated with MEBO medical cream.
- **Group D:** burned rats treated with an *Opuntia ficus-indica* (OFI) extract-based cream at a 5% concentration.
- **Group E:** burned rats treated with the natural extract-based cream at a 10% concentration.

• **Group F**: burned rats treated with the natural extract-based cream at a 20% concentration.

For experimental burn injury induction, the dorsal area of the animals was shaved 24 hours before the procedure under general anesthesia, which was induced by administering chloroform in a closed chamber. Cutaneous burns were created on the dorsal region of all animals, following the same anesthesia protocol, by applying a 2 cm diameter aluminum plate adapted to a temperature-controlled device set at 120°C. The plate was pressed against the skin for 6 seconds, inducing a first-degree burn.

Following burn induction, the animals were housed in individual cages. Apart from burn wound treatment protocols, no specific care was administered, except for animal handling during the experimental procedure. Treatments were initiated 24 hours post-injury and applied once daily at the same time for 21 consecutive days. The animals were euthanized anesthesia for sample collection.

For control purposes, untreated animals were subjected to sham treatments to account for potential wound contamination and bacterial infection, without receiving any therapeutic intervention.

The *OFI* extract-based cream (50 mg/day) was topically applied to the wound margins using a Pasteur pipette.

5.4. Parameters for Evaluating Burn Healing in an Excision Burn Model

5.4.1. Morphological evaluation: Following the method described by *(Fikru et al.,2012)* gradual changes in wound area throughout the treatment period were documented using a iPhone 8 Plus camera on days 1, 7, 14, 21, and upon complete healing of each wound.

5.4.2. Measurement of burn contraction: The size of the burns (cm^2) was monitored according to *(Arunachalam and Parimelazhagan ,2013),* as detailed by *(Fikru et al.,2012),* on days 1, 7, 14, 21, and 16. burn contraction was calculated as the percentage reduction in the original burn area, using the formula described by *(Subramanian et al.,2023).*(Fifure 12)

Burn Contraction (%)

$$= \left[\frac{\text{Burn Area on Day 0} - \text{wound Area on Day n}}{\text{Burn Area on Day 0}}\right] \times 100$$

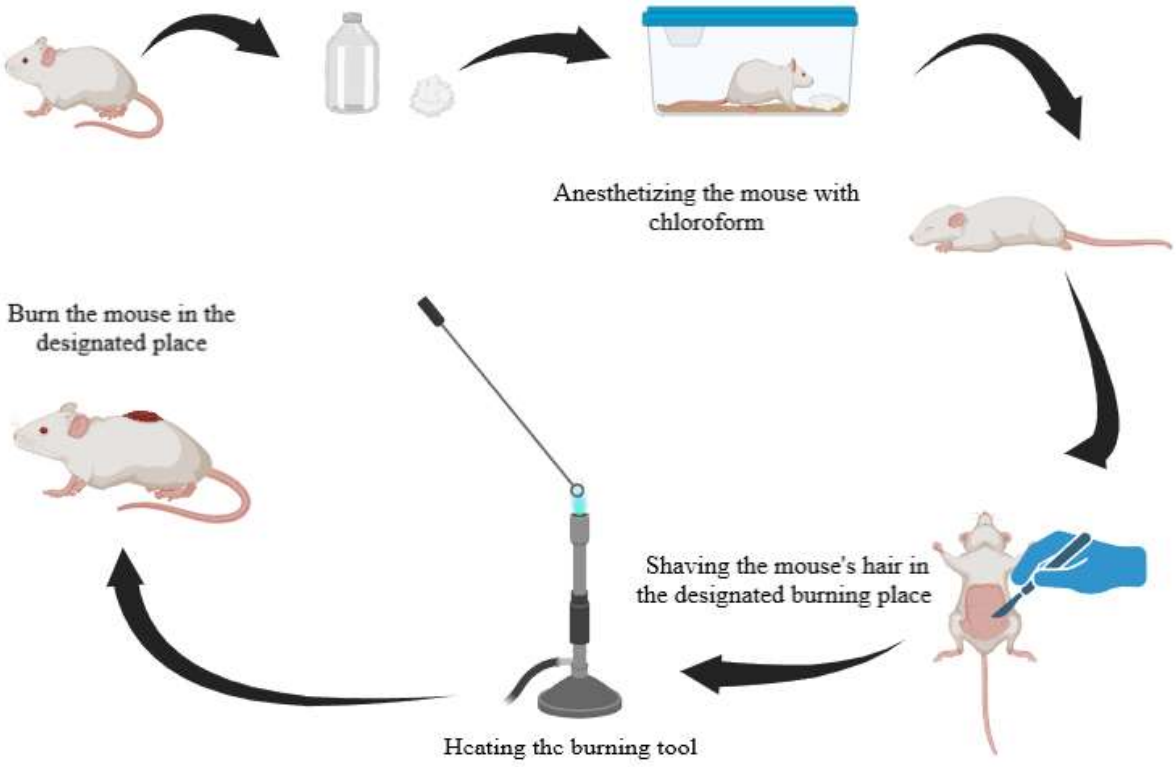

Figure12: Diagram explaining experimental Design and Burn Induction

5.5. Samples preparation:

5.5.1. Euthanasia and Blood collection:

Upon the conclusion of each treatment which was after 21 days, the rats were lightly anesthetized with 94% chloroform and decapitated. Subsequently, blood was drawn and placed into pre-labeled and pre-numbered EDTA tubes designated for each rat. This was done following 16 hours of fasting.

5.5.2. Hematological Parameters

Hematological parameters, including red blood cell (RBC) count, hemoglobin (Hb) concentration, hematocrit (HCT), white blood cell (WBC) count, and platelet count, were measured using an automated hematology analyzer. The Coulter's technique with a Medonic automatic hematological analyzer (Medonic CA620, Boule Diagnostics, Stockholm, Sweden) was employed to ensure accurate measurements.

5.5.2. Preparation of tissues samples:

Following euthanasia, the burn area on each mouse was carefully shaved on the dorsal side using a sterile scalpel to minimize contamination. A skin biopsy was then excised from the

burned region with a fresh, sharp blade. The tissue samples were immediately placed in 10% neutral-buffered formaldehyde for fixation to preserve cellular structure and prevent degradation. The fixed tissues were left in formaldehyde overnight, preparing them for subsequent histological analysis.

The fixed tissue samples were dehydrated using a graded series of ethanol solutions (60%, 70%, 80%, and 100%), with each solution carefully replaced to ensure complete tissue dehydration. After dehydration, the samples were cleared in xylene to remove any remaining alcohol and to facilitate embedding in paraffin. The paraffin-embedded tissue was sectioned into thin slices (4–6 μm) using a Thermo Scientific Micron HM 325 rotary microtome.

The tissue sections were then stained with hematoxylin and eosin (H&E), a standard staining method for evaluating cellular and structural features. For each animal, three slides were prepared and analyzed to assess potential morphological changes in the skin, such as epidermal thickness, dermal alterations, inflammatory response, and cellular abnormalities.

6. Statistical analysis

Statistical analysis was carried out using SPSS software (Version 26.0). Data are presented as mean ± standard error of the mean (SEM). Prior to analysis, the data were assessed for normality and homogeneity of variance to validate the use of parametric tests. One-way analysis of variance (ANOVA) was performed to detect significant differences among the experimental groups. Where significance was observed, Tukey's Honestly Significant Difference (HSD) post hoc test was employed to determine pairwise group differences. A p-value of less than 0.05 was considered statistically significant

Conclusion

Conclusion

In conclusion, this study has successfully illuminated the promising therapeutic potential of *Opuntia ficus-indica* (prickly pear) leaf extract in accelerating the healing of burn-induced wounds. Through a meticulous evaluation of its diverse biological activities, including antioxidant, anti-inflammatory, and antibacterial properties, the study has provided compelling evidence of the extract's multifaceted therapeutic benefits.

In vitro results have revealed that the extract is rich in phenolic compounds and flavonoids, which exhibited a strong ability to combat free radicals and reduce oxidative stress. This antioxidant activity is crucial in mitigating the damaging effects of oxidative stress, which is implicated in various chronic diseases and wound healing processes. Furthermore, the extract demonstrated significant anti-inflammatory activity by inhibiting the release of inflammatory cytokines such as TNF-α and IL-6, thereby reducing inflammation and promoting tissue repair. Additionally, the extract showed antibacterial activity against common pathogenic strains like *Staphylococcus aureus* and *Escherichia coli*, highlighting its potential in addressing antibiotic resistance and preventing infections in wound sites. The moderate sun protection factor (SPF) also suggests its added value in dermal applications, including protective skincare formulations.

In the *in vivo* model, topical application of 10% extract-based cream resulted in nearly complete wound closure by day 16, corroborated by histological evidence of epithelial regeneration and reduced inflammation. Importantly, the extract was found to be biocompatible and non-toxic, as confirmed by subacute toxicity assessments in Wistar rats, which showed no adverse effects on behavior, weight, or organ histology.

These findings collectively position *Opuntia ficus-indica* extract as a safe, effective, and multifunctional natural agent for use in wound healing, anti-inflammatory therapy, antimicrobial treatment, and skincare. Future studies should focus on clinical trials, molecular mechanism elucidation, and optimization of extraction techniques to enhance bioactive yield and therapeutic efficacy.

Together, these findings establish *Opuntia ficus-indica* leaf extract as a safe, multifunctional, and effective natural agent with applications in wound healing, anti-inflammatory therapy, antibacterial treatment, UV protection, and cosmetic skincare.

Future directions should include clinical validation, mechanistic studies, and optimization of extraction protocols to maximize therapeutic efficacy and bioactive yield. This research

supports the integration of *Opuntia ficus-indica* into modern phytotherapy and natural product-based healthcare, reinforcing the importance of sustainable plant resources in addressing current medical and cosmetic challenges.

❖ **Perspective**

Considering the importance of these results, they open the door to more thorough research and experimental strategies that should allow us to pinpoint the following:

✓ Synthesis of nanoparticles using *Opuntia ficus-indica* extract.

✓ **Development of nano-formulated therapeutic creams**: Building on the success of the 10% extract-based cream in accelerating burn wound healing, future studies could explore the integration of *O. ficus-indica*-mediated nanoparticles into advanced topical delivery systems (e.g., nanogels, emulsions, or hydrogel films) to improve skin absorption, sustained release, and synergistic healing properties.

✓ **Evaluation of broader pharmacological activities**: In addition to wound healing, the antioxidant, anti-inflammatory, and antimicrobial profile of *O. ficus-indica* extract positions it as a candidate for managing chronic conditions such as diabetic wounds, skin infections, and even UV-induced skin damage. Studies on SPF activity should be expanded to assess its potential in cosmetic formulations.

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Annexes

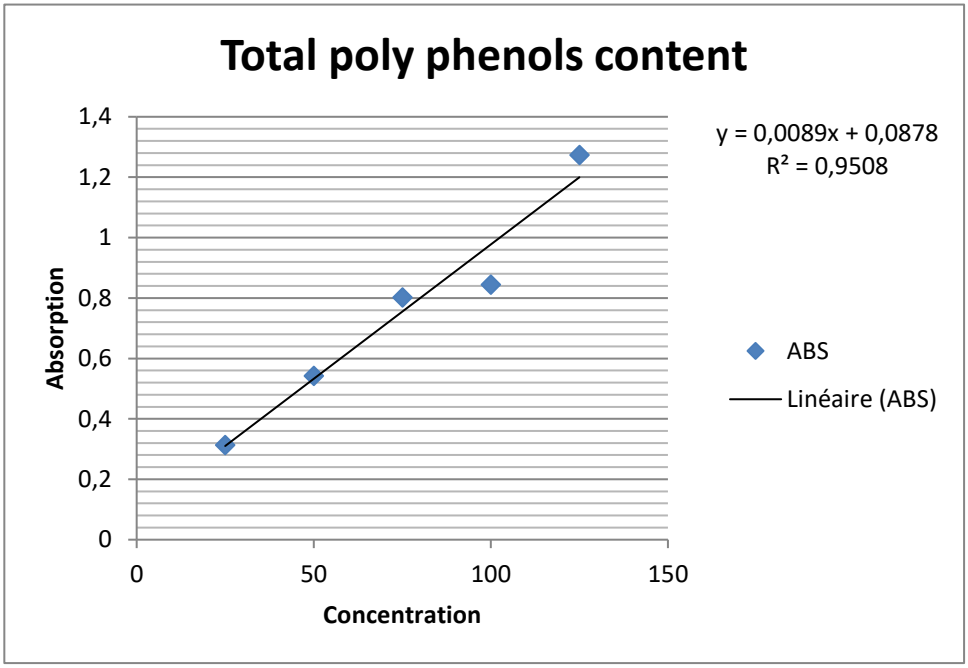

Figure : **Total poly phenols content of** *Opuntia ficus-indica*

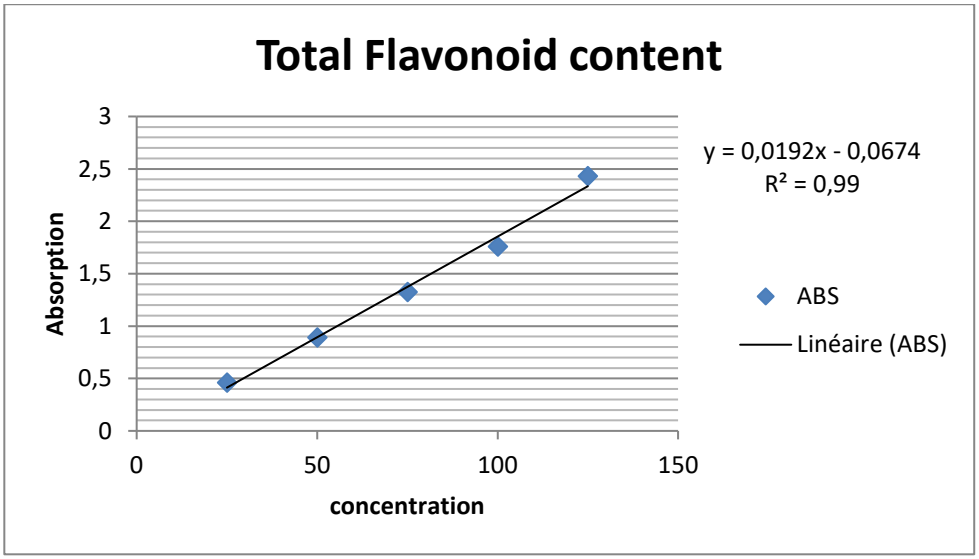

Figure : **Total Flavonoid content of** *Opuntia ficus-indica*

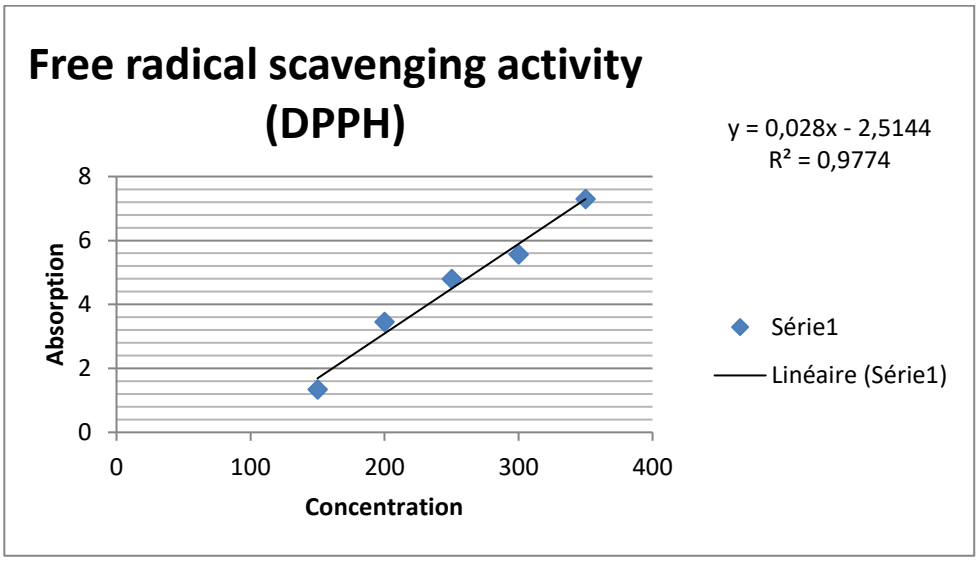

Figure : Free ragical scavenging activity (DPPH) **of** *Opuntia ficus-indica*

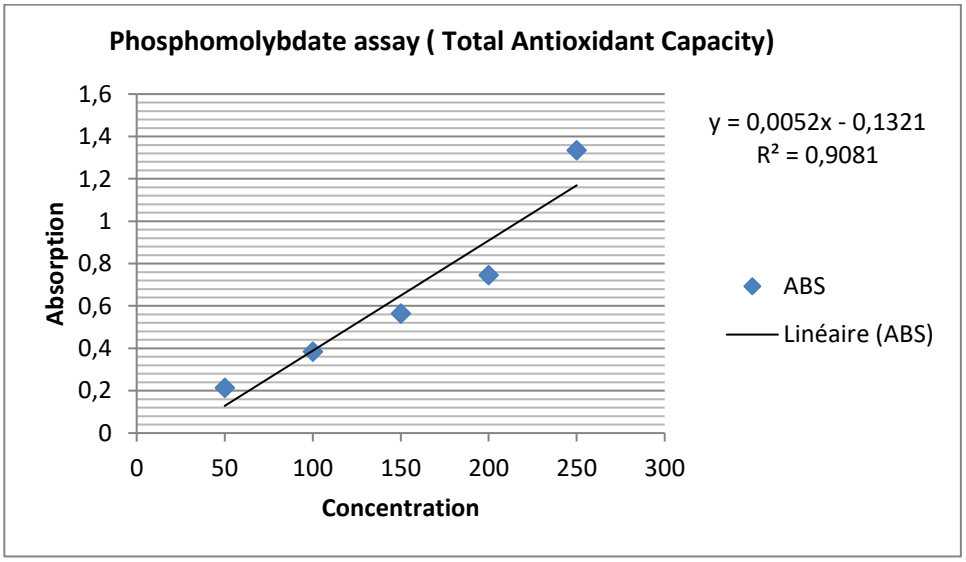

Figure : Phosphomolybdate assay (total antioxidant capacity) **of** *Opuntia ficus-indica*

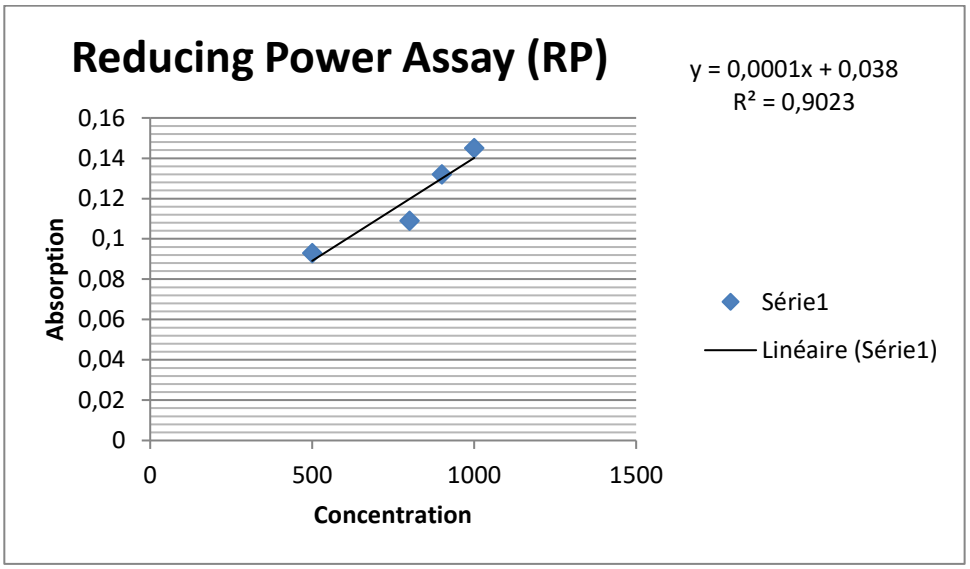

Figure : **Reducing power assay (RP) of** *Opuntia ficus-indica*

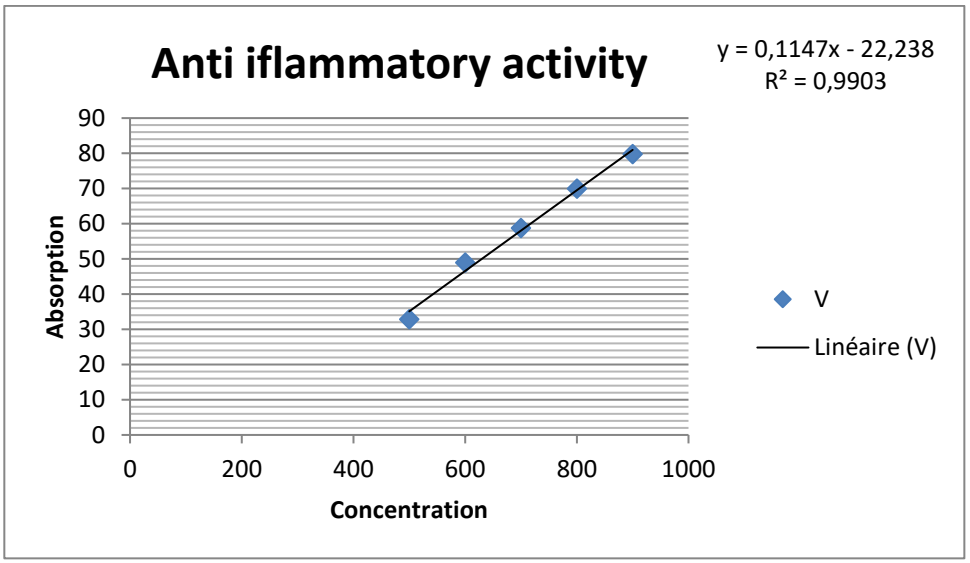

Figure : **Anti-inflammatury activity of** *Opuntia ficus-indica*

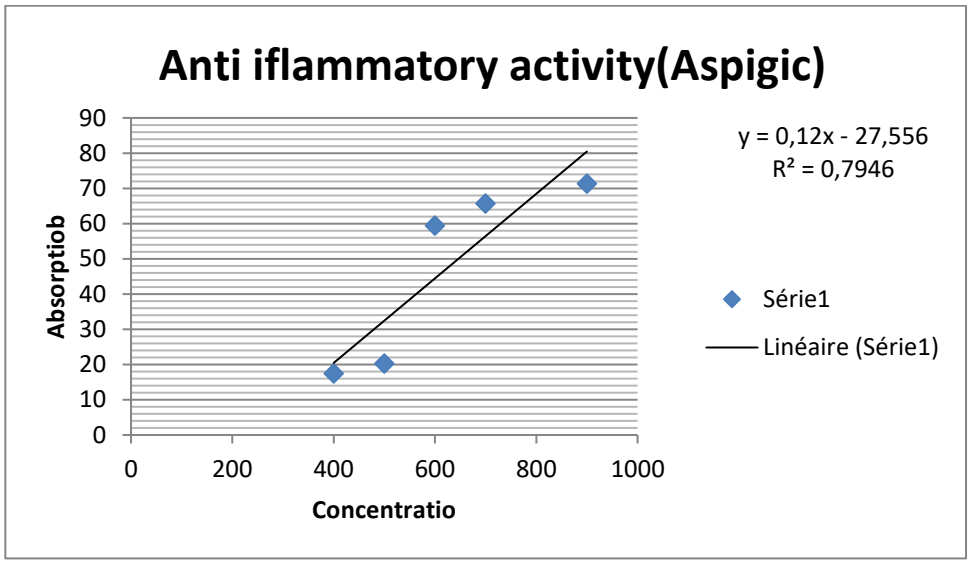

Figure : **Anti-inflammatury activity (Aspigic) of** *Opuntia ficus-indica*

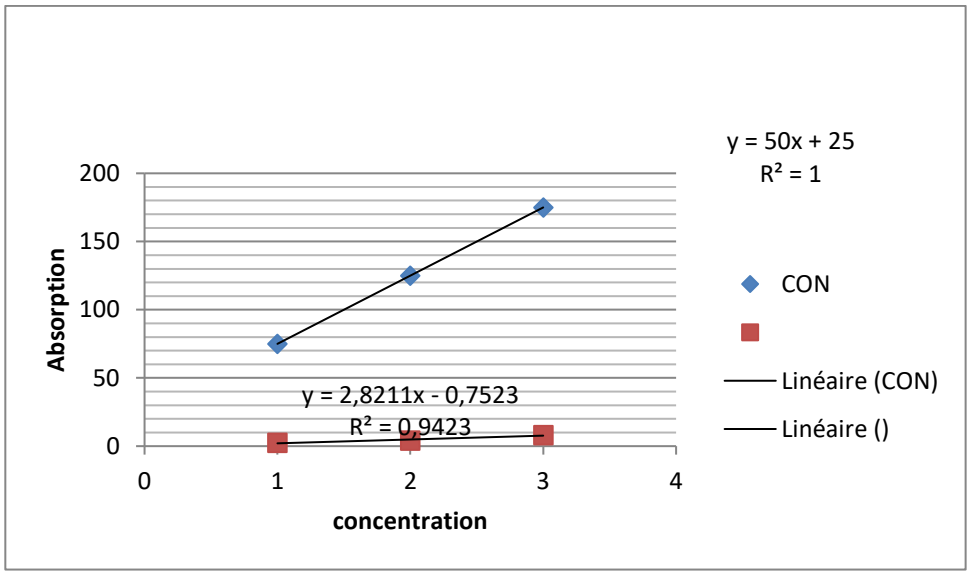

Figure : **Hemolytic activity of** *Opuntia ficus-in*الملحق