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Biological and gastro-protective activities of two medicinal plants (*Punica granatum* L. And *Juniperus phoenicea* L.) and their nano-formulation

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To my beloved father,

To my dear mother,

To my brothers and sister,

And to all those who hold a special place in my heart,

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steadfast support, boundless patience, and constant encouragement

Biological and gastro-protective activities of two medicinal plants (*Punica granatum* L. And *Juniperus phoenicea* L.) and their nano-formulation

This research seeks to reconcile traditional knowledge with contemporary scientific confirmation in treating stomach ulcers. *Punica granatum* L. and *Juniperus phoenicea* L. were chosen for the extraction of bioactive components, the green synthesis of ZnO nanoparticles (ZnO-NPs), and the assessment of their biological and gastroprotective activities. The experimental design involved several sequential stages. First, aqueous extracts (AQE-JP and AQE-PG) were prepared via decoction, which were notably rich in polyphenolic compounds vital for reducing and capping ZnO nanoparticles. These nanoparticles were successfully produced and characterized through various analytical techniques, including UV-VIS, FTIR, XRD, and SEM-EDX. The biosynthesized ZnO nanoparticles demonstrated a hexagonal wurtzite structure; ZnO-PG nanoparticles exhibited a spherical morphology with an average particle size of 34.08 ± 7.44 nm, while ZnO-JP nanoparticles presented an irregular shape averaging 30.16 ± 5.20 nm. Second, comprehensive *in vitro* evaluations were conducted. The antioxidant activity was examined using DPPH, FRAP, TAC, and β-carotene bleaching tests, whilst the anti-inflammatory effects were assessed by membrane stabilization and egg albumin denaturation assays, demonstrating the efficacy of these compounds in regulating inflammation. The antibacterial efficacy was evaluated utilizing the agar diffusion technique against six human pathogens. These tests revealed that both AQEs and their corresponding ZnO-NPs showed significant antioxidant, anti-inflammatory, and antibacterial properties. Finally, the *in vivo* gastroprotective efficacy was evaluated in an Indomethacin-induced gastric ulcer model. Male rats received a single oral dose of 50 mg/kg Indomethacin following a two-week pretreatment with the tested samples. The experimental groups comprised a standard control, an ulcer group, Omeprazole (20 mg), AQE-JP (200 mg), AQE-PG (200 mg), a combination of AQE-JP and AQE-PG (200 mg), ZnO-JP (10 mg), and ZnO-PG (10 mg). Multiple physiological and biochemical measures were assessed, such as gastric juice volume and pH, stomach tissue weight, ulcer index, and protection rate. The *in vivo* analysis revealed that all examined samples showed considerable gastroprotective effects, notably ZnO-JP and ZnO-PG NPs, which achieved the most significant protective rates of 94.80% and 97.41%, respectively. Furthermore, the study measured the impact on oxidative stress biomarkers. Indomethacin-induced oxidative stress markedly elevated lipid peroxidation markers (MDA) (7.43 ± 2.25 nmol/g of proteins in the ulcer group), concurrently diminishing GSH levels (0.027 ± 0.007 µmol/g of proteins) and antioxidant enzyme (CAT) activity (32.01 ± 26.69 U/min/g of proteins). Pretreatment with the examined samples, particularly the ZnO-NPs, diminished lipid peroxidation to levels akin to the control group (3.10 ± 0.36 and 2.96 ± 0.32 nmol/g of proteins for ZnO-JP and ZnO-PG, respectively), while markedly augmenting GSH content and CAT activity. The histopathological analysis of the stomach mucosa validated these gastroprotective properties. This research is unprecedented, emphasizing the promise of biosynthesized ZnO nanoparticles in treating stomach ulcers. Additional clinical trials are required to clarify the underlying mechanisms and evaluate their safety in additional organs.

Keywords; Ethnopharmacology, *Punica granatum* L., *Juniperus phoenicea* L., Aqueous decoction, ZnO-NPs, Gastric ulcer.

الأنشطة البيولوجية والخصائص الواقية للمعدة لنباتين طبيين (الرمان والعرعر الفينيقي) وتركيبتهما النانوية

هذا البحث يسعى إلى التوفيق بين المعرفة التقليدية والتأكيد العلمي المعاصر في علاج قرحة المعدة. تم اختيار نباتي الرمان (*Punica granatum L.*) والعرعر الفينيقي (*Juniperus phoenicea L.*) لاستخلاص مكوناتها النشطة بيولوجيًا، وللتخليق الأخضر لجسيمات أكسيد الزنك النانوية (ZnO-NPs)، وتقييم أنشطتها البيولوجية والوقائية للمعدة. شمل التصميم التجريبي عدة مراحل متسلسلة. أولاً، حُضّرت مستخلصات مائية (AQE-JP و AQE-PG) بطريقة الغلي، والتي كانت غنية بشكل ملحوظ بالمركبات متعددة الفينول الحيوية لاختزال وتثبيت جسيمات أكسيد الزنك النانوية. ثانيًا، تم إنتاج هذه الجسيمات النانوية بنجاح وتوصيفها بتقنيات تحليلية مختلفة، بما في ذلك UV-VIS و FTIR و XRD و SEM-EDX. أظهرت الجسيمات النانوية ZnO المُخلّقة حيويًا بنية سداسية من نوع الوورتزايت؛ حيث أظهرت جسيمات ZnO-PG النانوية شكلاً كرويًا بمتوسط حجم جسيمات قدره 34.08 ± 7.44 نانومتر، بينما أظهرت جسيمات ZnO-JP النانوية شكلاً غير منتظم بمتوسط حجم 30.16 ± 5.20 نانومتر. ثالثًا، أُجريت تقييمات شاملة في المختبر، حيث فحص النشاط المضاد للأكسدة باستخدام اختبارات DPPH و FRAP و TAC وتبييض بيتا-كاروتين، بينما قيمت التأثيرات المضادة للالتهابات من خلال اختبارات تثبيط تحلل البومين بيض واستقرار الغشاء، مما أثبت فعالية هذه المركبات في تنظيم الالتهاب. كما تم تقييم الفعالية المضادة للبكتيريا باستخدام تقنية الانتشار ضد ست سلالات بكتيرية . كشفت هذه الاختبارات أن كلاً من المستخلصات المائية والجسيمات النانوية ZnO-NPs المقابلة لها أظهرت خصائص كبيرة مضادة للأكسدة والالتهابات والبكتيريا. أخيرًا، تم تقييم الفعالية الوقائية للمعدة داخل الجسم الحي في نموذج قرحة المعدة المُحفّزة بالاندوميثاسين. حيث تلقى ذكور الجرذان جرعة فموية واحدة مقدارها 50 مغ/كغ من الاندوميثاسين بعد معالجة أولية لمدة أسبوعين بالعينات المختبرة. وشملت المجموعات التجريبية: مجموعة تحكم قياسية، ومجموعة قرحة غير معالجة، وأوميبرازول (20 مغ)، و AQE-JP (200 مغ)، و AQE-PG (200 مغ)، ومزيج من AQE-JP و AQE-PG (200 مغ)، و ZnO-JP (10 مغ)، و ZnO-PG (10 مغ). تم تقييم العديد من المؤشرات الفسيولوجية والكيميائية الحيوية، مثل حجم ودرجة حموضة العصارة المعدية (pH)، ووزن أنسجة المعدة، ومؤشر القرحة، ومعدل الحماية. وكشف التحليل داخل الجسم الحي أن جميع العينات المختبرة أظهرت تأثيرات وقائية كبيرة للمعدة، ولا سيما جسيمات ZnO-JP و ZnO-PG النانوية، حيث حققت أعلى معدلات حماية بلغت 94.80% و 97.41% على التوالي. علاوة على ذلك، قاست الدراسة التأثير على مؤشرات الإجهاد التأكسدي. أدى الإجهاد التأكسدي الناجم عن الاندوميثاسين إلى ارتفاع ملحوظ في علامات بيروكسيد الدهون (MDA) (7.43 ± 2.25 نانومول/غ من البروتينات في مجموعة القرحة)، مع انخفاض مستويات الجلوتاثيون (GSH) (0.027 ± 0.007 ميكرومول/غ من البروتينات) ونشاط إنزيم مضادات الأكسدة (CAT) (32.01 ± 26.69 وحدة/دقيقة/غ من البروتينات). أدت المعالجة المسبقة بالعينات المختبرة، وخاصة جسيمات ZnO-NPs، إلى تقليل بيروكسيد الدهون إلى مستويات مشابهة لمجموعة التحكم (3.10 ± 0.36 و 2.96 ± 0.32 نانومول/غ من البروتينات لـ ZnO-JP و ZnO-PG على التوالي)، مع زيادة ملحوظة في محتوى GSH ونشاط إنزيم CAT. كما أكد التحليل النسيجي لغشاء المعدة هذه الخصائص الوقائية للمعدة. يمثل هذا البحث إسهامًا مبتكرًا، حيث يؤكد على إمكانات جسيمات أكسيد الزنك النانوية المُخلّقة حيويًا في علاج قرحة المعدة. هناك حاجة إلى إجراء تجارب سريرية إضافية لتوضيح الآليات الأساسية وتقييم سلامتها في أعضاء أخرى.

الكلمات المفتاحية: الرمان (*Punica granatum L.*), العرعر الفينيقي (*Juniperus phoenicea* L), مغلي مائي، ZnO-NPs، قرحة المعدة.

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AA	Ascorbic Acid
APC	Analysis of Principal Component
AQE-JP	Aqueous Extract of *Juniperus phoenicea* L.
AQE-PG	Aqueous Extract of *Punica granatum* L.
BBC	β- Carotene Bleaching Assay
BHT	Butylated Hydroxytoluene
CAT	Catalase
COX	Cyclooxygenase
DMSO	Dimethyl sulfoxide
DPPH	2, 2-diphenyl-1-picryl- hydrazyl
DTNB	5, 5' -dithio-bis (2-nitrobenzoic acid)
FRAP	Ferric reducing antioxidant power assay
FTIR	Fourier Transmission Infra-Red
GPX	Glutathione peroxidase
GSH	Glutathione
GSSG	Reduced Glutathione
HE	Hematoxylin
IC 50%	Inhibitory concentration for 50% of activity
JCPDS	Joint Commette on Powder Diffraction Standards
LPO	Lipid peroxidation
MDA	Malondialdehyde
Mg/kg.bw	Milligram per kilogram of Body weight
mg Eq STDs/g DE	Milligrams Equivalent of used Standards per gramme of Dried Extract
NSAIDs	Non-steroidal anti-inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
PBS	Phosphate buffered saline
PG	Prostaglandin
PPIs	Proton Pump Inhibitors
RT	Room temperature

ROS	Reactive spices of Oxygen
SEM-EDX	Scanning Electron Microscopy with Energy Dispersive X-Ray
SOD	Superoxyde dismutase
TAC	Total Antioxidant Capacity
TBA	Thiobarbutiric acid
TBARs	TBA-reactive species
TCA	Trichloro-acetic acid
TCT	Total Condensed Tannins Content
TFC	Total Flavonoids Content
TPC	Total Polyphenols Content
UV-VIS	Ultraviolet-Visible
WHO	World Health Organization
XRD	X-Ray Diffraction
ZnO-NPs	Zinc oxide Nanoparticles
ZnO-JP	Zinc Oxide Nanoparticles of *Juniperus phoenicea* L. Extract
ZnO-PG	Zinc Oxide Nanoparticles of *Punica granatum* L. Extract

General Introduction

Digestive conditions constitute a serious global medical concern, profoundly affecting millions and imposing considerable burdens on healthcare systems worldwide. In 2019, these conditions accounted for approximately 2.27 billion cases and 2.56 million deaths worldwide, representing rises of 67.87% and 37.85%, respectively, since 1990 (Wang *et al.*, 2023).

Non-malignant upper gastrointestinal conditions, such as peptic ulcer disease, gastrointestinal issues, and gastroesophageal reflux disorder, are characterized by persistent inflammation and tissue injury. These disorders are prevalent and associated with significant morbidity, presenting a considerable burden to global health and the healthcare system in contemporary society (Bai *et al.*, 2024; Lu *et al.*, 2021). Non-malignant disorders, despite their considerable impact, frequently garner less study focus than malignant gastrointestinal diseases such as gastric cancer, which are prioritized due to their correlation with mortality (Clerx *et al.*, 2017). This mismatch emphasizes the necessity of addressing the research gap. It reinforces the significance of concentrating on illnesses that, although non-fatal, substantially diminish the quality of life and present problems to healthcare systems. These disorders are globally prevalent and can induce symptoms such as chronic pain and hunger, which substantially impair patients' quality of life. Moreover, we must acknowledge the economic cost imposed by non-malignant upper gastrointestinal illnesses (Shetty & Vishwanath, 2022). They not only increase direct medical expenses, including diagnosis, treatment, and hospitalization charges but also lead to indirect economic losses, including labor absenteeism and diminished productivity due to social withdrawal in certain patients stemming from the dread of symptom recurrence (Bai *et al*., 2024)**.** The significant illness burden of these nonmalignant disorders frequently coincides with low socioeconomic development and restricted healthcare access and efficiency. Conversely, new studies suggest that affluent socioeconomic regions or nations may also bear a disproportionately significant burden of these diseases. This gap indicates a complex interaction of causal factors, including lifestyle modifications, prevalent *Helicobacter pylori* infection, and genetic predisposition, all influencing these condition' prevalence and advancement (Bai *et al*., 2024)**.**

Peptic ulcer disorders (PUDs) are exceedingly common globally, prompting some academics to label them as the new epidemic of the 21st century (Beiranvand, 2022; Sumbul *et al.*, 2011). They are typically situated in the stomach and proximal duodenum, indicating acid-peptic damage to the digestive tract. Peptic ulcer diseases and their consequences, including perforation and hemorrhage, pose a substantial threat to the global population, being a significant cause of hospitalization and healthcare resource consumption worldwide (Xie *et al.*, 2022; Zhang *et al.*, 2023). In 2019, there were roughly 8.09 million prominent instances of PUDs, reflecting a 25.82% rise from 1990, which had 6.43 million prevalent cases from 1990 to 2019, the incidence of PUD cases rose from 2.82 million to over 3.59 million, reflecting a 27.3% rise in global occurrence instances of PUD (Xie *et al*., 2022). PUDs continues to be a significant global public health issue that requires our focus (Zhang *et al*., 2023).

Gastric ulcers are a chronic and recurrent disorder characterized by the intermittent genesis of lesions in the stomach's mucosal membranes (Shahzad *et al.*, 2024). Stomach ulceration appears to originate from multiple conditions, including inadequate blood flow to an organ, Crohn’s disease, hypersecretory problems (Zollinger–Ellison syndrome), cirrhosis, renal failure, and acute or chronic stress. Fortunately, the overuse of non-steroidal anti-inflammatory drugs (NSAIDs) and *H. pylori* infection are the primary contributors leading to stomach ulcers (Ahmad *et al.*, 2019). It is also influenced by individual lifestyles and choices, notably extreme alcohol consumption and extended psychological stress. Each of these factors has been implicated in the genesis of gastric ulcers (Shahzad *et al*., 2024). The global prevalence of *H. pylori* infection is approximately 50 percent, with the highest incidence observed in underdeveloped countries. It is predominantly observed in developing nations and among individuals in lower socio-economic and educational groups (Sun *et al.*, 2023). Since a protracted and persistent *H. pylori* infection is linked to over 90% of stomach malignancies, the International Agency for Research on Cancer (IARC) classified it as a class 1 carcinogen in 1994 (Smith *et al.*, 2021; Smith *et al.*, 2024).

Following the extraction of salicylate from willow bark in the 1830s and after discovering aspirin (acetylsalicylate) in 1897, NSAIDs have attained blockbuster status in the pharmaceutical business. Subsequently, successive generations of scientists have diligently contributed to advancing these 'miracle medications.' Currently, NSAIDs rank among the

most prevalent over-the-counter medications globally, accounting for 5% of all prescribed pharmaceuticals (Bindu *et al.*, 2020). Show up as standard-of-care analgesics for acute pain or inflammatory illnesses, including pain from rheumatic diseases, osteoarthritis, postoperative pain, bursitis, gout, dental pain, headache, menstrual pain, and dysmenorrhea (Nalamachu & Wortmann, 2014).

About 30 million individuals consume NSAIDs daily. The number has increased markedly due to the rising utilization of over-the-counter and prescription NSAIDs. The effectiveness of NSAIDs is unquestionable; nonetheless, their side effects are concerning. These pertain primarily to cardiovascular, renal, hepatic, and gastrointestinal tissues (Nalamachu & Wortmann, 2014). Recent scrutiny has focused on cardiovascular adverse effects; however, the prevalence and severity of gastrointestinal injury remain a significant issue (Bjarnason *et al.*, 2018). This issue has been exacerbated by the growing popularity of self-medication, which has become a "fashionable trend" increasingly adopted by individuals. Individuals attempt to figure out the nature of their suffering while trying to diagnose it and decide on suitable remedies for either therapy or prevention, all without seeking medical consultation. Globally, about 50% of all medications are administered, delivered, or marketed improperly, and 50% of patients do not adhere to the correct usage. Improper medication usage adversely affects patients and leads to resource wastage. This improper usage may manifest as excessive or inappropriate intake of prescription or over-the-counter medications (Boumelik *et al.*, 2023).

Phytomedicines, supported by traditional knowledge, have been relied on globally for centuries and are gaining recognition for their therapeutic efficacy in modern healthcare, mainly due to the emergence of various side effects associated with conventional drugs for numerous ailments. Medicinal plants have been considered as the primary supplier of potentially novel pharmaceuticals (Kuna *et al.*, 2019). In the past five years, the predominant pharmacological agents for managing peptic ulcers have been proton pump inhibitors (PPIs, such as lansoprazole and omeprazole) and H2-receptor antagonists (H2RAs, including ranitidine and famotidine), alongside antibiotic therapy for the eradication of *H. pylori*. Even so, they induce numerous detrimental effects. Proton pump inhibitors may induce hypomagnesemia, hypersensitivity, cutaneous lupus erythematosus,

fractures associated with osteoporosis, acute renal injury, and a heightened susceptibility to gastrointestinal infections. Ranitidine may cause cancer in humans due to the existence of impurities that contain N-nitroso-dimethylamine (Song *et al.*, 2020). On the other hand, the standard therapy for *H. pylori* eradication, which includes broad-spectrum antibiotics and proton pump inhibitors, has shown a notable reduction in efficacy, with eradication rates decreasing to 70%, significantly lower than the 90% standard established by the Maastricht Consensus (Chitas *et al.*, 2024; Safarov *et al.*, 2019; Smith *et al*., 2024). The decrease is mainly attributable to antibiotic resistance (Pujari *et al.*, 2024), inadequate patient adherence to complicated treatment protocols, and the limited stability and availability of these medications in the stomach milieu. Moreover, broad-spectrum antibiotics frequently disturb gut microbiota, resulting in dysbiosis and adversely affecting health. As a result, the WHO has designated *H. pylori* as one of the 12 most significant antibiotic-resistant bacteria, necessitating the urgent development of innovative therapies (Chitas *et al*., 2024; Safarov *et al*., 2019). In light of this, it is crucial to underline that although these medications are well-established for treating PUDs, they do not prevent a recurrence (Araujo de Lima *et al.*, 2021). Consequently, the search of pharmacologically active substances through the screening of numerous plant extracts led to the identification of more effective and safer alternative anti-ulcer medicines for treating peptic ulcer diseases, exhibiting fewer or no side effects (Kuna *et al*., 2019).

One of the most well-known branches of nanotechnology study is nano-phytotherapy. It employs nanotechnology to create highly focused therapeutic interventions for illness prevention and therapy. In clinical practice, nanoparticles are utilized to treat kidney conditions, tuberculosis, bacterial and viral infections, diabetes, skin-related disorders, Alzheimer's disease, various cancers, and the formulation of COVID-19 vaccines (Sim & Wong, 2021). The gastrointestinal tract is an attractive target system for the implementation of nanotechnology (Sahu *et al.*, 2021). It is the site of pharmaceutical absorption. Pure herbal medications are frequently seen as less efficacious than pure ingredients, which are primarily shown to have diminished intestinal absorption when taken orally. Nevertheless, nanoparticle plant extracts exhibit enhanced stability in high-protein settings and contribute to improved target selectivity (Lim *et al.*, 2022). Nanoscale devices of under 50 nanometers in diameter can readily infiltrate most cells, but devices

smaller than 20 nanometers can effortlessly traverse blood vessels during circulation throughout the body. Due to their small dimensions, nanoscale devices can readily interact with biomolecules on cellular surfaces and within the intracellular environment. Consequently, the nanoscale systems above are practical for the treatment of ulcers. (Mantry *et al.*, 2022).

The primary aim of this research is to bridge the gap between traditional knowledge and modern scientific validation in the management of gastric ulcers. This study seeks to document and evaluate traditional herbal remedies used by local populations in Algerian Sahara for controlling gastric ulcers through an ethnopharmacological investigation. Building on this, the experimental component aims to confirm the therapeutic potential of selected herbal remedies by employing innovative approaches such as the green synthesis of phytogenic zinc oxide nanoparticles (ZnO-NPs) using a traditional herbal preparation comprising two well-known medicinal plant species in our society *Punica granatum* L. and *Juniperus phoenicea* L. by comparing the effects of the aqueous extracts of these plants and their ZnO-NPs derivatives on NSAIDs-induced gastric ulcers in a rat model, this study endeavors to validate their traditional use, and explore their potential as effective and sustainable alternatives for gastric ulcer therapy. This Thesis is structured into two main parts:

The first part; of a bibliographic nature, is divided into four distinct chapters. These chapters provide the theoretical foundations necessary for a thorough understanding of the pathophysiological mechanisms associated with gastric ulcers. They successively address:

- The anatomical and physiological foundations of the stomach.
- The underlying mechanisms of gastric ulcer development, particularly those induced by non-steroidal anti-inflammatory drugs.
- A review of classical and alternative therapeutic approaches.
- Recent perspectives in Nanotechnology, green synthesis, and applications of Metal oxides nanoparticles in the treatment of peptic ulcers conditions.

The second part is dedicated to the experimental study and includes three major chapters:

- Ethno-pharmacological Study. This chapter describes an ethnopharmacological survey conducted in regions of the Algerian Sahara. The main objective of this study is to collect and document valuable information on the traditional remedies used by the local population to manage and treat gastric ulcers.
- The second chapter outlines the methodological approaches employed in this study. It includes the preparation of aqueous extracts from the selected medicinal plants and the green synthesis of zinc oxide nanoparticles (ZnO-NPs) from these traditional remedies. The chapter primarily focuses on evaluating their antioxidant, anti-inflammatory, antibacterial, and gastroprotective activities using an indomethacin-induced gastric ulcer model.
- Results and discussions; The last chapter presents a thorough analysis of the results obtained. It highlights the therapeutic effects of aqueous extracts and ZnO-NPs prepared from the above-mentioned medicinal species, comparing them to experimental models and contextualizing them with current knowledge. The discussions allow for the evaluation of the scientific and therapeutic implications of the obtained data, while identifying future research perspectives in this field.

Review of literature

CHAPTER I
STOMACH ANATOMY AND PHYSIOLOGY

"The stomach plays a crucial role in digestion, nutrient absorption, and protection. Its mucosal barrier defends against acidic and enzymatic damage, while proper regulation of gastric functions maintains homeostasis. Disruptions in these protective mechanisms can lead to ulcers. Therefore, understanding stomach anatomy and physiology is essential before assessing the gastroprotective effects of any tested sample."

I.1. Macroscopic Anatomy

The stomach is a muscular, dilated, cylindrical, J-shaped organ situated in the epigastric and left hypochondriac sections of the abdomen, aligned with the first lumbar vertebra (Wilson & Stevenson, 2019). It is the digestive organ where food transits from the esophagus and is subsequently fragmented before its nutrients are absorbed in the small intestine (Ravisankar *et al.*, 2016). The stomach displays two curvatures that delineate its inner and outer margins. They are referred to as the lower and greater curves, respectively (Stieger-Vanegas & Frank, 2018). It participates in mechanical and chemical digestion, the retention of food that has been partially digested, and the controlled availability to the small intestine. It can be categorized into functional and anatomical regions corresponding to these roles (Ravisankar *et al*., 2016). The stomach can be anatomically categorized into four macroscopic regions: the cardiac, fundus, body (corpus), and pyloric sections. The esophagus connects to the cardiac section of the stomach, whereas the pyloric section connects to the small intestine (McQuilken, 2021). The corpus constitutes the most significant section of the stomach and is inhabited by oxyntic glands (Engevik *et al.*, 2020).

I.2. Microscopic Anatomy

The stomach incorporates 5 concentric tissue layers **(Fig. I.1)** (Okamoto *et al.*, 2018): (1) the mucosal epithelium, which lines the stomach lumen; The stomach's mucosal lining consists of a uniformly arranged simple columnar epithelium (Wilson & Stevenson, 2019). Surface mucous cells (SMs) constitute the gastric pits (GPs), which extend into elongated, branched, tubular glands, imparting a foliate appearance to the gastric mucosa, called gastric foveolae. Each gland comprises specific sections from the surface downward: the stomach pit, isthmus, neck, and base (Di Mario & Goni, 2014)**.** The stomach is segmented into three glandular sections, each comprising distinct cell types: cardiac glands in the cardia, oxyntic glands in the fundus and body, and antral glands in the pyloric region

(Schubert & Peura, 2008). (2) Muscularis mucosae, a tiny layer of smooth muscle; (3) submucosa, comprising connective tissue and blood vessels; (4) tunica muscularis, wherein most segments of the gastrointestinal system feature two layers of muscle facilitating the movement of luminal contents. The stomach comprises three muscular layers facilitating food movement: an exterior longitudinal layer, a middle circular layer, and an interior oblique layer exclusive to the stomach (Feher, 2017; Sensoy, 2021). The serosa is oriented towards the peritoneal cavity (Brandstaeter *et al.*, 2019).

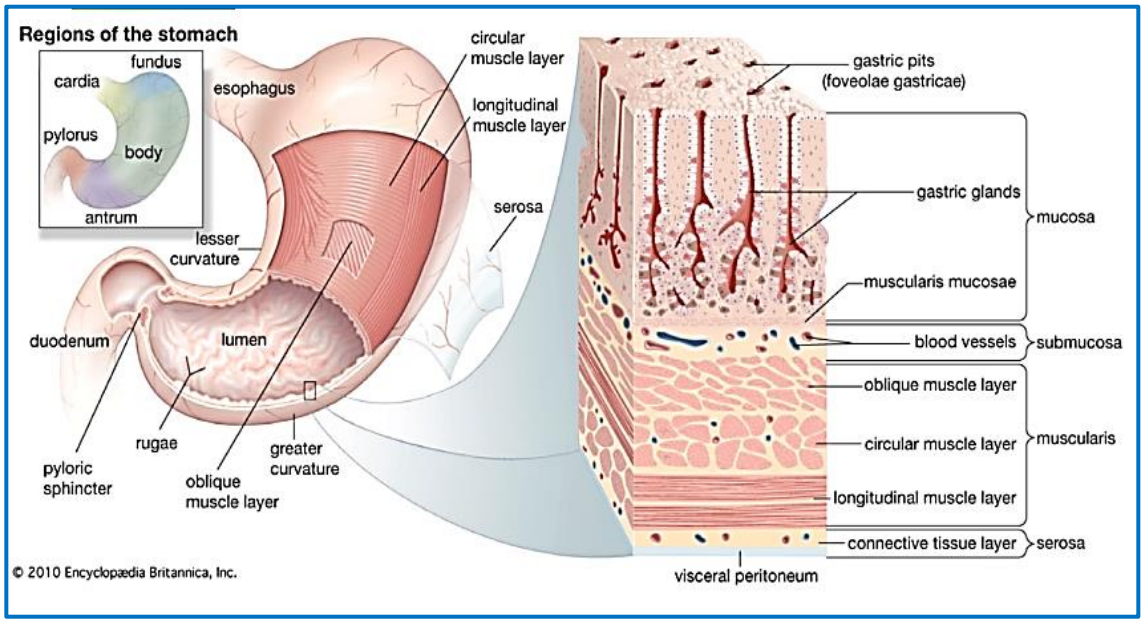

Figure I.1. Anatomical configuration of the stomach, featuring a sectional view of the gastric wall that highlights gastric glands inside the mucosa and the different tissue layers (Brandstaeter *et al*., 2019)

Gastric glands as shown in **Fig. I.2**, on a microscopic level, consist of three main varieties of secretory epithelial cells (Okamoto *et al*., 2018); Mucous neck cells generate a mucous glycoprotein different from that surface epithelial cells secreted, Chief cells serve as the leading suppliers of pepsinogen and leptin (Di Mario & Goni, 2014). In contrast, the many acid-secreting parietal cells are distributed along the entire gland length, with a higher concentration in the neck region. Due to their considerable size and relative prevalence, parietal cells constitute approximately 50%–60% of the mass of the secretory mucosa. The parietal cells also release intrinsic factors, a glycoprotein that complexes with vitamin B12

to facilitate optimal absorption of B12 (Okamoto *et al*., 2018). Adjacent to the glandular epithelial cells, many endocrine and paracrine cells are also seen. Enterochromaffin-like (ECL) cells release histamine to activate parietal cells through a paracrine mechanism (Schubert, 2015). D cells secrete the hormone somatostatin, which inhibits HCl secretion (Schubert, 2017). G cells release the hormone gastrin, which functions as a secretagogue for ECL cells and a trophic factor for parietal cells (Okamoto *et al*., 2018). The gastric glands exhibit stem cells in the neck area, where the glands connect to the pits. These stem cells are crucial for regenerating epithelial cells compromised by the stomach's harsh environment, hence significantly safeguarding the underlying layers (McQuilken, 2021).

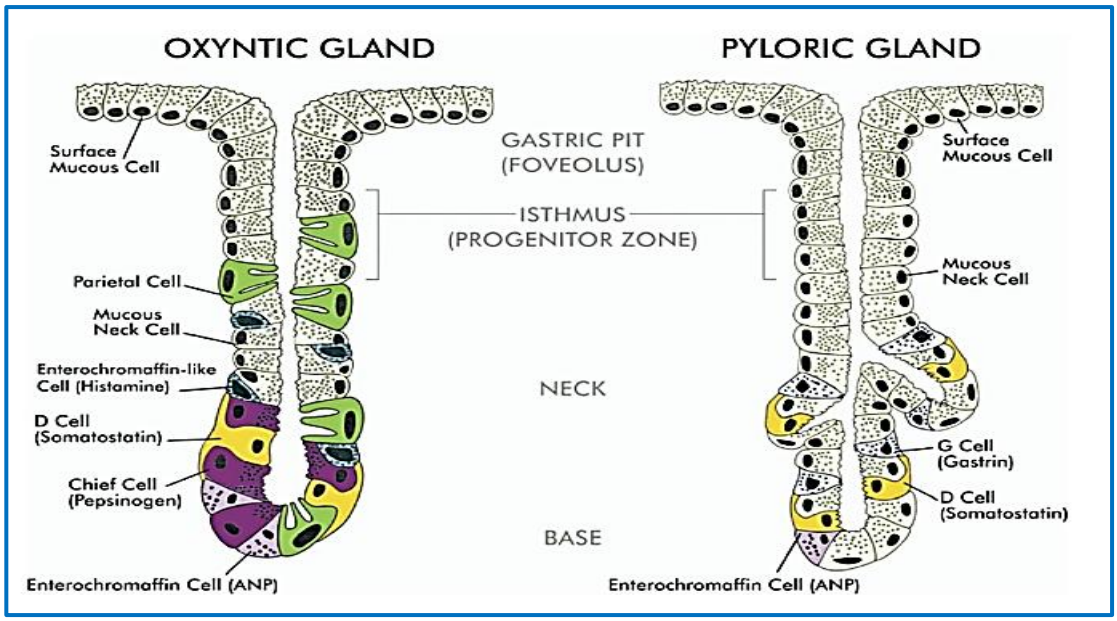

Figure I.2. Illustration of a gastric gland, highlighting the numerous cellular types within the gastric epithelium (Schubert & Peura, 2008)

I.3. Regulation of Gastric Acid Secretion

The stomach releases around 2–3 liters of gastric juices daily, comprising gastric acid, salts, and digestive enzymes such as pepsin and lipase (Li *et al.*, 2020). The gastric fluid is isosmotic with interstitial fluid and may possess a pH as low as one. Hydrochloric acid (HCl) serves an immunological function by killing germs and a digestive function by breaking down consumed proteins, thereby creating an ideal environment for digestive enzymes (McQuilken, 2021). Acid secretion stimulation is typically categorized into three

interdependent phases **(Fig. I.3)**: cephalic, gastric, and intestinal (Isackson & Ashley, 2017).

I.3.1. Cephalic phase

The vagus nerve exclusively regulates the cephalic phase of acid secretion, linking the brain's higher functions to gastric secretion through cholinergic/vagal processes. This phase commences before food enters the stomach, as inputs like visual, olfactory, and gustatory cues activate the release of gastrin hormone (Browning & Travagli, 2014; Feher, 2017; Sensoy, 2021). The cephalic phase constitutes roughly 30–50% of the overall postprandial acid secretion (O'Connor & O'Morain, 2014).

I.3.2. Gastric phase

The predominant secretion arises during the gastric phase, when food is present in the stomach (Di Mario & Goni, 2014). Alongside the ongoing vagal impacts from the cephalic phase, secretion is further enhanced by mechanical and chemical stimuli resulting from the meal's presence in the lumen (Di Mario & Goni, 2014). The parietal cell possesses a minimum of three types of activating receptors on its basolateral membrane: H2 receptors for histamine, M3 receptors for acetylcholine, and CCK-B receptors for gastrin, as illustrated in the figure. Parietal cells synthesize stomach acid when stimulated by these receptors (Isackson & Ashley, 2017; Schubert & Peura, 2008). The histamine receptors function by elevating intracellular cAMP, while the muscarinic (M3) and gastrin receptors raise intracellular Ca2+ concentrations. Both cAMP and Ca2+ function through protein kinases to enhance the transport of acid into the gastric lumen (Schubert & Peura, 2008). The synthesis of gastric acid in the stomach is meticulously controlled by positive regulators and inverse feedback pathways. This process involves four cell types: parietal cells, G cells, D cells, and enterochromaffin-like cells (ECL cells). Additionally, the terminals of the vagus nerve and the intramural neural plexus within the digestive system substantially affect secretion (Schubert, 2017; Schubert & Peura, 2008). Gastrin is released by antral G cells into the bloodstream in response to intraluminal food peptides. In the stomach body, gastrin circulates from the blood arteries into the submucosal tissue of the fundic glands, where it attaches to gastrin-CCK-B receptors on parietal cells and

enterochromaffin-like (ECL) cells (Schubert, 2017). The vagus nerve activates postganglionic neurons of the enteric nervous system to secrete acetylcholine (ACh), which interacts with M3 receptors on parietal and ECL cells. Activation of ECL cells by gastrin (CCK-B receptor) or acetylcholine (M3 receptor) promotes the secretion of histamine (Chen *et al.*, 2023).

Stomach acid is secreted via the canalicular membrane of parietal cells by the H+, K+ - ATPase (proton pump) into the stomach lumen (Geibel & Wagner, 2006). The hydrogen ions originate from a process facilitated by carbonic anhydrase, which concurrently generates bicarbonate. Bicarbonate is expelled from the parietal cell by a basolateral bicarbonate-chloride exchanger, resulting in an elevation of blood pH as it exits the stomach, a phenomenon referred to as alkaline tide. The entering chloride exits the apical surface of the cell through chloride channels to generate hydrochloric acid (McQuilken, 2021; O'Connor & O'Morain, 2014). The acidic pH in the stomach facilitates the activation of the proteolytic enzyme pepsin, which is secreted in its inactive precursor form, pepsinogen, by the main cells of gastric glands. The release of pepsinogen is facilitated by vagal stimulation, which occurs throughout the cephalic and Gastric phases of digestion (Isackson & Ashley, 2020; McQuilken, 2021).

I.3.3. Intestinal phase

Gastric acid secretion is meticulously regulated through a highly coordinated interplay among many effector, sensory, and feedback circuits, as both excessive and insufficient acid levels can lead to health disorders (Schubert, 2015). Acid secretion must ultimately be inhibited. Antral D cells are prompted to secrete somatostatin due to increased intraluminal H+ concentration and the release of CCK into the bloodstream by duodenal cells in reaction to proteins and lipids (Schubert & Peura, 2008). The somatostatin binding to receptors on neighboring antral G cells suppresses further gastrin secretion (Srikanta, 2010). Somatostatin and prostaglandins function to suppress acid secretion (O'Connor & O'Morain, 2014).

I.4. Mucus secretion as a defensive factor

Due to the extreme acidity of gastric juice (pH 1.5–3.5), the stomach requires a mechanism to protect against auto-digestion (O'Connor & O'Morain, 2014). The mucus-bicarbonate

layer plays a distinctive role due to its gelling properties, creating a physical barrier that protects the epithelium from self-digestion by HCl and pepsin. It encompasses the mucosal surface and facilitates acid neutralization, preserving the basophilic pH. Mucus is a viscoelastic hydrogel with a 200 to 300 nanometers thickness, primarily composed of mucin molecules synthesized by goblet cells (Isackson & Ashley, 2020; McQuilken, 2021). It possesses antioxidant and protective properties for epithelial surfaces against dehydration, shear stress, and infections while enhancing the stomach mucosa's defense against pathogens and gastrointestinal irritants (Isackson & Ashley, 2017, 2020).

The gastric mucus barrier has two layers: a highly adhering inner layer and a loosely adherent outer layer. This barrier comprises water (≤ 90%), various salts, carbohydrates, lipids, mucins, and lectins. The fundamental constituents of mucus are mucin glycoproteins and lectins. Mucus is highly permeable to H^+ and HCO^{3-} ions, inhibiting the majority of HCO^{3-} released by epithelial cells from interacting with acid, maintaining a practically neutral pH gradient. The pH gradient on the mucosal surface is nearly neutral owing to the retention of HCO^{3-}. HCO^{3-} is an inorganic alkaline compound that neutralizes surplus stomach acidity. The transformation of CO_2 to HCO^{3-} is facilitated by carbonic anhydrase (metalloenzymes) under low pH conditions and hypoxia in the stomach mucosa (Araujo de Lima *et al*., 2021) Prostaglandin E synthase (PGES) in the stomach catalyzes the conversion of prostaglandin H2 to prostaglandin E2 (PGE2), a crucial process. PGE2 elevates intracellular calcium and cyclic adenosine monophosphate (AMP), enhancing bicarbonate secretion (Yandrapu & Sarosiek, 2015).

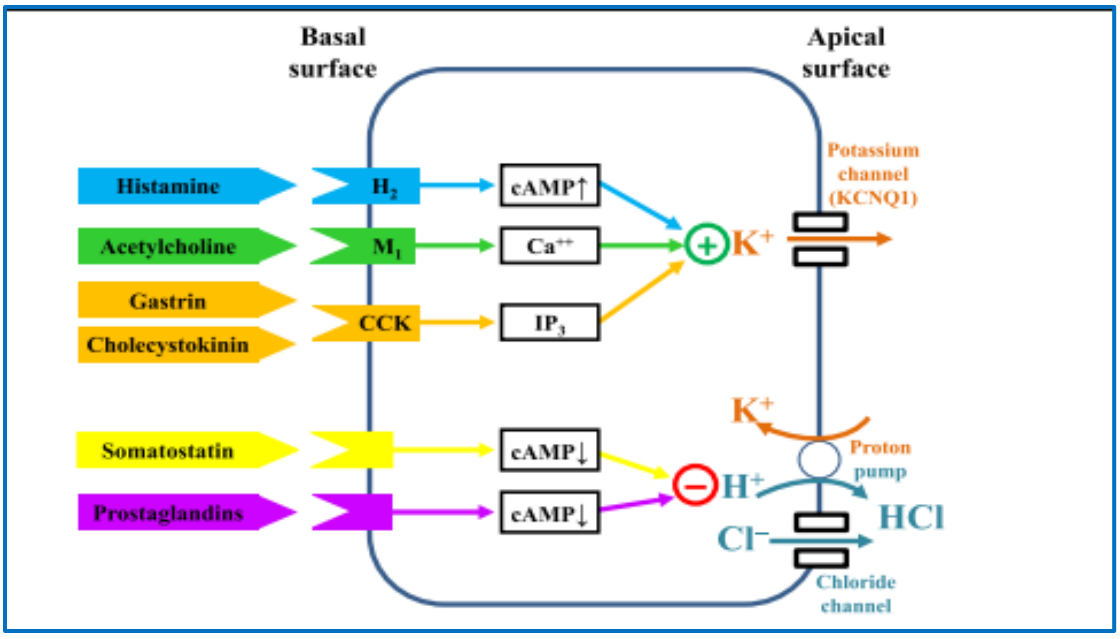

Figure I.3. A concise overview of the physiology of stomach acid secretion (Aronson, 2016)

CHAPTER II
GASTRIC ULCERS

II.1. Peptic Ulcers

The term peptic originates from the Greek word peptikos, signifying digestion (Beiranvand, 2022). Ulcers describe themselves as a disruption in the mucosa gauging at least 5 mm in diameter, penetrating through the muscularis mucosa into the submucosa or deeper, resulting from an imbalance between the aggressive acidic and proteolytic nature of gastric juice and the mucosa's capacity for withstanding it (Hunt *et al.*, 2015; Ravisankar *et al*., 2016). These ulcers are categorized into two prevalent categories. A peptic ulcer in the stomach is called a gastric ulcer, whereas an ulcer in the duodenum is termed a duodenal ulcer (Mittal *et al.*, 2020).

II.2. Clinical Presentation

The main characteristic of peptic ulceration is epigastric pain; nevertheless, additional dyspeptic symptoms may also manifest (Shiotani & Graham, 2002; Waller & Sampson, 2018). The Manifestation of a stomach ulcer may encompass one or more of the following: Epigastric pain is closely associated with mealtimes, decreased appetite and weight reduction, abdominal distension and fullness, and nausea accompanied by excessive vomiting (Ithape *et al.*, 2023), Hematemesis (the expulsion of blood through vomiting) may arise from hemorrhage originating from a stomach ulcer or esophageal injury resulting from severe or persistent vomiting (Kempenich & Sirinek, 2018),or Melana (dark, malodorous feces resulting from the presence of oxidized iron derived from hemoglobin).

Ultimately, in uncommon instances, an ulcer may result in gastrointestinal complications that encompass hemorrhage and perforation, resulting in acute peritonitis and severe, stabbing pain, necessitating urgent surgical intervention (Srivastav *et al.*, 2023).

II.3. Etiology and Pathophysiology

Gastric ulcers typically occur due to an imbalance in the protective systems that safeguard the gastroduodenal mucosa from an increased amount of acid and pepsin in the lumen (Shiotani & Graham, 2002). The utilization of NSAIDs and *H. pylori* infection are the primary factors contributing to peptic ulcer formation. It is also influenced by individual

lifestyle. All these components have been impaired in the etiology of peptic ulcer (Ahmad *et al*., 2019).

II.3.1. *H. pylori* infection

Marshall and Warren were the pioneers in culturing the bacterium associated with gastritis. In the early 1980s, they informed other researchers about the potential involvement of bacterial infection in the onset of gastritis, peptic ulcers, and stomach cancer (Shiotani & Graham, 2002; Zahid *et al.*, 2020). A significant risk factor linked to peptic ulcers is infection of the stomach and duodenum by the Gram-negative bacteria *H. pylori* (Woods & Carey, 2017). *H. pylori* colonization is not a disease; nevertheless, an infection may result in multiple clinical problems within the upper gastrointestinal tract (Chatterjee *et al.*, 2012). Responsible for 90% of duodenal ulcers and 70% to 90% of stomach ulcers, *H. pylori infection* is prevalent among those of lower socioeconomic class and is often contracted during childhood (Joshi *et al.*, 2024). The majority of patients are asymptomatic; hence, infection and chronic gastritis may persist for several years (Woods & Carey, 2017). *Helicobacter pylori* is a spiral-shaped bacterium measuring 2 to 4 mm in length, characterized by one or more sheathed flagella and exhibiting significant urease activity (Woods & Carey, 2017). *H. pylori* are trophic for gastric mucosa and may not only endure but even flourish in the inhospitable environment of the stomach. A defining hallmark of this disease is the production of urease, which was the initial virulence factor examined (Chitas *et al*., 2024). This enzyme may elucidate the remarkable capacity of bacteria to inhabit the stomach mucosa and endure in an acidic environment. Due to the abundant urea in the ecological niches of these bacteria, they facilitate urea hydrolysis, resulting in the production of ammonium (NH_3), carbon dioxide, and hydroxyl ions (Shiotani & Graham, 2002; Waller & Sampson, 2018). Through this technique, *H. pylori* neutralize the surrounding gastric acid, so safeguarding itself from the stomach's high acidity. Conversely, while the neutralization of stomach acid is advantageous for bacteria, the compounds produced by urease activity are detrimental to gastric epithelial cells. The generated ammonium interacts with OCl^- produced by active neutrophils, resulting in the formation of the highly poisonous monochloramine (NH_2Cl) in the stomach, which is indicative of *H. pylori* infection (Ahmad *et al*., 2019). Inhibition of *H. pylori* urease has

been demonstrated to markedly reduce this toxicity, indicating that ammonia is at least largely accountable for the cytotoxicity associated with this bacterium. Furthermore, hydroxide ions are regarded as harmful to stomach epithelial cells (Maria Izabel & Francisca Cléa, 2011). In addition to urease activity, another significant virulence feature of *H. pylori* is its motility, enabling the bacterium to swiftly navigate through mucus to evade hostile environments and access preferred locations **(Fig. II.1)** (El-Assaad *et al.*, 2019)**.**

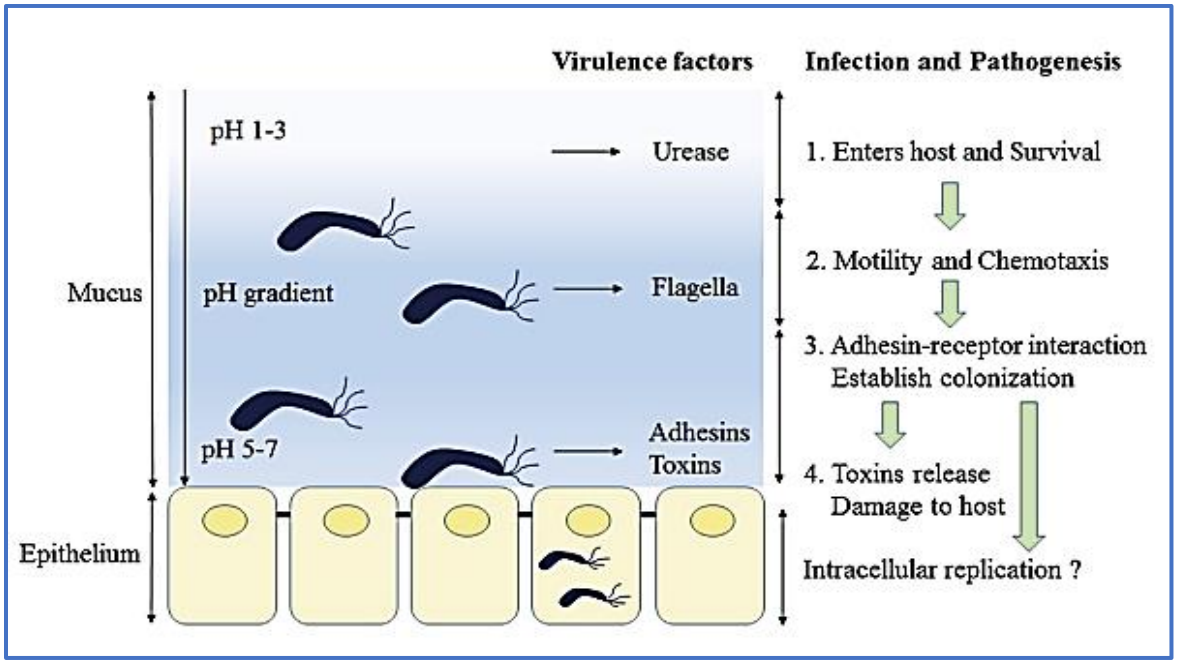

Figure II.1. Graphical visualization of *Helicobacter pylori* infection and pathogenesis (Kao *et al.*, 2016)

Virulent *H. pylori* strains adhere to the gastric epithelium, releasing various effector proteins and toxins, such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), which compromise membrane integrity and prompt host cells to secrete toxic proteins, cytotoxins, platelet-activating factor, and lipopolysaccharides, all of which exacerbate damage to the gastric mucosa (Kao *et al*., 2016; Maria Izabel & Francisca Cléa, 2011)**.** These modifications would expedite apoptosis and proliferation inside the mucosal layer. *H. pylori* induce an inflammatory response characterized by the presence of

neutrophils, lymphocytes, plasma cells, and macrophages in the mucosal layer, leading to degeneration and damage of epithelial cells (Ahmad *et al*., 2019; Sen *et al.*, 2009).

II.3.2. NSAIDs-Induced gastric ulcer

NSAIDs are prescribed indiscriminately for the management of pain, fever, inflammation, rheumatic conditions, and cardiovascular diseases due to their analgesic, antipyretic, and anti-inflammatory properties (Beiranvand, 2022). NSAIDs can be categorized into salicylates, aryl and hetero-arylacetic acid derivatives, indole/indene acetic acid derivatives, anthranilates, and oxicams (enol acids) based on their chemical structure **(Fig. II.2.)** (Bindu *et al*., 2020).

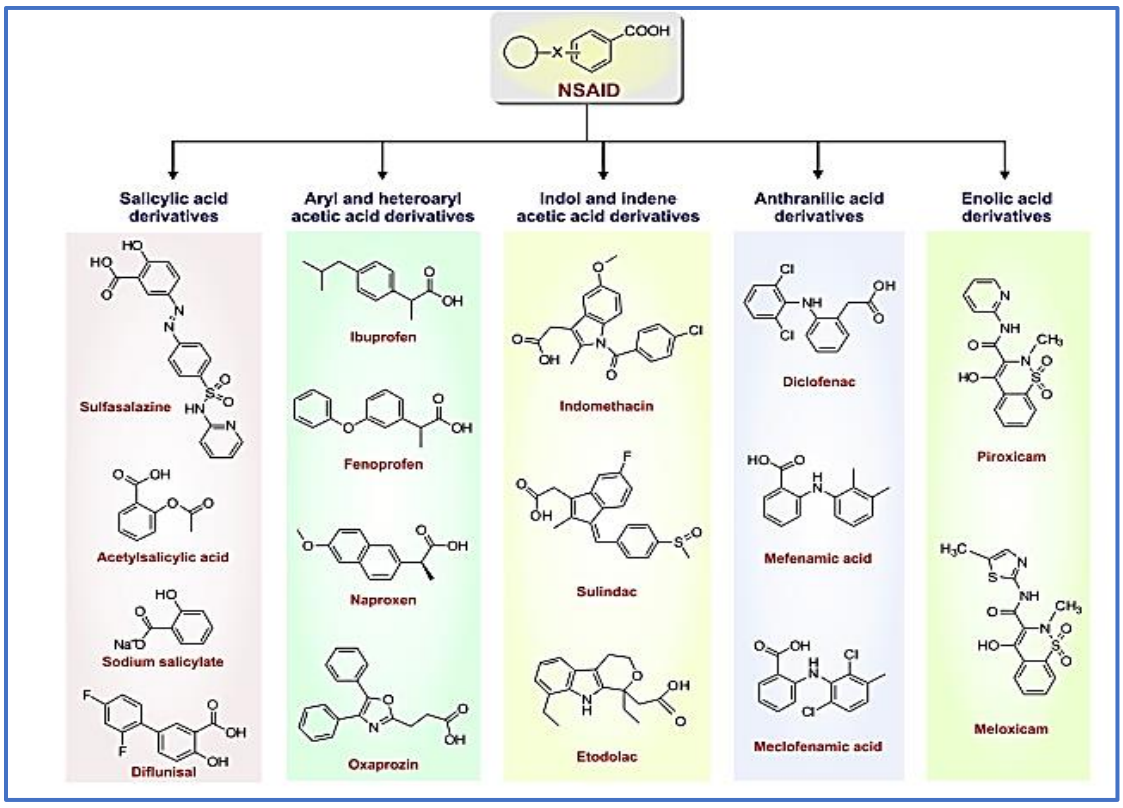

Figure II.2. Categorization of Non-Steroidal Anti-Inflammatory Drugs Depending on Structure (Bindu *et al*., 2020)

Extended use of these pharmaceuticals may lead to numerous detrimental gastrointestinal consequences, including gastric erosions, gastric or duodenal ulcers, and serious problems such as gastrointestinal hemorrhage and perforation (Sen *et al*., 2009). The pathogenesis

of these issues is mainly attributed to the action of NSAIDs on prostaglandin (PG) synthesis from arachidonic acid by inhibiting the enzyme cyclooxygenase (COX) (Hamid Khan *et al.*, 2023; Hnepa *et al.*, 2021). NSAID-induced ulcers are becoming more prevalent due to the widespread and rising consumption among our elderly demographic (Shiotani & Graham, 2002). NSAIDs can exert their pathophysiological effects on stomach tissues through two mechanisms;

II.3.2.1. PG-dependent NSAID-induced gastric injury

NSAIDs stop cyclooxygenase enzymes (COX-1 and COX-2) from working (**Fig. II.3)**, which stops arachidonic acid from changing into prostaglandins (Ithape *et al*., 2023; Matsui *et al.*, 2011). Prostaglandins serve as protective agents in the mucosa, preserving its integrity and enhancing nearly all mucosal defensive systems. A cluster of prostaglandin receptors (EP) 1–4 contributes to gastric protection (Beiranvand, 2022). They regulate the circulation of blood within the mucosa and the synthesis of acid, mucus, and bicarbonate. Recent animal studies indicate that the inhibition of both COX-1 and COX-2 is essential for the development of gastric ulcers. The outcome questions the notion that alone COX1 fulfills a housekeeping function in the stomach. New research suggests that both COX-1 and COX-2 may help make prostaglandins and keep the integrity of the mucosa in the stomach (Takeuchi, 2012; Wallace, 2001). COX-2 functions as a supplementary mechanism by reinstating prostaglandin levels when COX-1 is inhibited (Ahmad *et al*., 2019; Bjarnason *et al*., 2018). Moreover, prostaglandins inhibit the adhesion of mast cells, leukocytes, and platelets to the endothelium of blood vessels. These medications stimulate the synthesis of prostaglandins. They inhibit the circulation of blood to the mucosa, the synthesis of mucus and bicarbonate, the regeneration of epithelial cells, and the aggregation of platelets by obstructing the creation of thromboxane (Matsui *et al*., 2011). NSAIDs inhibit the activity of cyclooxygenase enzymes; they also activate neutrophils, induce local reactive oxygen species (ROS) production, and elevate lipid peroxidation levels. All of these result in injury to the gastric lining. Gastric acid exacerbates mucosal damage caused by NSAIDs by deepening superficial lesions, inhibiting platelet aggregation, and impeding wound healing (Ithape *et al*., 2023).

II.3.2.2. PG independent NSAID-induced stomach injury

The mechanism of NSAID-induced mucosal damage that is unrelated to systemic prostaglandin deficit centers around local damages caused by these drugs. The vast majority of NSAIDs are weak organic acids (Gelberg, 2018). In the stomach fluid (pH 2), they are non-ionized and lipid-soluble. These NSAIDs infiltrate gastrointestinal mucosal epithelial cell walls into the cytoplasm, where the pH is neutral. At neutral pH (pH 7.4), NSAIDs are transformed into a re-ionized and significantly lipophobic state. Consequently, NSAIDs become sequestered and accumulate within cells, resulting in cellular damage. The mechanisms by which NSAIDs cause localized harm to mucosal cells are yet to be clarified; nonetheless, *in vitro* studies suggest that mitochondria are the principal target of NSAIDs, as addressed in subsequent sections (Bindu *et al*., 2020). However, this 'trapping' notion may not apply to the small intestinal mucosa, where luminal pH is nearly neutral. Given the *in vitro* experimental findings indicating that NSAIDs are absorbed into small intestine cells at neuronal pH, we propose that "trapping" may not be critical for causing minor intestinal injuries. Still, it may exacerbate the severity of injury by enhancing NSAID absorption (Matsui *et al*., 2011). Administered NSAIDs impede or uncouple oxidative phosphorylation, resulting in the dissipation of the mitochondrial transmembrane potential (MTP). This process facilitates the release of cytochrome c from the mitochondrial intermembranous space into the cytosol and the generation of reactive oxygen species (ROS) such as superoxide ($O2^{\bullet-}$) and hydrogen peroxide (H_2O_2). Consequently, this triggers the activation of caspase nine and caspase 3, along with cellular lipid peroxidation, ultimately leading to cellular apoptosis (Chinmay, 2023; Gelberg, 2018). The disconnection of mitochondria also reduced intracellular ATP levels, caused Ca2+ leakage from mitochondria, induced cellular osmotic imbalance, and compromised control over intracellular junctions, leading to heightened permeability and eventual mucosal injury. It may lead to localized damage, accelerated epithelial cell necrosis, superficial bleeding, and erosions (Bindu *et al*., 2020; Bjarnason *et al*., 2018)

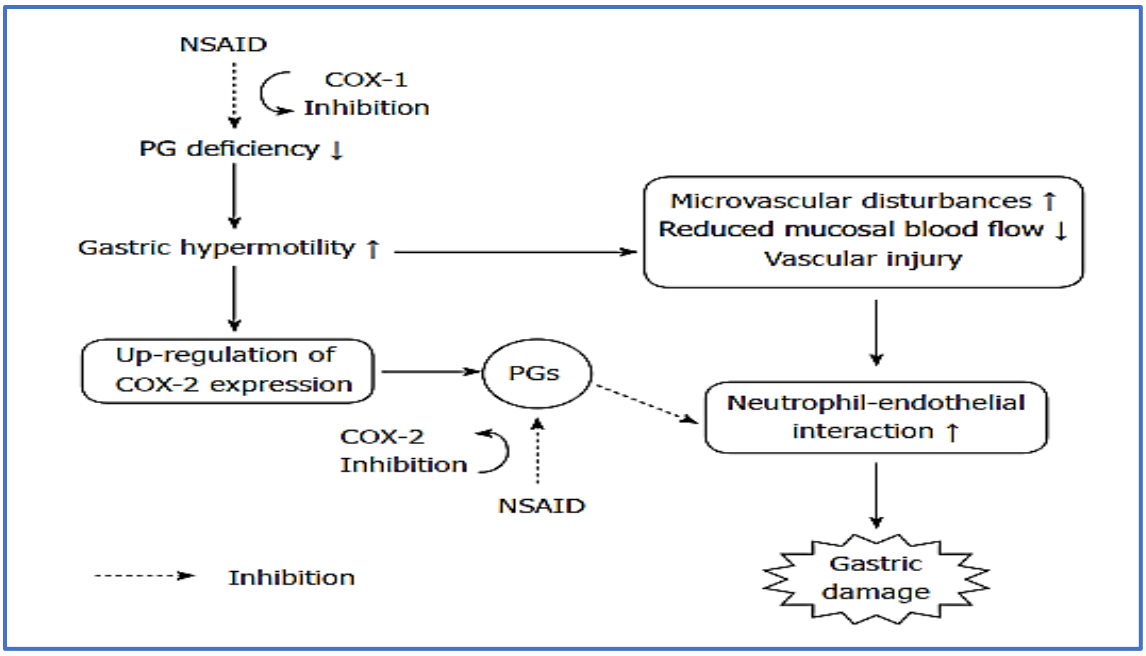

Figure II.3. Working hypothesis on the roles of COX-1 and COX-2 in the pathogenic mechanism of non-steroidal anti-inflammatory drug-induced gastric damage (Takeuchi, 2012)

Other therapeutic agents that rarely associated with gastric erosive and/or inflammatory lesions include chemotherapeutic, antimicrobial, anticoagulant, cardiovascular drugs bisphosphonates, selective serotonin reuptake inhibitors and spironolactone (Engevik *et al*., 2020; Waller & Sampson, 2018).

II.4. Gastric ulcer and risk factors

Mucosal lesions in the stomach lining mark gastric ulcers. Genetic predisposition, environmental influences, and many triggering agents, including *H. pylori* infection, NSAID consumption, and excessive gastric acid production, can influence them (Anmol *et al.*, 2023; Pujari *et al*., 2024).

II.4.1. Genetic and Ethnic Factors

A familial history of peptic ulcer disease, particularly among first-degree relatives, indicates a hereditary predisposition. Particular genetic variants affect an individual's vulnerability to peptic ulcers. Specific ethnic groups, such as African, American, and

Hispanic populations, demonstrate heightened susceptibility to PUD. The mechanisms underlying these differences require additional investigation (Joshi *et al*., 2024).

II.4.2. Lifestyle factors

II.4.2.1. Stress

Stress significantly contributes to the etiopathology of gastroduodenal ulceration (Sen *et al*., 2009). The impact is probably associated with increased acid secretion, which amplifies aggressive factors for people predisposed to peptic ulcers or aggravates preexisting ulcers (Shiotani & Graham, 2002). Physiological stress resulting from sepsis, extensive burn injuries, head trauma linked to elevated intracranial pressure, severe trauma, and multiple organ failure can induce stress-related erosive syndrome. The complex etiology involves ischemia that undermines gastric mucosal integrity, while luminal acid forms various erosive lesions. Psychological stress is likely significant in conventional peptic ulcers, regardless of association with *H. pylori* or NSAIDs (Shiotani & Graham, 2002). It induces heightened stomach motility, excessive vagal activity, mast cell degranulation, reduced gastric mucosal blood flow, and diminished prostaglandin synthesis, leading to ulcers. Stress likely induces ulceration by releasing histamine, which increases acid output and diminishes mucus production (Sen *et al*., 2009; Shahzad *et al*., 2024).

II.4.2.2. Dietary factors

While there is limited evidence of a correlation between alcohol use and peptic ulcers, ulcers are prevalent among individuals with cirrhosis of the liver, a condition associated with excessive alcohol intake (Sen *et al*., 2009). Conversely, new research indicates that persistent alcohol consumption disrupts the stomach mucosal barrier by inhibiting COX-1 receptor enzymes, hence diminishing the synthesis of cytoprotective prostaglandins. Cigarette smoking reduces the circulating epidermal growth factor and elevates free radical generation in the stomach mucosa. Some studies have identified links between smoking and the production of ulcers. Some researchers have specifically examined the associated risks and determined that smoking alone may not provide a significant danger unless it is linked to *H. pylori* infection (Mustafa *et al.*, 2015). Smoking and excessive alcohol consumption generally impede the healing of existing ulcers and elevate the likelihood of

ulcer recurrence; nevertheless, there is limited evidence linking them to the onset of ulcers (Sen *et al*., 2009; Waller & Sampson, 2018). Sen *et al*. (2009), report that caffeine enhances gastric acid output and may exacerbate an existing ulcer. And increased salt consumption can promote gastritis in experimental animals.

II.4.2.3. Other Rares contributors

Stomach ulceration can result from several conditions, including insufficient blood supply to an organ (ischemia), Crohn's disease, and hypersecretory disorders (Kanjanopas *et al.*, 2022) such as Zollinger–Ellison syndrome, which is caused by tumors that produce elevated levels of gastrin, leading to excessive stomach acid production (Ahmad *et al*., 2019)**.**

II.5. Current Treatment Options

The objective of ulcer disease therapy is to alleviate symptoms, promote healing of lesions, avoid recurrences, and prevent complications. (Ithape *et al*., 2023). The main sites of action of the most frequently used pharmacological therapies for peptic ulcer are demonstrated in **(Fig. II.4.).**

II.5.1. Eradication of *Helicobacter pylori*

Based on acid suppression and antimicrobial therapy, several indications for *H. pylori* eradication have been put forth. Numerous eradication protocols exist, with the most typical being a high dosage of proton pump inhibitors paired with two antibiotics, administered for one week to enhance efficacy and reduce resistance week (Waller & Sampson, 2018)**.** The primary antibacterial option is clarithromycin combined with either amoxicillin or metronidazole; nevertheless, it is crucial to refrain from using an antibacterial recently administered for other illnesses. The elimination of *H. pylori* infection promotes ulcer healing and diminishes recurrence. A two-week treatment schedule exhibits a superior eradication rate; nevertheless, adverse effects frequently diminish adherence, constraining the overall success rate (Kempenich & Sirinek, 2018). If *H. pylori* are not eliminated, 80% of ulcers will recur within a year; after complete elimination, the recurrence rate is below 20% (Waller & Sampson, 2018).

II.5.2. Antisecretory drugs

Antisecretory medications decrease stomach acid production. Raising intragastric pH above 3 for many hours daily is sufficient to accelerate the healing of most peptic ulcers. Various drugs exhibit antisecretory effects on the stomach mucosa (Waller & Sampson, 2018).

II.5.2.1. Proton pump inhibitors (PPIs)

Proton pump inhibitors such as omeprazole, esomeprazole, lansoprazole, and pantoprazole are prodrugs swiftly absorbed from the small intestine (Mantry *et al*., 2022). Weak bases preferentially accumulate from the bloodstream into the acidic milieu of the secretory canaliculi of stomach parietal cells. The medicines are subsequently transformed into active derivatives through protonation, covalently binding to and irreversibly inhibiting the proton pump (Beserra *et al.*, 2016)**.** The resurgence of acid secretion relies on the production of new proton pumps. Protonation occurs solely at acidic pH, resulting in these medications exerting a selective effect on stomach parietal cells, while proton pumps in other body regions remain uninhibited. A solitary proton pump inhibitor administration suppresses acid secretion by as much as 90% for roughly 24 hours (Waller & Sampson, 2018).

II.5.2.2. Histamine H2 receptor antagonists'

Histamine-2 Receptor Antagonists (H2RAs), including ranitidine and famotidine, are commonly utilized in treating stomach ulcers; nonetheless, they are deemed less efficacious than PPIs in facilitating ulcer healing and alleviating symptoms. They competitively obstruct histamine H2 receptors on gastric parietal cells, reducing stomach acid output (Beserra *et al*., 2016; Waller & Sampson, 2018). Clinical investigations indicate that H2R antagonists may serve as maintenance therapy to prevent ulcer recurrence in specific patients, notably those with low-risk ulcers and no evidence of *H. pylori* infection. Nonetheless, prolonged usage of H2 receptor antagonists may lead to tolerance and tachyphylaxis, constraining their effectiveness in treating stomach ulcers (Pujari *et al*., 2024).

II.5.3. Antacids

Antacids consist of a mixture of different magnesium, calcium, or aluminum salts. Antacids function by directly neutralizing stomach acid, elevating gastric pH, diminishing pepsin activity, reestablishing acid-base equilibrium, and enhancing bicarbonate and prostaglandin secretion (Shetty & Vishwanath, 2022). Antacids transform hydrochloric acid into carbon dioxide and water, thus neutralizing the acid. Nonetheless, the alleviation of antacids is ephemeral, as they may provoke a rebound impact in hydrochloric acid production (Beserra *et al*.,2016). Their effects are extended when consumed postprandially. When consumed without meals, the effect endures for no longer than one hour due to swift stomach emptying. Antacids swiftly alleviate symptoms of peptic ulcer illness; nonetheless, substantial doses are necessary for ulcer healing. The majority of antacids exhibit limited absorption in the gastrointestinal tract (Waller & Sampson, 2018).

II.5.4. Cytoprotective drugs

Sucralfate is a compound composed of aluminum hydroxide and sucrose octa-sulfate. It dissociates in the stomach's acidic environment to its anionic form, which adheres to the ulcer base (Tseng & Wolfe, 2000). It establishes a protective barrier against pepsin and bile while impeding the flow of stomach acid. Sucralfate further promotes the stomach production of bicarbonate and prostaglandins (Waller & Sampson, 2018). Analogs of prostaglandins Misoprostol is a PGE1 analog with many activities that safeguard the gastric and duodenal mucosae (Tseng & Wolfe, 2000). It is predominantly utilized to avert NSAID-induced ulcers and is offered in combination formulations with diclofenac or naproxen (Waller & Sampson, 2018).

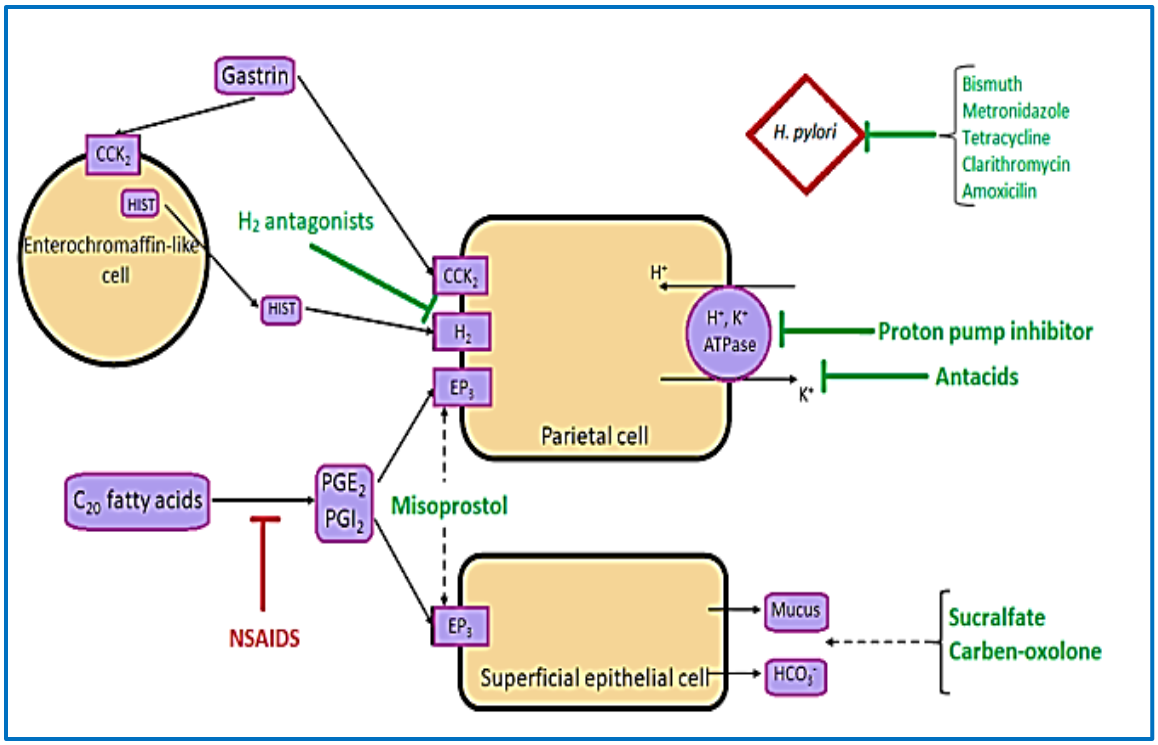

Figure II.4. Schematic representation of the primary pathophysiological mechanisms contributing to the growth of peptic ulcer disease, alongside the sites of action of the most frequently used pharmaceutical treatments for this condition (Kempenich & Sirinek, 2018) CCK2 = Cholecystokinin Receptor; PGE2 = Prostaglandin E2; PGI2 = Prostaglandin I2; EP3 = Prostaglandin E receptor 3; HIST = Histamine

CHAPTER III
GEEN SYNTHESIS & APPLICATIONS OF NANOPARTICLES FOR PEPTIC ULCERS TREATEMENT

III.1. Phytotherapy &General Challenges

Plants have been utilized for medical purposes for 6,000 years, and numerous substances have evolved into conventional or allopathic medicine. Despite the predominance of traditional medicine in industrialized nations, a substantial segment of the population continues to utilize phyto-therapeutic remedies for healthcare (Lim *et al*., 2022)**.** Interest in alternative medicines, especially those derived from medicinal plants, has increased due to the potential adverse effects of conventional pharmaceuticals for various ailments. Medicinal plants possess medical capabilities because they generate renewable secondary metabolites, referred to as phytoconstituents, which exhibit a variable chemical makeup (Kuna *et al*., 2019)**.** The distribution of these elements remains problematic and constrained, facing unresolved challenges, including immunological reaction, inadequate water solubility, permeability, short circulation duration, significant first-pass metabolism by the liver, absorption efficiency, elevated scaling costs, and environmental influences (Khomendra Kumar Sarwa *et al.*, 2022; Kuna *et al*., 2019). A nanotechnological technique can resolve these challenges, yielding safety and reduced circulation time. The potential of medicinal plants as a source of novel pharmaceuticals is intriguing (Khomendra Kumar Sarwa *et al*., 2022).

III.2. Nanotechnology

Nanotechnology is an emerging field that explores the design, synthesis, characterization, and development of nanomaterials (Hamed *et al.*, 2023). These nanomaterials, referred to as nanoparticles with dimensions ranging from 1 to 100 nm, exhibit superior strength, reduced weight, enhanced control over the light spectrum, and increased reactivity compared to their larger counterparts (Bahramikia & Izadi, 2023). Nanotechnology possesses significant potential for strengthening medical science, particularly in drug-delivery systems, contrast agents, and diagnostic instruments. Many have previously received approval or are undergoing clinical evaluation by the Food and Drug Administration (FDA) for human use (Chandrakala *et al.*, 2022; Upadhyay *et al.*, 2022)**.**

The creation of nanomaterials adheres to either top-down or bottom-up methodologies (Khan *et al.*, 2017). The top-down strategy involves disintegrating bulk material into small particles by appropriate mechanical procedures, including sputtering, grinding, and

milling. The majority of the physical methods adhere to this approach. Bottom-up refers to the formation of nanoparticles through the self-assembly of atoms into new nuclei, which subsequently develop into particles with nanoscopic dimensions, utilizing various chemical and biological techniques **(Fig. III.1)** (Kumar & Seth, 2021). Extreme conditions, including elevated concentrations of toxic substances, high pressure, and elevated temperatures, are necessary for physical or chemical processes that impact the environment or need sophisticated apparatus. Consequently, it is essential to devise an eco-friendly method for synthesizing nanoparticles that employs mild techniques and non-toxic materials (Abdelkader *et al.*, 2022).

In recent years, substantial progress has been made in developing green synthesis techniques for various nanoparticles, encompassing metallic, metal oxide, and semiconductor types (Bist, 2024). Green synthesis is an appropriate alternative to chemical and physical processes. This approach is secure, rapid, straightforward, and eco-friendly and may be executed at standard temperature and atmospheric pressure (Bahramikia & Izadi, 2023).

Nanoparticles are classified into several categories based on their morphology, size, and chemical properties. Notable classes include dendrimers, lipid nanoparticles, liposomes, polymeric micelles, fullerenes, metallic nanoparticles (MNPs), metal-oxide nanoparticles (MONPs), ceramic nanoparticles, and polymeric nanoparticles (Khan *et al*., 2017; Safarov *et al*., 2019). Currently, MONPs are utilized in various domains, including medical therapies, industries such as solar and oxide fuel batteries for energy storage, cosmetics and sunscreens, and textiles. The MONPs comprise iron oxide (Fe_2O_3 NPs and Fe_3O_4 NPs), magnesium oxide, zinc oxide (MgO-NPs), titanium dioxide (TiO-NPs), and copper oxide (CuO-NPs). Among all these MONPs, ZnO nanoparticles have garnered considerable attention owing to their unique physicochemical features and prospective medicinal uses, including antibacterial, anticancer, antidiabetic, antioxidant, antifungal, antiviral, antiparasitic, anti-inflammatory, and wound healing capabilities (Hamed *et al*., 2023).

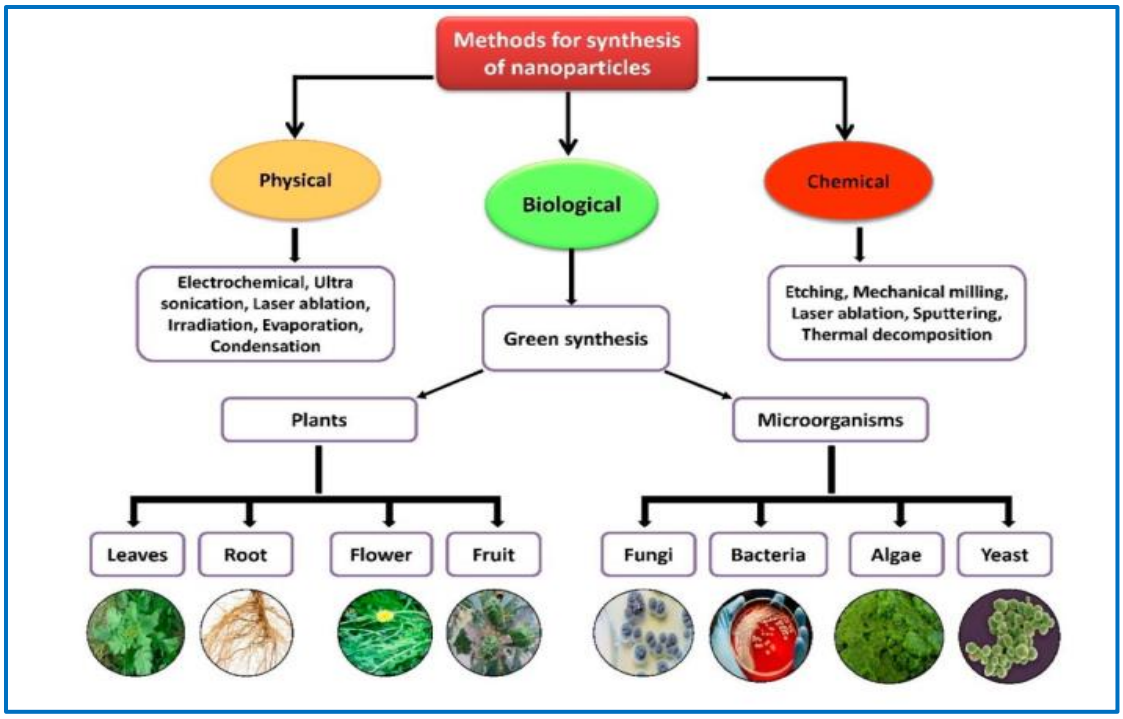

Figure III.1. Diverse methodologies for Nanoparticles synthesis (Mathur & Singh Bahadur, 2024)

III.3. Zinc Oxide Nanoparticles (ZnONPs)

III.3.1. General properties

Zinc oxide exists naturally in the earth's crust as the mineral zincite Nevertheless, owing to its scarcity, most commercial items are manufactured synthetically. Zinc oxide manifests as a white, odorless crystalline powder (Cheng *et al.*, 2024). Zinc oxide nanoparticles are significant metal oxide materials extensively utilized in materials science owing to their distinctive physical, chemical, and biological features, including biocompatibility, environmental friendliness, cost-effectiveness, and non-toxicity (Alwan *et al.*, 2015; Salahuddin *et al.*, 2015). Due to their remarkable capabilities, ZnO nanoparticles have been utilized as a functional advanced material to address several societal issues, particularly in catalysis for wastewater treatment, as well as in cosmetics and antibacterial additives (Muhammad Salman Ajmal *et al.*, 2024). ZnO nanoparticles have numerous advantages, including distinctive chemical and thermal stability, durability, and extended shelf life compared to conventional metal oxides. Zinc oxide manifests in three phases: hexagonal

quartzite, cubic zinc blende, and cubic rock salt (Muhammad Salman Ajmal *et al*., 2024). The wurtzite structure is predominant because of its stability under ambient circumstances, wherein each zinc atom is tetrahedrally coupled with four oxygen atoms (Barhoum *et al.*, 2018). The Food and Drug Administration (FDA) recognizes zinc oxide as one of the safest metal oxides used in the food industry (Shaba *et al.*, 2021)**.** ZnONPs are regarded as ideal candidates due to their vast band gap (~3.37 eV) and substantial binding energy (~60 meV). It also exhibits exceptional chemical stability in solutions with an acidic pH (<6) (Muhammad Salman Ajmal *et al*., 2024).

III.3.2. Plants-Mediated Green Synthesis

Green nanoparticles are produced utilizing natural sources, including plant extracts, microorganisms, and other biocompatible components (Bist, 2024)**.** Among the diverse green synthesis methodologies, bio-mediated plant synthesis has surfaced as a preferable option to conventional nanoparticle synthesis techniques (Bano, 2022; Mathur & Singh Bahadur, 2024). This approach has considerable potential owing to many plant species' phytochemicals, which are essential in the synthesis process. Plants contain many secondary metabolites, such as reducing, capping, and stabilizing agents. These compounds impede the aggregation and agglomeration of diverse metallic nanoparticles, such as silver, gold, palladium, copper, and metal oxides (Bano, 2022; Bist, 2024; Gul *et al.*, 2024). Contrast to microorganism-mediated synthesis, utilizing the green components of plants—such as leaves, flowers, seeds, stems, bark, and rhizomes—provides a more straightforward and accessible method for generating metal or metal oxide nanoparticles (Kurhade *et al.*, 2021; Muhammad Salman Ajmal *et al*., 2024). The efficacy of plant-mediated synthesis is attributed to the presence of diverse phytochemicals, such as terpenoids, aldehydes, polyphenols, carboxylic acids, flavonoids, saponins, steroids, alkaloids, and tannins (Kurhade *et al*., 2021). Moreover, proteins, glucosides, polysaccharides, and vitamins also affect production (Huston *et al.*, 2021; Muhammad Salman Ajmal *et al*., 2024). These molecules fulfill two main functions: (1) they act as redox mediators for the bio-reduction of metal ions at the nanoscale, and (2) they serve as capping agents to prevent agglomeration and enhance surface modification, thus improving nanoparticle stability and biocompatibility (Muhammad Salman Ajmal *et al*., 2024).

Creating zinc oxide nanoparticles (ZnO-NPs) using plant-mediated methods is very beneficial. The accessibility of plant materials and their rich phytochemical content make them attractive. Moreover, their extensive historical utilization in ethnomedicine for antioxidant, anticancer, and antibacterial purposes highlights their promise as safer alternatives for biological applications (Cheng *et al*., 2024). The framework for nanoparticle synthesis using plant extracts is illustrated in **(Fig. III.2.).**

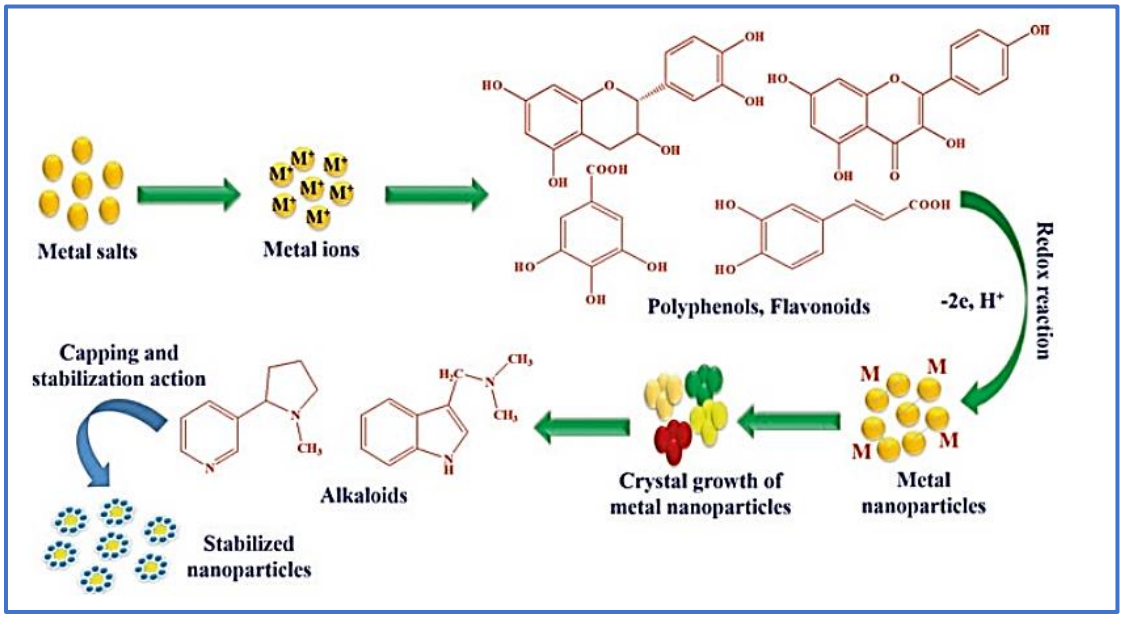

Figure III.2. Schematic representation displaying the basic mechanism of the phytochemical-mediated synthesis pathway for the biosynthesis of nanoparticles by plants (Shakeel & Chun-Sing, 2020)

III.4. Nanoparticles for gastric Ulcer management

Nanoscale devices with a diameter under 50 nm can readily infiltrate most cells, and devices under 20 nm can effortlessly traverse blood vessels during circulation throughout the body. Nanoscale devices, owing to their diminutive dimensions, can readily engage with biomolecules both on cellular surfaces and within the intracellular environment. Smaller particle diameters facilitate quicker passage through mucus to colon cells; particles with a diameter of 14 nm enter in 2 minutes, while those with a 415 nm penetrate in 4 minutes. Particles of 1000 nm cannot traverse this barrier, taking 30 minutes (Mantry *et al*., 2022) .Nanoparticles from biological sources can be effective antibacterial, anticancer, and antifungal agents (Huq *et al.*, 2023).

The utilization of MONPs is advantageous due to their little toxicity and chemical stability. Their notable antibacterial and antifungal properties render these nanoparticles a compelling approach to address the escalating issue of resistance to already employed antimicrobials (De Souza *et al.*, 2021). Metallic nanoparticles can operate as catalysts in several processes, including hydrogenation and dehydrogenation. These nanoparticles demonstrate their antibacterial efficacy (Kumar & Seth, 2021)**.** This activity is ascribed to various pathways, including suppression of cell membrane formation, enzymatic inactivation, creation of reactive oxygen species (ROS), and accumulation of surface characteristics on the cell (Kumar & Seth, 2021)**.** The toxicity of reactive oxygen species (ROS) damages cell membranes, induces protein denaturation, and harms genetic material, potentially resulting in cell apoptosis (Bahramikia & Izadi, 2023; De Souza *et al*., 2021) demonstrated that nanoparticles of polymers, metals, and metal oxides generated from plants can effectively heal stomach ulcers, particularly those induced by *H. pylori*, ethanol, and NSAIDs. Numerous research studies have evaluated metallic nanoparticles' *in vitro* antibacterial mechanisms against *H. pylori*. Lim *et al*. (2022), stated in a review that silver nanoparticles encapsulated with *Toxicodendron vernicifluum* extract had efficacy against enteropathogenic bacteria, *E. coli* and *H. Pylori*, with minimum inhibitory concentrations (MIC) of 8.12 µg/mL and 18.14 µg/mL, respectively. The extract of *Acorus calamus Lim* encapsulated with silver nanoparticles has demonstrated substantial suppression of *H. pylori* development at a dose of 350 µg/mL. Gold nanoparticles infused with *Tribulus terrestris* extracts showed efficacy against *H. pylori* in a size-dependent manner, exhibiting a minimum inhibitory concentration (MIC) of 16.75 µg/mL at 55 nm and 18 µg/mL at 7 nm nanoparticle size (Lim *et al*., 2022). Silver nanoparticles exhibit remarkable antibacterial efficacy by disrupting bacterial cell membranes, inhibiting urease, or enhancing reactive oxygen species generation. They have been utilized for the treatment of *H. pylori* infections. Amin *et al.* (2012), developed an eco-friendly synthetic method for synthesizing silver nanoparticles using the berry extract of *S. xanthocarpum*. The synthesized Ag NPs exhibited excellent stability and potent anti-H. *Pylori* efficacy, including against multidrug-resistant strains. Furthermore, Ag NPs exhibited a linear inhibition of urease activity. Studies with *H. pylori*-infected rats confirmed that 16 mg/kg of silver nanoparticles (Ag NPs) eradicated *H. pylori* from the stomach following a seven-

day treatment period. All evidence suggests that Ag NPs can successfully address *H. pylori* infection in animal models. ZnO nanoparticles exhibited antibacterial efficacy against several gram-positive and gram-negative bacteria while maintaining acceptable biosafety levels (Li *et al.*, 2024). In 2013, Chakraborti *et al.* (2013) synthesized polyethyleneimine-functionalized ZnO nanoparticles (ZnO-PEI NPs) to treat *H. pylori* infection. Bacterial cells markedly absorbed ZnO-PEI nanoparticles, leading to oxidative stress, elevated reactive oxygen species levels, morphological alterations, and rRNA degradation in *H. pylori*. ZnO-PEI nanoparticles had moderate antibacterial efficacy (40% inhibition) at a safe dose (20 μg/mL); however, when these nanoparticles were coupled with 1 μg/mL ampicillin, over 80% inhibition of *H. pylori* was noted .

Attia *et al.* (2022), found that ZnO nanoparticles, combined with amoxicillin, dramatically decreased *H. pylori* activity compared to amoxicillin alone .Conversely, the *in vivo* gastroprotective effects of green-produced metallic nanoparticles have been examined in multiple studies employing various models of caused stomach ulcers. Ibrahim *et al.* (2022), demonstrated that silver nanoparticles synthesized from a combination of Melissa extract and Arabic gum, tested at concentrations of 175 and 350 ppm (p.o.), mitigated the detrimental effects of ethanol-induced gastric damage, as evidenced by a reduction in ulcer index and an increase in ulcer prevention percentage. Markedly diminished ethanol-induced gastric lesions were demonstrated by enhanced mucus secretion and stomach content pH, reduced ulcer area, absence of edema, and leukocyte infiltration of the subcutaneous layer. In gastric homogenate, Ag NPs exhibited a significant increase in superoxide dismutase (SOD) and catalase (CAT) activity, along with a substantial decrease in malondialdehyde (MDA) levels. This observation was similarly noted by (Shareef *et al.*, 2022) where gold nanoparticles synthesized from *Zingiber officinale* rhizome extract were subjected to testing. Salem *et al.* (2018), examined the potential protective mechanisms of silver oxide nanoparticles against indomethacin-induced gastric ulcers and reported that beneficial effects were mediated through the suppression of gastric inflammation, inhibition of oxidative stress, reduction of apoptosis, and enhancement of gastric antioxidant defense mechanisms. The advantageous effects of nano-silver oxide (PVA/PVP/chitosan/Ag nanocomposite; 350 ppm) exceeded those of the reference antiulcer medication Omeprazole.

CHAPTER IV

Juniperus phoenicea L. & *Punica granatum* L.

Prior to designing the laboratory methodologies for this research, an ethnopharmacological investigation was undertaken to collect traditional herbal remedies used by local people in Algerian Sahara for alleviate gastric ulcers symptoms. Tow medicinal species were selected for their widespread application in the Algerian Sahara as a natural remedy.

IV.1. *Juniperus phoenicea* L.

IV.1.1. Botanical description and distribution

Juniperus phoenicea L., also known as the Phoenician juniper, is a member of the Cupressaceae family **(Table IV.1)**, which includes approximately 60 species spread across the northern hemisphere (Abdel Raoof & Mohamed Nagy, 2023). The genus Juniperus is categorized into three sections: Caryocedrus, Oxycedrus, and Sabina, comprising roughly 50 species. Algeria possesses five species from the genus: *J. phoenicea*, *J. oxycedrus*, *J. thurifera*, *J. communis*, and *J. sabina* (Berber *et al.*, 2022). The distribution of *J. phoenicea* encompasses the whole Mediterranean basin, extending from Portugal on the western Atlantic coast to the Atlas Mountains. Jordan, the Sinai Peninsula, and Saudi Arabia define its eastern boundary. It is located between these eastern and western boundaries in Spain, France, Algeria, Italy, Tunisia, Libya, Croatia, Greece, Turkey, Cyprus, and the Canary Islands **(Fig.IV.1)**. The term "Phoenicia" is derived from the Greek "phoenixes," signifying "purple red," and pertains to the mature color of the female cones of this tree (Mathiaux, 2017).

Table IV.1. Scientific classification of *Juniperus phoenicea* L.

Kingdom	Plantae
Phylum	Streptophyta
Clade	Tracheophytes
Clade	Gymnospermae
Division	Pinophyta
Class	Pinopsida
Subclass	Pinidae
Order	Cupressales
Family	Cupressaceae
Genus	Juniperus
Species	*Juniperus phoenicea* L. (APG III system, 2009)
Vernacular Name	العرعار

Figure IV.1. Map demonstrates the general distribution of Phoenician Juniper (World Flora Online, 2024)

J. phoenicea represents a large shrub or tiny tree to heights of 1 to 8 meters, including a trunk diameter of 1 to 2 meters and a rounded or irregular crown (Mathiaux, 2017). The bark, capable of being stripped, is a dark grayish-brown color (El-Shatshat & Abdosalam, 2019). Its leaves exhibit two forms: juvenile needle-like leaves measuring 5-14 mm in length and 1 mm in width on seedlings, and adult scale leaves measuring 1-2 mm in length on mature plants, displaying a green to blue-green color; they are organized in opposite oriented pairs or in whorls of three (Maaoui, 2014). It is predominantly monoecious, while certain individual plants are dioecious. The female cones are berry-shaped, measuring 6 to 14 mm in diameter, orange-brown, occasionally exhibiting a pinkish waxy bloom. Male cones measure 2-4 mm in length and emit pollen in early spring, then distributed by the wind (Berber *et al*., 2022). Flowers with club-shaped inflorescences, unisexual. Solitary female flowers, inconspicuous, located at the terminal ends of the branches (Maaoui, 2014). **(Fig. IV.2).**

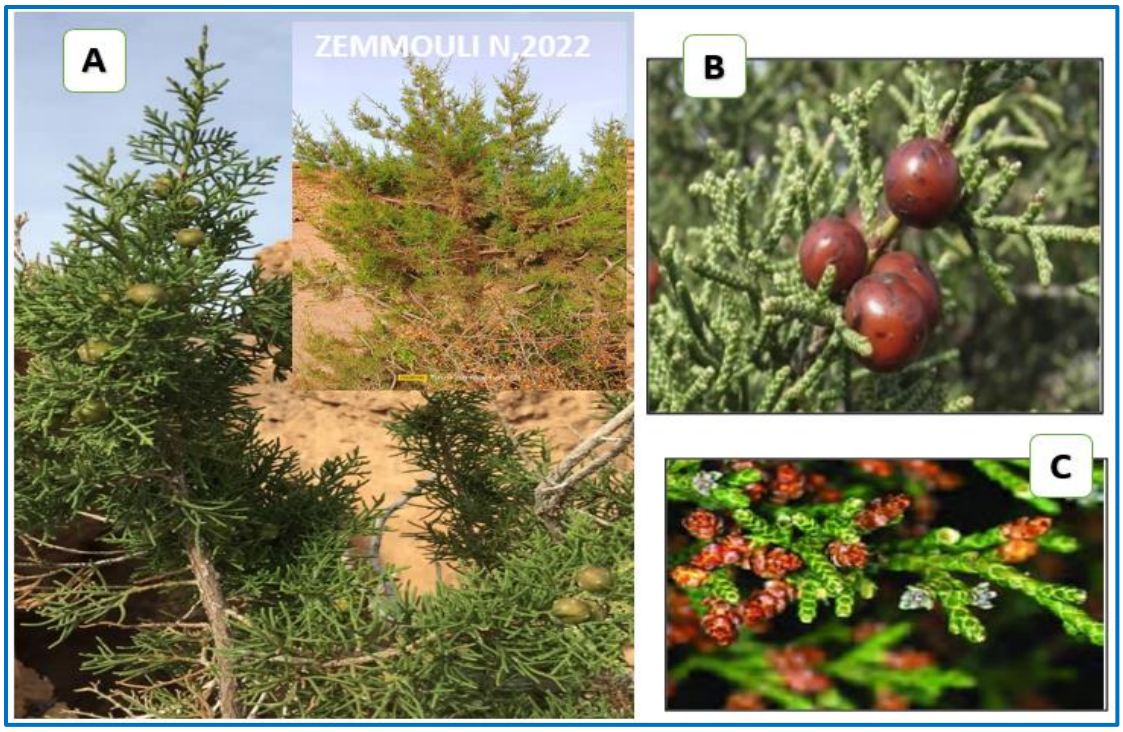

Figure IV.2. *Juniperus phoenicea L.* (A) Tree; (B) Leaves and berries; (C) Leaves and flowers

IV.1.2. Chemical composition

The leaves and berries of *J. phoenicea* yield essential oils that contribute to various biological functions. In certain areas, wood, leaves, and berries are all used to extract the essential oils (Abu-Darwish *et al.*, 2014). The essential oils derived from the leaves of *J. phoenicea* exhibit significant chemical variability; nonetheless, most published studies indicate a predominance of monoterpene hydrocarbons, with α-pinene as the principal component, succeeded by oxygenated monoterpenes (Adams *et al.*, 2009; Mansouri *et al.*, 2011). In addition to the essential oils derived from the leaves and berries of *J. phoenicea*, this species is a source of various biologically active primary and secondary metabolites, including carbohydrates, lipids, minerals, and phenolic compounds (Al Masoudi *et al.*, 2023). Abdelli (2017), reported that *J. phoenicea* leaves contains resin, fatty acids, tannins, flavonoids, alkaloids, sterols, triterpenes, and carbohydrates.

IV.1.3. Traditional uses

The medicinal applications of Juniperus plants are spread in Saudi Arabia, Lebanon, Bosnia, and Turkey. According to traditional medicine, it has been used to enhance appetite

(Abdel Raoof & Mohamed Nagy, 2023) and treat conditions of the respiratory system and skin, rheumatism, gall bladder stones, and urinary problems (Al Masoudi *et al*., 2023). Several researchers have examined the impact of juniper berries as a potential remedy for diet-induced diabetes (Al Masoudi *et al*., 2023). In Algeria, Jordan, and Morocco, a decoction of berries and leaves, along with the powdered berries of *J. phoenicea*, is utilized as a hypoglycemic agent (Orhan, 2019). According to Al-Mustafa *et al.* (2021), Leaves of *J. phoenicea* are used in decoction to treat diabetes, diarrhea, and rheumatism and as a diuretic for bronchopulmonary ailments**.**

IV.2. *Punica granatum* L.

IV.2.1. Botanical description and distribution

The pomegranate (*Punica granatum* L.), frequently referred to as the "Fruit of Heaven," is indigenous to Iran and the northwestern Himalayas (Syed Zameer *et al.*, 2021). Its existence has been recognized for millennia, cultivated in ancient Egypt, early Greece, Italy, and Iraq. Subsequently, it disseminated throughout Asian nations such as Turkmenistan, Afghanistan, Iran, India, China, North Africa, and Mediterranean Europe **(Fig. IV.3)** (Melgarejo *et al.*, 2020; Teixeira da Silva *et al.*, 2013).

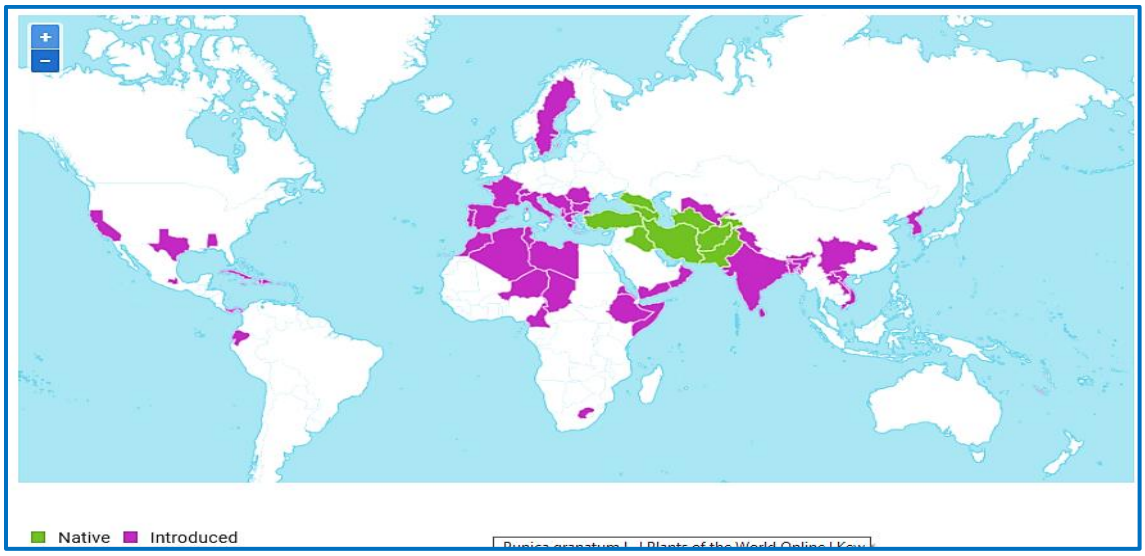

Figure IV.3. Map demonstrates the general distribution of *Punica granatum* L. (World Flora Online, 2024).

The name originates from the Latin terms pōmum (meaning apple) and grānātum (meaning seeded). This Latin term has impacted the vernacular designation for pomegranate across numerous languages (e.g., Granada in Spanish, Granatapfel or Grenadine in German, grenade in French, granatäpple in Swedish, pomogranà in Venetian) (Vaseem Fateh *et al.*, 2013).

P. granatum is classified within the order Myrtales and likely originates from Saxifragales. The Lythraceae family is a precursor to the Sonneratiaceae and Punicaceae families (APG II, 2003). The genus Punica, first described by Linnaeus in 1753, had tropical ancestors related to Lythraceae and Sonneratiaceae. The Punicaceae family is monogeneric, comprising the sole genus Punica, which includes two species: *P. granatum* L. and *P. protopunica Balf*. The latter is unique to Socotra Island (Yemen), whereas Punica nana, a variant of *P. granatum*, is frequently regarded as a third species under the genus *Punica*. Notwithstanding the numerous cited studies, the taxonomic status of the genus *Punica* remains ambiguous. Until further research clarifies this matter, the prevailing taxonomy adheres to the APG-III classification of 2009, which designates Punica as a genus within the family Lythraceae (Teixeira da Silva *et al*., 2013) **Table IV.2.**

Table IV.2. Scientific classification of *P. granatum.*

Kingdom	Plantae
Phylum	Streptophyta
Clade	Tracheophytes
Clade	Angiosperms
Division	Pinophyta
Class	Equisetopsida
Sub-Class	Magnoliidae
Order	Myrtales
Family	Lythraceae
Genus	Punica
Species	*Punica granatum* L. (APG III system, 2009)
Vernacular name	الرمان

The pomegranate plant es represented in **(Fig. IV.4.)** is a deciduous, evergreen shrub that can reach heights of 6 to 10 meters and has a long lifespan. Its tree has several thorny branches (Syed Zameer et al., 2021).

IV.2.1.1. *P. granatum* bark

The bark of *P. granatum* is distinguished by its robust, twisted, brown color and can reach a height of up to 5 meters (Maphetu *et al.*, 2022).

IV.2.1.2. *P. granatum* flowers

The pomegranate flowers include stacked oval petals, measuring 3 cm in width, that exhibit a light pink color, alongside red pointed sepals and multiple stamens (Maphetu *et al*., 2022). Each branch features two to seven flowers at its periphery. Blooming occurs from May to August; fruiting takes place at the end of September (Khojimatov *et al.*, 2024).

IV.2.1.3. *P. granatum leaves*

Leaves of *P. granatum* are brilliant green and oval, reaching a maximum length of 3 cm. The plant's leaves are perennial. The plant's leaves are evergreen, measuring 1–10 cm in length, and are clustered in groups of 5–6 on short stems along the branches (Maphetu *et al*., 2022; Syed Zameer *et al*., 2021).

IV.2.1.4. *P. granatum* fruits

The pomegranate, known as balausta, is a fleshy berry, covered by a persistent calyx; it possesses a thick, leathery skin that can exhibit a range of colors from reddish-yellow to green with reddish patches, and even scarlet red, depending on the type (Melgarejo *et al*., 2020; Valero-Mendoza *et al.*, 2023) hexagonal fruit is 6–12 cm in width and weighs between less than 200 g and more than 800 g (Rabiea, 2021; Syed Zameer *et al*., 2021)**.** The inside fruit is abundant in seeds, enveloped by crimson arils, and can be found in many, angular forms measuring 8–14 mm in length and 5–8 mm in width (Khojimatov *et al*., 2024; Maphetu *et al*., 2022; Melgarejo *et al*., 2020)**.** The edible portion constitutes 50% of the entire weight, while the remaining 50% pertains to the peel (Valero-Mendoza *et al*., 2023).

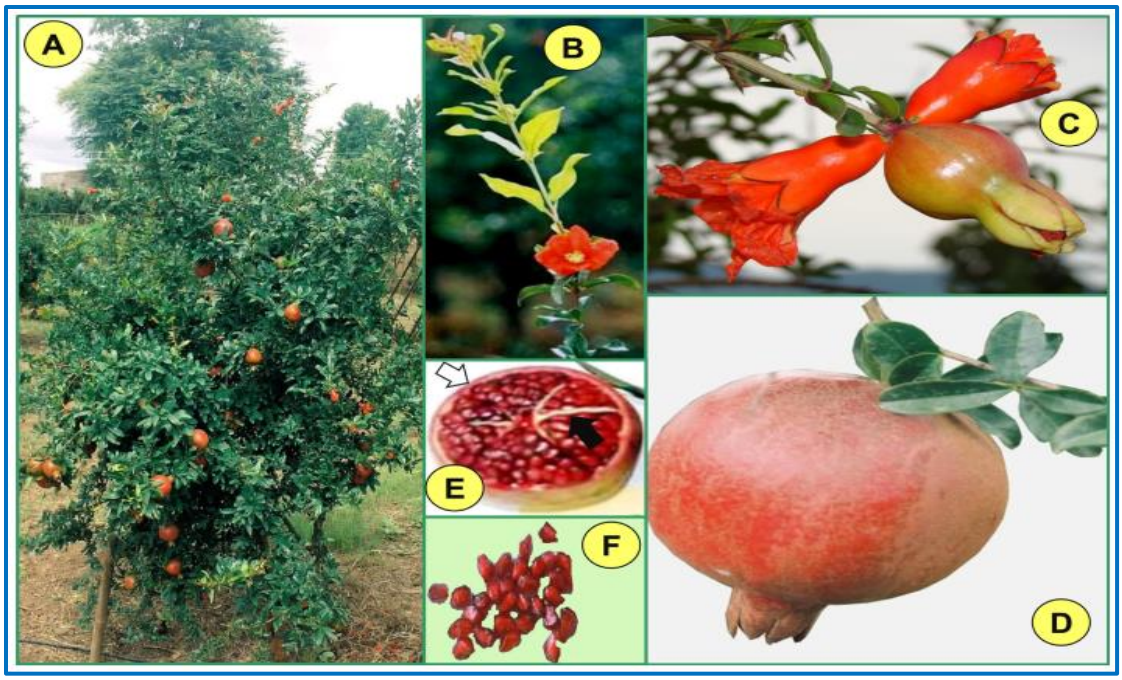

Figure IV.4. *Punica. granatum* L. (A) Plant habit; (B) Flowering stem; (C) Developing fruit; (D) Matured fruit split open (E) to reveal (F) seeds with aril. Source; (Teixeira da Silva *et al*., 2013)

IV.2.2. Chemical composition

Pomegranate is a nutrient-dense fruit with a low caloric value relative to other fruits and provides all vital, easily absorbed elements (Syed Zameer *et al*., 2021). Pomegranate fruits are a superior source of vitamins and minerals, including vitamin K and tocopherol (vitamin E) (Khojimatov *et al*., 2024). Pomegranate contains significant B complex vitamins, including pantothenic acid (B5) and folic acid (B9). Moreover, thiamine, riboflavin, and niacin are present in minimal quantities. In contrast to most fruits, pomegranate is a comparatively deficient source of ascorbic acid (Syed Zameer *et al*., 2021). Pomegranate fruits yield up to 60% juice, with a high phenolic content. Polyphenolic chemicals, including anthocyanins, punicalagin, and punicalin, were extracted from pomegranate juice (Khojimatov *et al*., 2024; Maphetu *et al*., 2022). They are a moderately good supply of carbohydrate proteins and a moderate quantity of non-digestible carbohydrates and lignans. Pomegranate fruits contain minimal fat, with only 0.72 g per 100 g of fruit weight (Syed Zameer *et al*., 2021). Pomegranate juice and seeds possess a rich mineral composition, including Fe, Ca, Ce, Cl, Co, Cr, Cs, Cu, K, Mg, Mn,

Mo, Na, Rb, Sc, Sn, Sr, Zn, and Se. Selenium is a crucial trace element and a cofactor in synthesizing seleno-proteins (Chaturvedula & Indra, 2011; Syed Zameer *et al*., 2021). More than 100 compounds have been found in pomegranate fruit. Pomegranate phenolic compounds comprise both simple molecules and heavily polymerized entities (Syed Zameer *et al*., 2021). The primary phenolic compounds documented in the literature comprise flavonoids (anthocyanins, cyanidin and their derivatives, as well as anthoxanthins such as catechin, epicatechin, and quercetin), tannins (ellagitannins and ellagic acid derivatives), and phenolic acids (such as chlorogenic, caffeic, p-coumaric, ferulic, ellagic, gallic, and cinnamic acid). The color of pomegranate is determined by its chemicals, particularly anthocyanin (Rabiea, 2021)**.** The seeds, bark, and leaves contain many potentially active compounds such as lignins, sterols, and terpenoids; alkaloids are present in the bark and leaves; and seed oil comprises fatty acids and triglycerides (Teixeira da Silva *et al*., 2013).

IV.2.3. Traditional uses

P. grantum is considered "nature's power fruit." All components of the pomegranate tree, including its aril, peel, seeds, flowers, leaves, bark, and roots, have been historically esteemed in traditional medicine for their various therapeutic applications, and comprehensive studies have underscored their promise in treating numerous human health conditions. Nevertheless, the global scientific community has primarily concentrated on the fruit, specifically its juice, owing to its abundant bioactive constituents and several health advantages, while the peel and seeds are being examined incrementally (Yu *et al.*, 2024)**.** It is challenging to consolidate all traditional and pharmaceutical applications into a single title; therefore, only the most prominent usage is referenced below. Here are some review papers that emphasize the pharmacological use of various sections of the pomegranate (Imdad, 2021; Jacob *et al.*, 2019; Lestari *et al.*, 2016; Rabiea, 2021; Rahmani *et al.*, 2017; Saeed *et al.*, 2018; Teixeira da Silva *et al*., 2013; Valero-Mendoza *et al*., 2023; Vaseem Fateh *et al*., 2013) indicated that numerous scientific investigations have identified various bioactive compounds, including ellagitannins such as punicalagin, punicalin, punicic acid, and ellagic acid, which exert advantageous effects on human health. These compounds have been assessed through *in vitro* and *in vivo* assays for their potential to

mitigate certain diseases, including cancer, obesity, diabetes, various viruses such as influenza, bacterial infections, and inflammation. In addition, Adebodun *et al.* (2023), revealed that pomegranate seeds enhance male fertility and are utilized in the treatment of cardiovascular disorders. Fresh or dried root barks or ethanol extracts of pomegranate are utilized to eliminate intestinal parasites because to the presence of alkaloids Dardona (2023); Rabiea (2021), reported the advantageous effects of pomegranate juice in situations of anemia. Rabiea (2021), emphasizes that the tannin content of pomegranate seeds is not significant. It is typically utilized for the treatment of vaginal discharge in women and for wound healing (Vaseem Fateh *et al*., 2013). The seed oil of *P. granatum* possesses anti-inflammatory properties. Vaseem Fateh *et al*. (2013), indicated that *P. granatum* flowers are utilized for the management of diabetes, obesity, cardiovascular disorders, and the treatment of bacterial infections. Also, Adebodun *et al*. (2023) reported that leaves and peels possess anti-inflammatory, anti-cancer, anti-cholinesterase, and anti-diabetic effects, antioxidant, anti-cancer, and anti-proliferative effects.

Concerning the anti-ulcer efficacy of pomegranate peels is substantiated by the examination of numerous research studies investigating *in vivo* anti-ulcer activity across diverse experimental models (Adebodun *et al*., 2023).

Experimental Part

Ethno-pharmacological Investigation

I.1. Introduction

The use of herbal sources is rooted in ancient civilizations and has been preserved over generations (Telli et al., 2022). Traditional medicine is widely perceived as safer and less harmful than modern treatments, particularly in developing countries, where 70–95% of the population depends on it for primary healthcare (WHO, 2013; Moshi & Mhame, 2013). Concerns about the adverse effects of chemical drugs, combined with increased life expectancy and the growing prevalence of chronic diseases, have reinforced interest in medicinal plants as promising therapeutic resources (Boakye-Yiadom et al., 2021).

Gastric ulcer remains one of the most prevalent gastrointestinal disorders in clinical practice (Bi et al., 2014; Sumbul et al., 2011). Although conventional treatments such as antacids, proton pump inhibitors, and H_2 receptor antagonists are effective, their long-term use is associated with adverse effects and high recurrence rates, resulting in a significant economic burden on patients and healthcare systems. Therefore, exploring safe and effective natural gastroprotective agents is of increasing importance (Mahmoud et al., 2023; Reda Abdelaleem et al., 2024).

Algeria is characterized by a rich and diverse medicinal flora supported by varied climates and landscapes, alongside deep-rooted indigenous phytotherapeutic knowledge transmitted orally across generations (Ilbert et al., 2016). However, urbanization and lifestyle changes have contributed to the decline of traditional practices, underscoring the need to document and preserve this knowledge (Bouasla & Bouasla, 2017; Khalfa et al., 2023). Numerous ethnobotanical studies have aimed to record indigenous medicinal knowledge and conserve plant biodiversity, particularly endangered species (Baziz et al., 2020; Belhouala & Benarba, 2021; Bendif et al., 2021; Benlarbi et al., 2023; Boudjelal et al., 2013; Djahafi et al., 2021; Lakhdari et al., 2016; Miara et al., 2019; Senouci et al., 2019; Senouci et al., 2023; Taïbi et al., 2021). Despite Algeria's vast natural resources, traditional medicine remains underexplored (Khalfa et al., 2023) .The limited availability of comprehensive scientific data on medicinal plants with proven anti-ulcer activity highlights a significant research gap. Given the historical use of herbal remedies in gastrointestinal disorders, further investigation into plant-based therapies for gastric ulcers is warranted. This survey

aims to address this gap by exploring novel therapeutic approaches while preserving and documenting Algeria's cultural and ethnopharmacological heritage.

I.2. Methodology

I.2.1. Study areas

The Algerian Sahara constitutes 20% of the Greater African Sahara, covering approximately two million square kilometers and representing more than 80% of its total area. The Algerian Sahara was partitioned into four separate sections **(Fig.I.1.)**. An ethnopharmacological survey was conducted in the Algerian Septentrional Sahara from June 2022 to March 2023. This region encompasses an area of almost one million square kilometers (Sadine, 2018; Telli *et al*., 2022). Owing to its vast expanse, it was analyzed across five regions per the contemporary administrative division of 2019.

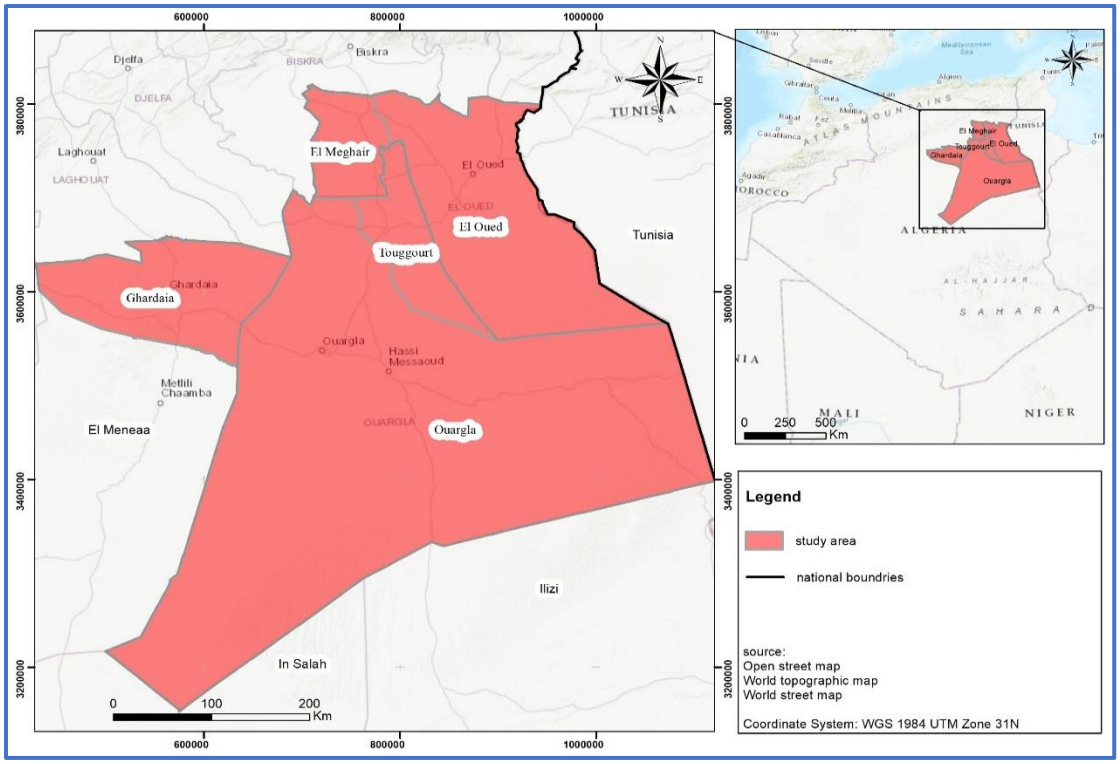

Figure. I.1. Map of the study areas (generated by Author via Arc-GIS Pro software Version3.4)

I.2.2. Socio-demographic data collection

Data collection was conducted via direct conversations with 300 individuals in total. Survey participants originated from five distinct Algerian provinces: 120 from El-Oued, 80 from El-M'Ghair, 38 from Ouargla, 25 from Touggourt, and 37 from Ghardaia. Participation in this survey was voluntary, contingent upon the interviewers' approval. Informants were requested to specify herbal treatments based on their understanding of conventional therapies for alleviating stomach ulcers. This ethnopharmacological prospective study was derived from a semi-structured questionnaire with three sections: The study encompassed socio-demographic data like age, gender, social status, educational attainment, and information regarding the participants' sources of knowledge. The research also encompassed ethnobotanical criteria, like vernacular names of plants and the sections that were utilized. Ethno-pharmacological factors include preparation procedures, administration instructions, dose, treatment duration, toxicity, and adverse effects (**Refer to Appendix/01).**

I.2.3. Identification of plants species

The botanical identification of the specified plant species and their scientific nomenclature was predominantly derived from local names, aided by informants including traditional healers and herbalists and existing bibliographic materials on Algerian flora (Chehma, 2006). For taxonomic verification, the World Flora Database (WFO) was utilized (https://www.worldfloraonline.org)

I.2.4. Data analysis

Various indices were employed to enhance the expression and importance of the results.

I.2.4.1. Relative Frequency of Citation (RFC); This index serves as a measure of the significance of each species in the region under investigation. It was calculated by dividing the number of respondents who mentioned the species by the total number of informants, without considering the use categories. Calculations are made using the following formula **(Eq.1)**:

$$\mathbf{RFC} = \frac{\mathbf{FC}}{\mathbf{N}} \ (\mathbf{0} < \mathbf{RFC} < \mathbf{1}) \qquad \boldsymbol{Eq.(1)}$$

Where; FC; is the Frequency of citation of each species and N; is the total number of respondents

I.2.4.2. Informant consensus factor (FIC): Trotter and Logan developed a structure based on "informant consensus" to identify potentially significant therapeutic herbs. The formula shown below **(Eq.2)** is utilized to calculate the IFC (Telli *et al*., 2022);

$$\mathbf{IFC} = \frac{\mathbf{nresp} - \mathbf{nt}}{\mathbf{nresp} - \mathbf{1}} \qquad \boldsymbol{Eq.(2)}$$

Where; *nresp* is the number of use-reports for each species and *nt* is the number of taxa mentioned.

The obtained ethno-pharmacological data underwent statistical analysis utilizing the Statistical Package for the Social Sciences (SPSS version 22) at a level of significance of 5%. Categorical variables were examined to provide frequencies and percentages. The Chi-squared test was employed to assess the correlation between the surveyed population, various socio-demographic attributes, and their comprehension of traditional medicinal plant utilization for the treatment of stomach ulcers.

I.3. Results

I.3.1. Sociodemographic parameters

Among the 300 participants, 66.3 % were female and 33.7% were male. The participants' ages varied from 23 to 84 years, with a mean age of 43.61±12.751. A few participants in their late 20s and early 30s contributed to reducing this average somewhat. However, these individuals typically acquired their knowledge from familial elders. The data suggested that younger individuals possessed superior knowledge compared to older individuals. Approximately 85% of the interviewees reported acquiring knowledge about herbal therapies through the experiences of others utilizing medicinal plants to address specific ailments. This supports the notion that traditional knowledge and hereditary characteristics are transmitted between generations. The remaining 15% reported having consulted herbalists, pharmacists, or conventional Arab medicinal documents (Bentahar, 2017). The

Chi-square test **(Table I.1)** indicated that there is a notable correlation between the understanding of medicinal plants utilized in traditional phototherapy for gastric ulcers and the socio-demographic characteristics of the surveyed population.

Table I.1. Socio-demographic breakdown of the population surveyed and the Chi-square test.

Parameters	Frequency	Percentage (%)	Chi-Square Analysis
Sexe			
Men	101	33.7	$\chi2$ =32.013b,
Women	199	66.3	P < 0.000
Age ranges			
23-38 years	146	48.7	$\chi2$ =124.187a
38-53 years	87	29	P < 0.000
53-68 years	52	17.3	
68-84 years	15	5	
Social status			
Married	227	75.7	$\chi2$ =428.453a,
Single	52	17.3	P < 0.000
Divorced	1	0.3	
Widower	20	6.7	
Residence			
EL-Oued	120	40	$\chi2$ =103.967c,
EL-M'Ghair	80	26.7	P < 0.000
Touggourt	25	8.3	
Ouargla	38	12.7	
Ghardaia	37	12.3	
Education level			
Illiterate	38	12.7	$\chi2$ =123.120a,
Intermediate-secondary	95	31.7	P < 0.000
Universal	144	48	
Post-graduate	23	7.7	
Occupations			
Herbalist or herbal seller	45	15	$\chi2$ =307.580d,
Traditional healers	13	4.3	P < 0.000
Citizens	242	80.7	
Source of knowledge			$\chi2$ =578.987,
Experiences of others	255	85	P < 0.000
Herbalist	19	6.3	
Books	23	7.7	
pharmacists	3	1	

I.3.2. Botanical diversity and quantitative analysis

This survey successfully established a comprehensive database involving 35 medicinal plants. The indigenous population utilizes these species as conventional natural remedies for gastric ulcers **(Table I.2)** A comprehensive inventory of species in the study area was assembled, including their scientific nomenclature, systematic classifications, and popular names utilized beyond the study area. The data has been organized in a table structured into two separate sections. The upper section consists of 35 species mainly employed as therapeutics. The lower section lists 12 plant species used as additives to the first class of plants, creating traditional herbal mixtures. This research revealed the widespread use of medicinal plants by the people of Algeria living in the Sahara region for treating stomach ulcers. Thirty-five species from 16 botanical groups were identified for this traditional therapy. 34 species belong to the Plantae domain, and all are angiosperms, except for two species, which are gymnosperms (*J. phoenicea* and *T. articulata*). For clarity, *A. platensis* was calculated with the other species, even though it is a Cyanobacteria. The informants used it as a natural remedy.

The Informant Consensus Factor (IFC) was only applicable to three out of the thirty-five species mentioned in the study. The IFC is a measure used to assess the level of agreement among informants (people providing knowledge about the uses of plants) regarding the uses of a particular species. A higher IFC suggests a stronger consensus or agreement among informants. The text discusses the species *P. granatum* with a IFC value estimated by 0.732 followed by *J. phoenicea* with a IFC value of 0.125, and *A. herba alba* with a IFC of 0.0311. Overall, these findings point to the possibility that *P. granatum, J. phoenicea*, and *A. herba alba* may be the most commonly and widely used species for stomach ulcer management among the interviewed population, while the remains species may have more limited or less recognized roles in this regard.

Table I.2. List of medicinal plants identified during the ethnobotanical survey as treatments for gastric ulcers.

Botanical Family	Scientific Name	English Name	Names Of Species in The Study Area	FC	RFC	IFC
Lythraceae	*Punica* granatum L.	Pomegranate	الرمان	**128**	**0.426**	0.732
	Lawsonia inermis L.	Hennatree	الحناء	3	0.01	/
Asteraceae	*Artemisia herba-alba* Asso	White wormwood	الشيح	**39**	**0.13**	0.0314
	Artemisia campestris L.	Northern wormwood	تاقوفت / عشبة اللال	5	0.0166	/
	Matricaria chamomilla L.	Chamomile	البابونج	3	0.01	/
	Onopordum maracanthum Schousb.	Cotton thistle	التاسكرة	1	0.0033	/
Lamiaceae	*Rosmarinus officinalis* L.	Rosemary	الاكليل	3	0.01	/
	Thymus vulgaris L.	Thyme	الزعتر	10	0.033	/
	Teucrium polium L.	Felty germander	الخياطة	5	0.0166	/
	Origanum majorana L.	Marjoram	المردقوش	2	0.0066	/
	Mentha spicata L.	Garden mint	النعناع	3	0.01	/
	Ocimum basilicum L.	Basil	الحبق – نعناع بوشوشة	1	0.0033	/
	Salvia officinalis L.	Common sage	الميرمية	1	0.0033	/
	Salvia hispanica L.	Chia	الشيا	1	0.0033	/
Cupressaceae	*Juniperus phoenicea* L.	Phoenician juniper	العرعار	**51**	**0.17**	0.125
	Tetraclinis articulata (Vahl) Mast.	Sandarac tree Thuja articulata	الدباغ	4	0.0133	/
Fabaceae	*Trigonella foenum-graecum* L.	Fenugreek	الحلبة	6	0.02	/
	Glycyrrhiza glabra L.	Liquorice	عرق السوس	10	0.033	/
	Cicer arietinum L.	Chickpea	الحمص	1	0.0033	/
	Ceratonia siliqua L.	Carob	الخروب	1	0.0033	/
	Acacia senegal (L.) Willd.	Gum arabic tree	اللبان العربي	1	0.0033	/
Zingibraceae	*Curcuma longa* L.	Curcuma	الكركم	1	0.0033	/
	Zingiber officinale Roscoe	Gingembre	الزنجبيل	4	0.0133	/
Apiaceae	*Cuminum cyminum* L.	Cumin	الكمون	1	0.0033	/
	Daucus carota L.	Carrot	الجزر	1	0.0033	/
	Pimpinella anisum L.	Anise	اليانسون	5	0.0166	/
Poaceae	*Triticum durum* Desf.	Durum wheat	القمح	1	0.0033	/
Rhamnaceae	*Ziziphus lotus* Lam.	Jujube	السدرة	1	0.0033	/
Pedaliaceae	*Sesamum indicum* L.	Sesame	الجلجلان	1	0.0033	/
Rutaceae	*Citrus limon* (L.) Osbeck	Lemon	الليمون	1	0.0033	/
Gentianaceae	*Erythrea centaurium* Rafn	Common centaury	مرارة لحنش/ القنطريون	1	0.0033	/
Anacardiaceae	*Pistacia lentiscus* L.	Lentisk	الضرو	1	0.0033	/
Solanaceae	*Solanum tuberosum* L.	Potato	البطاطا	1	0.0033	/

Lauraceae	*Laurus nobilis* L.	Bay laurel	الرند	1	0.0033	/
Microcoleaceae	*Arthrospira platensis* Gomont	Spirulina	طحالب خضراء	1	0.0033	/
Plant species used associated with the previous list to form herbal mixture						
Fabaceae	*Vicia faba* L.	Fava Bean	الفول			
Myrtaceae	*Syzygium aromaticum* (L.) Merr. & L.M.Perry	Clove	القرنفل			
Oleaceae	*Olea europaea* L.	Olive	الزيتون			
Rosaceae	*Rosa Damascena* Mill.	Damask rose	الورد			
Pinaceae	*Pinus halepensis* Mill.	Aleppo pine	الصنوبر			
Lamiaceae	*Mentha pelegium* L.	Mint	نعناع فليو			
Rutaceae	*Citrus sinensis* (L.) Osbeck	Orange	تشينة			
Poaceae	*Hordeum vulgare* L.	Barley	الشعير			
Apiaceae	*Foeniculum vulgare* Mill.	Fennel	زريعة البسباس			

I.3.3. Used parts

Peels constitute the predominant component in our research areas, representing 43% of all applications. Subsequently, the distribution is as follows: leaves (26%), aerial portions (12.33%), seeds (5.33%), roots (5.33%), leaves and stems (5%), and various parts (3%), featuring flowers, fruits, and resin **(Fig.I.2.)**. Owing to their off-season availability, those plant parts were typically employed in a dried condition (94.67%). The majority of the plant's bioactive compounds are preserved due to drying and preservation procedures performed in obscurity.

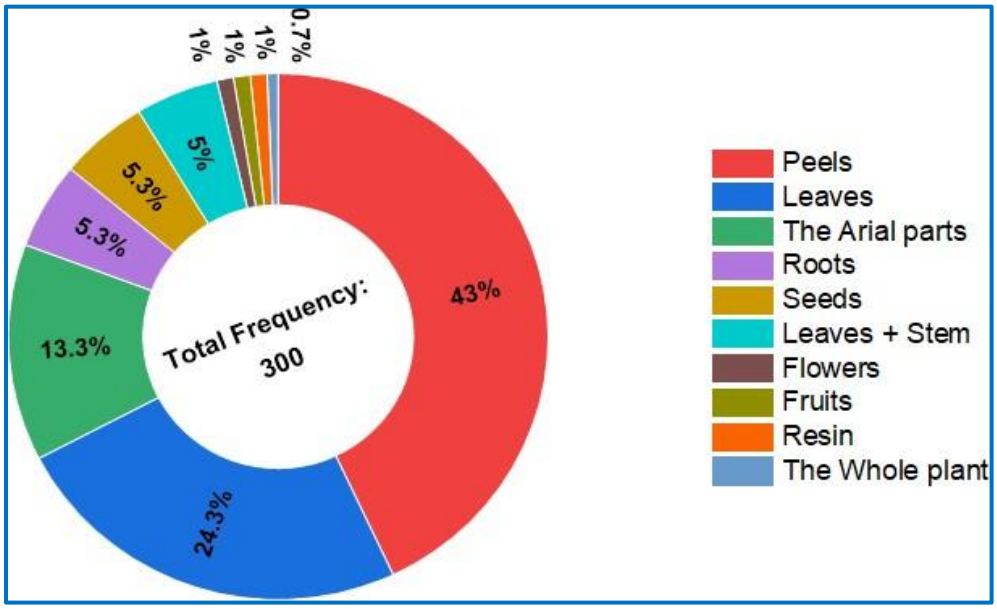

Figure. I.2. The frequency of plant parts used as treatment

V.3.4. Ethnopharmacological features

While medicinal plants may be administered individually or in various combinations, the practice of mixing two or more species was especially valued by informants, with a prevalence of 41.33%. While medicinal plants may be ingested individually or in various combinations, informants mainly prefer amalgamating two or more species, with a prevalence of 41.33%. An examination of the study's overall findings indicates that the local populace in the research areas predominantly utilizes pomegranate (*P. granatum*) and juniper (*J. phoenicea*). Combining the two species as herbal treatments constitutes 13%, with a total FC of 39, as detailed in **Appendix 02**. The therapeutic efficacy of medicinal plants is dictated by their constituents, allowing for the utilization of either the whole plant or particular segments for medicinal applications. Decoction, infusion, powder, maceration, and raw are procedures utilized to facilitate the delivery of the active component. Users are constantly searching for the most straightforward approach to developing green therapies. A majority of the plants in our collection are processed as powder (52.67%), decoction (24.33%), or infusion (18.67%). Upon examining the data from the pharmacological aspects portion of the questionnaire **(Fig. I.3, 4, and 5)**, it was concluded that most respondents (64.67%) utilize therapeutic herbal treatments until they experience improvement. A substantial percentage of responders (27.33%) favored administering these medicines on an empty stomach once a day. The dosage was established according to the specified method of administration **(Refer to Appendix 02(A, B)).**

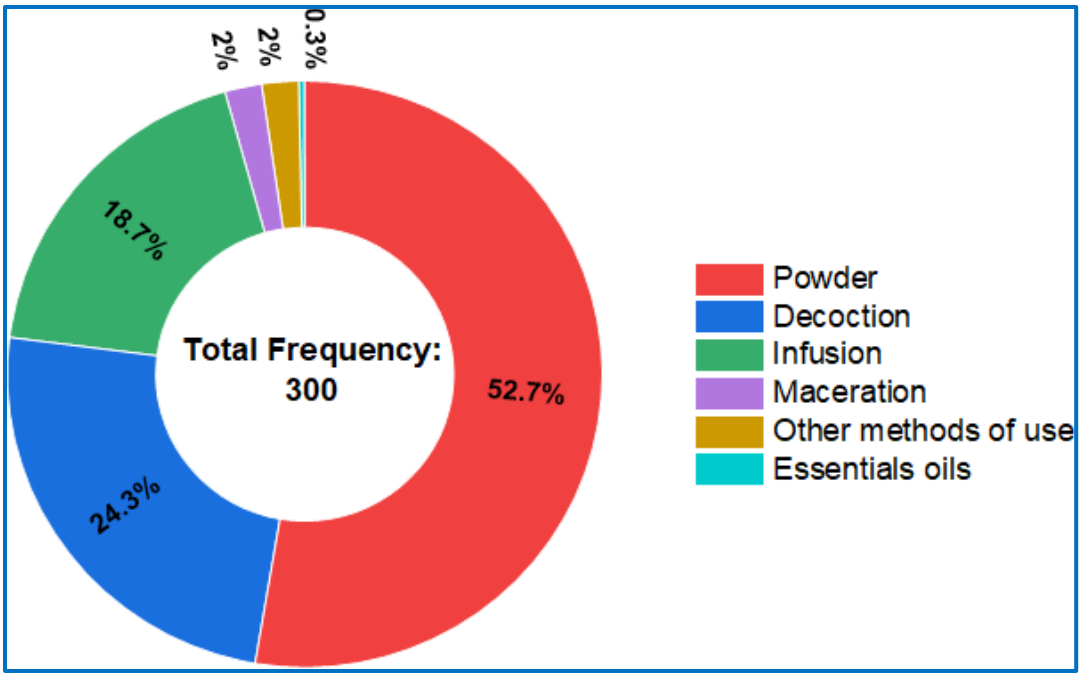

Figure.I.3. Frequency of the mode of preparation of herbal remedies declared by interviewed people

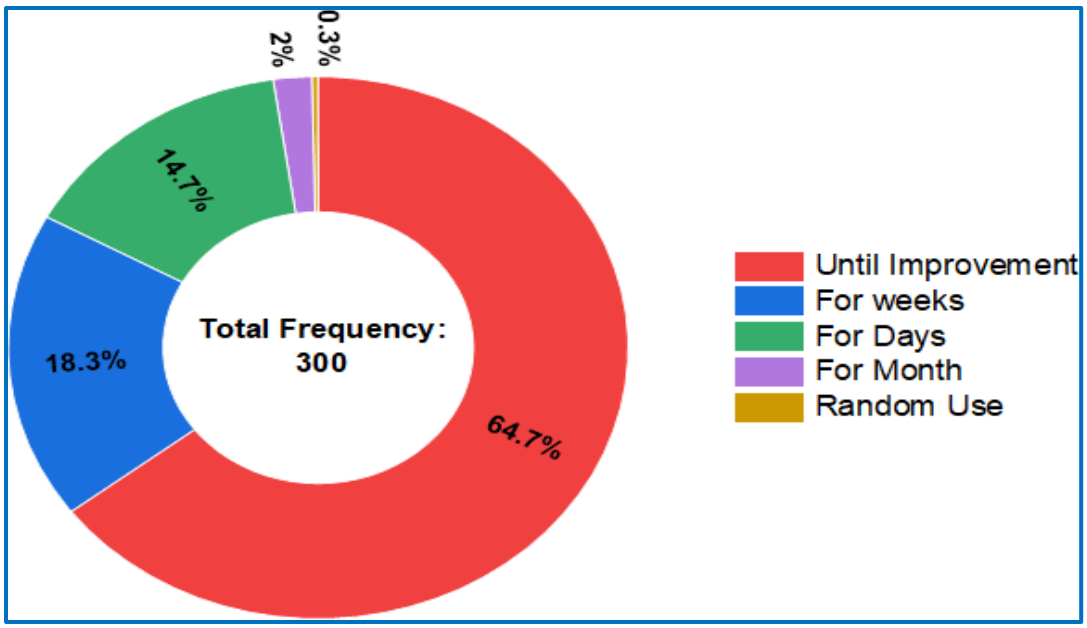

Figure.I.4. Frequency of duration of use of herbal remedies declared by the interviewed people

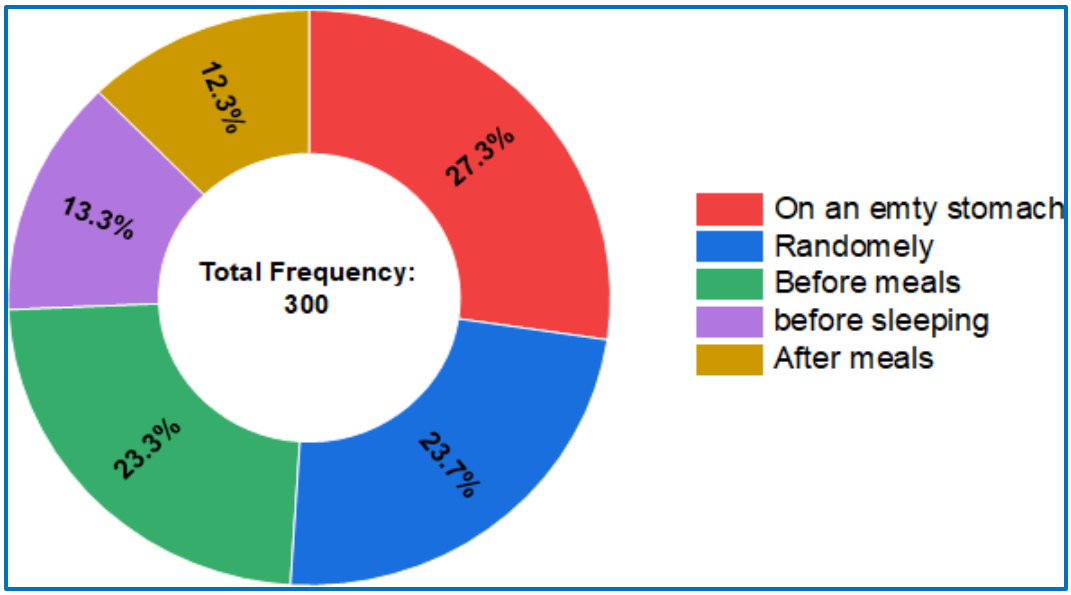

Figure. I.5. Frequency of time of use of herbal remedies mentioned by the questioned pe

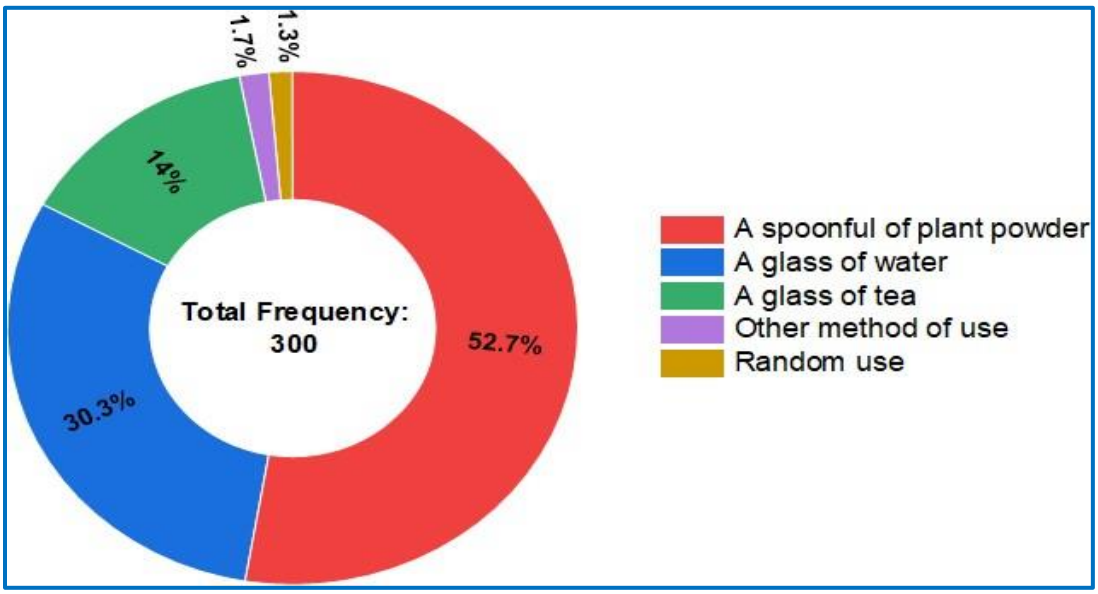

Figure.I.6. Frequency of the dose used as treatment by interviewed people

I.3.5. Side effects and other uses of the species mentioned above

None of the informants recorded any adverse consequences of the medicinal plants and herbal treatments discussed in this study. The anti-ulcer herbs mentioned help treat ulcers. According to the surveyed herbalists and conventional healers, they may be used for

alleviating pain, reducing inflammation, and managing various chronic illnesses **(Refer to Appendix 02 (C)).**

I.4. Discussion

The potential of medicinal plants to treat peptic ulcers globally is discussed in several review papers (Awuchi *et al.*, 2023; Farzaei *et al.*, 2013; Idayat & Mubo, 2019; Mittal *et al*., 2020; Sen *et al.*, 2022; Tadesse *et al.*, 2022). A comparison review of the data with international research revealed that only a limited number of medicinal species found in this study have been recorded for analogous antiulcer applications in other countries. Tadesse *et al*. (2022), documented the utilization of 82 medicinal plants by local groups in Ethiopia, of which four species—*Zingiber officinale*, *Trigonella foenum-graecum*, *Solanum tuberosum*, and *Cicer arietinum*—were also identified in this survey. Thakur *et al.* (2020), compiled a catalog of 40 species utilized for various gastrointestinal illnesses in Northwestern Himalaya, India, including nine species for ulcer care, including *P. granatum*. Idayat and Mubo (2019), recorded a catalog of 92 medicinal species employed for gastric ulcer treatment by people in southwestern Nigeria, including *Citrus sinensis*, *Ocimum basilicum*, and *Zingiber officinale*. The widespread acknowledgment of these species as antiulcer agents might be ascribed to their extensive availability and historic utilization across various civilizations globally. In Algeria, a study conducted by Djahra *et al.* (2023) documented the utilization of 40 species from 16 families and various genres by the local population of El-Oued for the treatment of gastrointestinal ailment, among them 6 species recorded by our population (*Rosmarinus officinalis, Pimpinella anisum, Matricaria chamomilla, Lowsonia inermis, Punica granatum, and Pinus halepensis*). Also, Bentahar (2017) documented a compilation of 32 plant species and herbal formulations employed by the inhabitants of Setif as potent anti-helicobacter agents. Furthermore, Senouci *et al*. (2023) Listed 33 plant species from 22 families frequently used by the locals in Chlef to cure various gastrointestinal conditions.

This survey focuses on studying the indigenous knowledge of local populations in Algeria's septentrional Sahara about traditional medicines for treating stomach ulcers. It is one of the few scientific efforts dedicated to this topic. One significant discovery from the research reveals a discrepancy between genders, with men demonstrating lower knowledge of the

traded species of medicinal plants compared to females. This discovery suggests that there may be variations in how men and women in these cultures acquire and pass on knowledge about medicinal plants. Women, who often take on the primary caregiving duties in families, may have a stronger sense of duty towards the health and well-being of their homes. As a result, they are more likely to actively search for and remember knowledge of traditional treatments (Chaachouay *et al.*, 2023). This attitude may arise from a desire to make educated choices about healthcare practices for their family, emphasizing the interplay of gender roles, indigenous knowledge, and healthcare dynamics among these communities (Bentahar, 2017; Chaachouay *et al*., 2023). Adults over 40 have a greater understanding of plant species than people under that age (Bentahar, 2017; Chaachouay *et al*., 2023). Our study reveals a significant change in how information on herbal therapies in the Algerian desert is spread. Younger folks (aged 23–38) are also receiving this knowledge, as is the elderly. This pattern indicates a dynamic transfer of cultural legacy, showing that traditional knowledge is not limited to older generations but is actively handed down to younger groups. The availability of information via diverse outlets such as literature, social networking sites, and other resources is likely to contribute to the transmission of knowledge across different generations.

This research reveals the widespread use of medicinal plants by the people of Algeria living in the Sahara region for treating stomach ulcers. Thirty-five species from 16 botanical groups were identified for this traditional therapy. Of all the families mentioned, Lythraceae stands out as the most dominant, accounting for 43.7% of the species used. This highlights its importance in the local pharmacopeia. Cupressaceae ranks second behind Lythraceae, with 19% of the total. This family includes two plants that are often used in traditional ulcer treatment. In addition, Asteraceae is notable for its 15.3% prevalence, consisting of four species, while Fabaceae less common, adds to the therapy options with five species. The selection of plant families such as Lythraceae, Cupressaceae, Astearceae, and Fabaceae for the treatment of ulcers among the Saharan people is likely influenced by a combination of factors, including their abundance in the local environment and chemical makeup.

Relying on experimental studies, various authors describe the antiulcer proprieties of several species reported in this study in different induced gastric ulcer models (Abdelfadeel & Alazouny, 2019; Aleid *et al.*, 2021; Alkhatib *et al.*, 2022; Bahramikia & Yazdanparast, 2012; Dina H.Sayed *et al.*, 2022; Elaoufi *et al.*, 2022; Ellithey *et al.*, 2019; Jabbar Taresh *et al.*, 2020; Jacob *et al*., 2019; Loucif *et al.*, 2023; Mahmoud & Abd El-Ghffar, 2019; Marghich *et al.*, 2022; Noreen *et al.*, 2021; Ogbuagu *et al.*, 2020; Shosha *et al.*, 2022; Syed *et al.*, 2020). It is crucial to identify that while some plant species listed in this research have gastroprotective effects, their documentation and references in the current literature may be limited. This emphasizes a prospective domain for more investigation and study in herbal medicine. The species mentioned, such as *O. maracanthum, E. centaurium, L. inermis, R. officinalis, S. officinalis, Z. lotus, S. indicum, S. hispanica, A. senegal, and T. durum*, show exciting possibilities for studying their capacity to treat ulcers. Further research might explore these less-known botanical species by performing pharmacological tests, clinical trials, and ethnopharmacological surveys to confirm their effectiveness and safety in treating gastric ulcers. By focusing on these lesser-studied species, scientists may expand our knowledge of traditional medical practices and discover new therapeutic substances for controlling stomach ulcers. This will contribute to the progress of natural medicine and healthcare.

Using many plant species as antiulcer remedies can provide beneficial synergistic effects. Also, it helps to reduce the adverse effects or toxicity that may result from individual plants in the combination. In addition, these formulations may contain excipients or adjunct ingredients such as honey, oils, milk, olive oil, butter, water, or yogurt. These ingredients can improve the taste, make it easier to take, and reduce certain herbal mixtures' bitter or spicy flavor. These adjuncts enhance the therapy's overall efficacy and help improve patient adherence and acceptance of conventional treatments (Taibi *et al.*, 2021). Furthermore, the investigation of medicinal plant-derived formulas specifically designed to treat gastric ulcers provides a chance to tackle metabolic problems linked to ulceration. This could offer comprehensive methods for managing ulcers beyond simply alleviating symptoms and promoting overall health and well-being (Bentahar, 2017; Taibi *et al*., 2021).

According to our survey, peels are the most often used portion of plants, accounting for 43% of all applications. Leaves are the second most generally employed element, making for 26% of the uses, followed by aerial parts. The abundance of peels in traditional medical practices may be linked to their high concentration of bioactive chemicals and therapeutic capabilities. In addition, Tadesse *et al.* (2022), show that approximately 24 percent of those interviewed prefer utilizing dried plant components. Most of the plant species referenced by the interviewees in this survey were utilized in dried form (94.67%). This suggests a preference for dried preparations because they are convenient and available all year round (Alamgir, 2017). It is essential to mention that the preservation of these plant parts, whether dried or fresh, is done without light to guarantee the preservation of their active components. This highlights the need for appropriate storage methods to retain medicinal effectiveness.

Traditional medicine often employs three basic procedures for preparing and using herbal medications: infusion, decoction, and maceration (Abubakar & Haque, 2020)**.** Infusion involves immersing fragile plant components such as leaves and blossoms in hot water to extract soluble substances, making it well-suited for plants with abundant volatile oils and vitamins. A decoction is a process where more complex portions of plants, such as roots and bark, are simmered in water for a long time to extract substances such as alkaloids and polysaccharides (Abubakar & Haque, 2020; Alamgir, 2017). This method is often used for medical reasons since it extracts denser contents. However, the decoction allows for the collection of the most potent substances and reduces or eliminates the poisonous effects of some formulas. Maceration is when plants are soaked in alcohol or oil to extract lipophilic components such as essential oils and resins. This method is often used to create tinctures and infused oils. Each technique provides distinct benefits customized to the herbs' characteristics and the intended therapeutic results, demonstrating the many subtle ways within traditional herbal therapy (Oueld el hadj *et al.*, 2003). According to the findings of our study, a considerable proportion of participants (52.67%) employ pulverized plant species to prepare herbal remedies, suggesting that this is a widespread practice among the surveyed populace. This process reduces Pretrained plant material to a fine powder; the resulting powder may be encapsulated, incorporated into beverages, or utilized in other preparations. On the contrary, the remaining participants choose to extract the active

components from the plants through various techniques to formulate herbal remedies, indicating a heterogeneous perspective towards traditional medicine practices. Infusions, decoctions, maceration, and other techniques that seek to isolate and concentrate the beneficial compounds present in the plants may be utilized in these extraction processes.

The high occurrence of prescriptions for orally administered medications, as shown by the majority in our study, is likely due to the recognition that the targeted disorders are linked to internal organs. The preference for oral administration is in line with the need for systemizing medicinal substances to treat internal organ illnesses effectively (Bentahar, 2017).

All participants in this research failed to consider the possible adverse effects linked to the medicinal plants and herbal treatments addressed. The study found that the antiulcer herbs, mainly used for treating ulcers, were also effective in relieving pain, reducing inflammation, and treating other chronic conditions. The herbalists and conventional healers offer valuable knowledge about the various uses of these medicinal plants in local healing practices. This highlights their in-depth understanding of the plant's medicinal properties and the careful approach to healthcare in these communities. Nevertheless, the absence of regard for possible adverse reactions necessitates more examination and emphasizes the need to conduct safety evaluations while using herbal treatments.

Materials & Methods

II.1. Materials

II.1.1. Chemicals and pharmaceuticals

All compounds used to conduct this study are of analytical grade. Methanol (99.7%), Chloroform (99.8%), Acide hydrochloric (HCL; 37%), Dimethyl sulfoxide (DMSO; 99.7%), Folin-Ciocalteu Reagent (99%), from Biochem (Chemopharma Co, France). Aluminum Trichloride ($AlCl_3$), Ferric Chloride ($FeCl_3$; 99.99%), Sodium Carbonate (Na_2CO_3; 99.5%), Trichloroacetic Acid (TCA; 99%) from Prolabo (USA). Sodium Hydroxide (NaOH;98%) Ascorbic Acid (99%), Gallic Acid (99%), DPPH (2,2- Diphenyl-1-picrylHydrazyl radical; 99%), Potassium Ferricyanide ($(K_3[Fe(CN)_6]$;99%), Quercetin (95%), Zinc acetate dehydrate ($Zn(CH_3CO_2)_2$;99%), β-Carotene (93%) from Sigma Aldrich (St Louis, MO, USA). Muller Hinton Agar from Honeywell Expertise. Antibiotics (Amoxicilin10ug/disk and Ciprofloxacin 30ug/disk), Diclofenac sodium 50 mg (Geofenac®; from GED-PHARM; Algeria), Indomethacin (Indomet®; from SAIDAL-Group; Algeria), and Omeprazole (Omedar®; from Dar EL-Dawa; Algeria) were all purchased from a local pharmacy in EL-Oued province, Algeria.

II.1.2. Plant material

The botanical samples chosen for this study were collected in September 2022 from Northeast Algeria. The leaves of *J. phoenicea* originated from Sidi-Masmoudi in Biskra province, located at coordinates (34°51'8.68"N 6°18'53.539"E). Mr. Khelef Yahia, an Associate Professor at EL-Oued University's Faculty of Nature and Life Sciences in Algeria, was then identified the collected material. The fruits of *P. granatum* were precisely acquired from local farms in Taghzout EL-Oued province (33°28'N 6°47'25.99'E). The collected samples were rinsed with running tap water and distilled-water to eliminate dirt and extraneous particles. Subsequently, it underwent a dehydration procedure (in a shaded area, out of direct sunlight), pulverization, and preservation for future use.

II.1.3. Animals

This study involved 40 mature male Wistar albino rats, with an average weight of 204.05± 13.92g. The lab animals are kept in the animal house of the Molecular and Cellular Biology

Department, Faculty of Natural and Life Sciences, University of El-Oued, Algeria. Animals were acclimated for two weeks under consistent laboratory circumstances of a 12-hour light/dark photoperiod at a temperature of 25±1°C. Standard rat diet and tap water were provided freely throughout the experiments. The experimental protocols and procedures employed in this work received approval from the Local Ethics Committee for Animal Experiments at the Faculty of Natural and Life Sciences, EL-Oued University, Algeria (No; 19/S.C/FLNS/EU/2023) **(Refer to Appendix N°:3).**

II.1.4. Bacterial Strains

Bacterial Strains used in this work were acquired from Pasteur Institute's laboratory in Algeria. The strains included *Bacillus subtilis* ATCC 6633, *Listeria innocua* CLP 74915, *Escherichia coli* ATCC 8737, *Pseudomonas aeruginosa* ATCC 6538, *Staphylococcus aureus* ATCC 6538, and *Salmonella typhimurium* ATCC 14028.

II.2. Methods

II.2.1. Plants Aqueous Extracts (AQEs) Preparation

The decoction method has been employed to extract active compounds from plant material in an aqueous phase, as described by Bentahar (2017); Turrini *et al.* (2020)**.** The pulverized plant material was mixed with distilled water in a 1:10 ratio to produce the aqueous extracts. The resultant mixture was subjected to boiling for 10-15 minutes using a continuous magnetic stirrer. The homogenate is initially filtered through two layers of muslin and subsequently filtered with Whatman paper for future use in ZnO-NPs green production protocols (The pH of filtrated homogenate was measured using digital pH meter (WTW-PH7110)). The gathered recoverable residues were dehydrated in an oven at 45°C. The samples were designated as AQE-JP for *J. phoenicea* extract and AQE-PG for *P. granatum* extract. Subsequently, stored in amber-hued bottles under aseptic conditions to avert degradation from light, and then refrigerated for future use. The extraction yield was determined using the following equation **(Eq.3):**

$$\textbf{\textit{Yield of extraction}}\ (\%) = \frac{\boldsymbol{W1}}{\boldsymbol{W2}}\ \boldsymbol{x\ 100} \qquad \textbf{\textit{Eq.}}\ (\mathbf{3})$$

Where W_1; is the weight of the extract and W_2; is the weight of the dried powder of plant material.

II.2.2. Phytochemical Screening

A phytochemical screening was conducted to identify the various classes of bioactive molecules in our decoction-prepared extracts, employing methods that rely on colorimetric changes in the reaction mixture or precipitate formation, as outlined by Laib (2023); Mouffouk *et al.* (2023); Sharma *et al.* (2020); Sindhu *et al.* (2021).

- **Polyphenols Test;** Two milliliters of the extract were treated with a few drops of a 2% (w/v) $FeCl_3$ solution. $FeCl_3$ has a greenish or blackish-blue hue in the presence of polyphenol derivatives.
- **Tannins Test;** Two milliliters of diluted extracts were combined with one milliliter of a 1% ferric chloride solution produced in water. Following agitation, the emergence of a greenish or bluish hue indicated the existence of tannins.
- **Steroids Test;** Each sample and chloroform ($CHCl_3$) were combined in an equivalent volume of 2 mL with 500 µL of acetic anhydride and 3 drops (0.15 mL) of concentrated sulfuric acid. Following agitation, the emergence of a blue hue signified the presence of steroids.
- **Flavonoids Test;** 5 mL of the extract was mixed with an equivalent proportion of 5 mL of dilute ammonia and 1 mL of H_2SO_4. The presence of flavonoids is indicated by the appearance of a yellow hue.
- **Triterpenoids Test;** In a test tube, we combined 5 mL of plant extract with 2 mL of chloroform and 3 mL of concentrated sulfuric acid. The presence of terpenoids produces a reddish-brown hue.
- **Saponins Test;** One milliliter of the decoction was combined with four milliliters of distilled water. The prepared mixture was agitated in a graduated cylinder for 15 minutes. The examination of the foam indicated the presence of saponins.
- **Alkaloids Test;** 0.15 mL of Dragendorff reagent was added to 1 mL of the examined extracts. The formation of an orange-red precipitate indicated the presence of alkaloids.

- **Reducing sugar Test:** To 0.5 mL of plant extract, add 1 mL of water and 5-8 drops of Fehling's solution, then heat at 70°C for 2 minutes. The formation of brick red precipitate signified the presence of reducing sugar.

II.2.3. Quantification of secondary metabolites by colorimetric methods

The content of polyphenolic components in AQE extracts was quantified using spectrophotometric methods;

- The total phenolic content (TPC) was evaluated using the Folin-Ciocalteu reagent, per the standard protocols Li *et al.* (2007). A 200 µl of extract or standard was combined with 1000 µl of diluted Folin-Ciocalteu reagent (tenfold dilution). After roughly four minutes, 800 microliters of 7.5% sodium carbonate solution (Na_2CO_3) were introduced. The resultant mixture was stirred and maintained in a dark area at room temperature for 30 minutes. The absorbance was quantified at 765 nm.
- The aluminum chloride assay measured the total flavonoid content (TFC). In summary, identical quantities of each analyzed extract or standard (quercetin) were amalgamated with 2% $AlCl_3$. The absorbance at 420 nm was measured relative to a produced blank following a 20-minute incubation period (Menaceur *et al.*, 2013).
- The concentration of condensed tannins (TCT) in the extracts was quantified utilizing the modified vanillin assay (Douaouri & Djebli, 2018)**.** In conclusion, 1 milliliter of the samples (dissolved in methanol) was amalgamated with 5 milliliters of the assay reagent, which comprised 2.5 milliliters of a 1% vanillin solution combined with 2.5 milliliters of an 8% HCl solution, prepared by adding 8 milliliters of HCl to 100 milliliters of methanol. The resultant mixture was swiftly stirred. Five milliliters of the 4% hydrochloric acid solution were added. The reaction mixture was incubated in darkness for 20 minutes, and its optical density was measured at 500 nm.

The outcomes of TPC, TFC, and TCT were quantified as standard equivalents per gram of dry plant extract weight (mg STDs E/g DE) utilizing calibration curves for Gallic acid (y=0.011x+0.0282/ R2=0.9961), Quercetin (y=2.5985x+0.0008/ R2=0.9917), and Catechin (y=0.0006x+0.097/ R2=0.9944), respectively **(Refer to Appendix N°:4).**

II.2.4. Green synthesis of ZnO-NPs from AQEs

The synthesis of ZnO nanoparticles via green methods followed the protocol established by Ezealisiji *et al.* (2019) with a few modifications. An aqueous solution of 0.1 M zinc acetate dihydrate was mixed with freshly prepared aqueous extracts (AQEs) in a 9:1 ratio and subsequently treated with NaOH solution (1 M) to achieve a pH of 10. The reaction commenced with the ions supplied by the zinc acetate solution. The resulting mixture was continually agitated at 70 °C without light to inhibit photo-catalysis. The observation of a distinct off-yellow hue signified the formation of ZnO nanoparticles. Following 24 hours of incubation at room temperature, the resultant product was subjected to further purification using centrifugation and subsequently washed separately with distilled water and ethanol. The sample was subsequently dried at 100° C overnight and stored in an amber-colored bottle until required **(Fig. VI.1).**

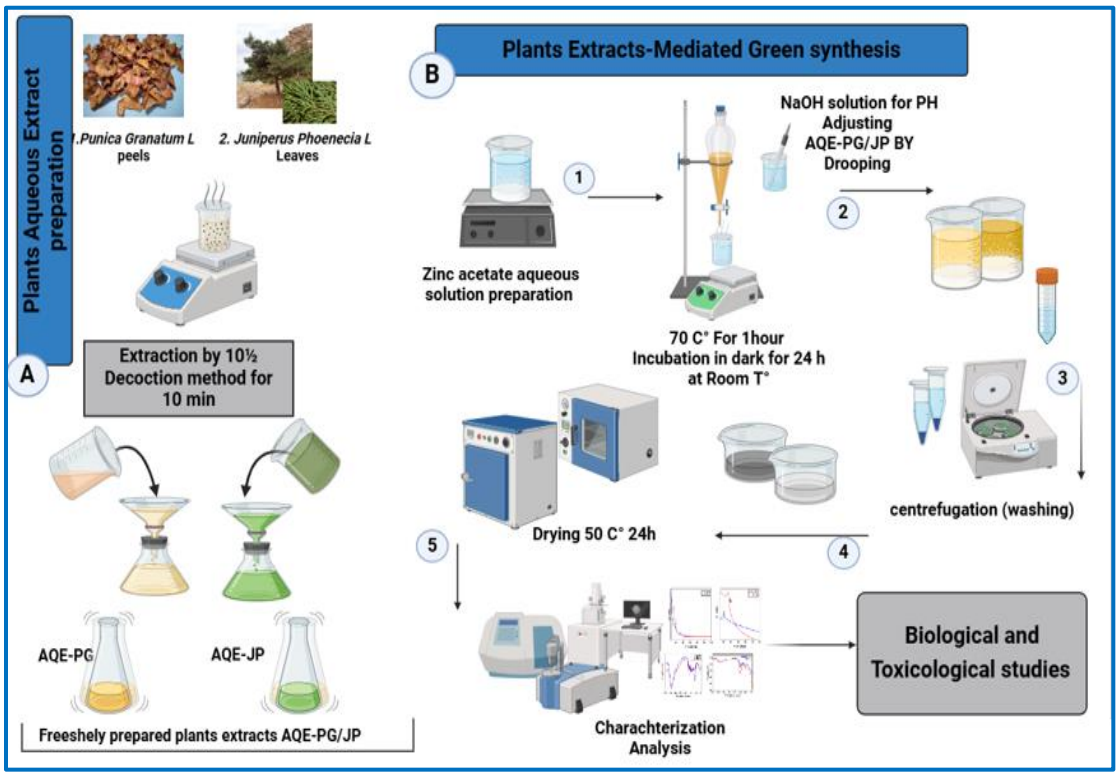

Figure.II.1. Schematic presentation showing the aqueous plants extract (AQE-JP/PG)-mediated synthesis of ZnO-NPs

II.2.5. Characterization of ZnO-NPs

A UV-Vis spectrophotometer (Uvi-Line® Series, SECOMAM GROUPE AQUALABO; France) was employed to assess the optical properties of ZnO nanoparticles. Data were collected within the 200 to 800 nm wavelength spectrum. The functional groups in our samples (AQEs and ZnO-NPs) were evaluated using a Fourier transform infrared spectrometer (FTIR, Agilent Cary 630 model, Agilent Technologies); the spectra were collected in the range of 4000–400 cm^{-1} with a resolution of 4 cm^{-1}. The crystalline structure was analyzed utilizing X-ray powder Diffraction (PROTO AXRD Benchtop) with CuKα radiation (30 kV and 20 mA), with a wavelength of 0.154281 nm and a scanning speed of 0.05°/min. We conducted an X-ray examination of distinctively mixed materials throughout a 2θ range of 20–80°. The crystallite size was determined using the Scherrer formula **(Eq. 4)** by picking the peak with the highest intensity:

$$D = \frac{K\lambda}{\beta \cos \theta} \qquad Eq.(4)$$

Where D; represents the crystallite size, k the so-called shape factor (0.9), λ is the wavelength (0.154281 nm, CuKα), FWHM refers to the Full Width at Half Maximum, and θ signifies the diffraction angle. Micrographs of ZnO nanoparticles were obtained using a Scanning Electron Microscope (SEM) from Phenom-World, operated at an accelerating voltage of 5 kV, revealing the morphology, size, and form of the green ZnO nanoparticles. Energy dispersive X-ray (EDX) examination of ZnO nanoparticles was conducted using the same apparatus to assess the sample's elemental composition. The diameter distribution function of the NPs was derived using a statistical analysis of the acquired SEM images using Image J software.

II.2.6. Evaluation of *in vitro* antioxidant activity

The DPPH scavenging activity assay, reducing power assay, phosphomolybdate assay, and β-carotene bleaching method are tests employed to assess the antioxidant capacity of the generated AQEs and their biosynthesized ZnO-NPs. All experiments were conducted in triplicate with a JENWAY 7315 spectrophotometer.

II.2.6.1. Assessment of DPPH scavenging activity

The DPPH assay quantified the color change from purple to yellow of the DPPH radical at a wavelength of 517 nm after its interaction with an antioxidant molecule. The effect of antioxidants on DPPH radicals is thought to stem from their ability to donate hydrogen. 2,2-Diphenyl-1-picrylhydrazyl (DPPH)· is a stable free radical capable of accepting an electron or hydrogen radical, resulting in a stable diamagnetic molecule (Shekhar & Anju, 2014)**.** The samples were examined for their DPPH free radical scavenging activity using spectrophotometry. The reduction of DPPH at 517 nm was observed to assess the scavenging activity, following the procedure established by Kavaz and El Faraj (2023) with minor modifications. In summary, 200 µl of samples (AQEs / ZnO-NPs) or a standard solution (ascorbic acid/BHT) at varying concentrations, dissolved in 99% methanol, was mixed with 800 µl of DPPH reagent (0.004%). Methanol was utilized as a reagent blank. The reagents were amalgamated and incubated for 30 minutes in darkness at ambient temperature. The percentages of DPPH free radical scavenging activity were calculated using the following formula **(Eq.5)**:

$$\textit{Inhibition}\ (\%) = \frac{A_C - A_S}{A_C} \times 100 \qquad \text{Eq. (5)}$$

Where; the absorbance of the control is represented by Ac and As is the absorbance of the sample.

II.2.6.2. Reducing power assay

The reduction capabilities of the evaluated samples (AQEs and ZnO-NPs) were determined using the methods described by (Elkoraichi *et al.*, 2022). 0.1 ml from each sample, prepared at varying concentrations, was combined with an equal volume of phosphate buffer (0.2M; pH 6.6) and 1% potassium ferricyanide. The produced mixture was then incubated at 50 °C for 20 minutes. The reaction was interrupted by adding 0.25 ml of 1% trichloroacetic acid to the mixture, which was centrifuged at 3000 g for 10 minutes. 0.25 ml of the supernatant was mixed with 0.25 ml of distilled water and 0.5 ml of a 0.1% $FeCl_3$ solution. Ascorbic acid and BHT functioned as standards. Absorbance measurements for all samples

were performed at 700 nm. The sample concentration that yields an absorbance of 0.5 is called the effective concentration (EC50).

II.2.6.3. Total antioxidant capacity

The phosphomolybdate assay depends on the samples' capacity to reduce Mo (VI) to Mo (V), thereby forming a green phosphate/Mo (V) complex in acidic conditions. The total antioxidant capacity of the samples analyzed was determined using the methodology outlined by Mouffouk *et al*. (2023). In conclusion, 0.1 ml of extract was combined with 1 ml of a reagent comprising 0.6 M sulfuric acid H_2SO_4, 28 mM sodium phosphate $NaPO_4$, and four mM ammonium molybdate. The reaction mixture was incubated in tubes for 90 minutes at 95 degrees Celsius. Following cooling, the absorbance of the reaction solution was assessed at 695 nm compared to a blank. The blank is replaced with 0.1 ml of distilled water instead of the samples. A standard curve for ascorbic acid approached the ascorbic acid equivalents ($Y = 0.0046X + 0.0236$; $R^2 = 0.9932$**/ Refer to Appendix N°:4**). Results are presented as (mg AA Eq/g DE).

II.2.6.4. β-carotene bleaching assay

The BCB assay was conducted using the methodology outlined by Morales *et al.* (2012) A solution of β-carotene was prepared by dissolving two milligrams of β-carotene in ten milliliters of chloroform. Two milliliters of this solution were put into a round-bottom flask. After the chloroform evaporated under vacuum at 40 °C, a combination of linoleic acid (40 mg), Tween 80 emulsifier (400 mg), and ultra-pure distilled water (100 mL) was added to the flask and agitated vigorously. Aliquots of 4.8 mL of this emulsion were dispensed into individual test tubes, each containing 0.2 mL of different concentrations of the tested samples or reference (BHT). After adding the emulsion to each tube, the tubes were agitated and positioned in a water bath maintained at 50 °C for 2 hours. The absorbance at 470 nm was recorded immediately following the addition of the β-Carotene emulsion at the commencement of the experiment and after 120 minutes of incubation. The suppression of β-Carotene degradation was assessed using the following formula **(Eq.6)**:

$$\boldsymbol{\beta - Carotene\ bleaching\ Inhibition}\ (\%) = \frac{\boldsymbol{A_{2H}}}{\boldsymbol{A_0}} \times \mathbf{100} \qquad \textbf{Eq. (6)}$$

Where; Abs_{2h} denotes the absorbance of β-carotene after 2 hours of the assay, and Abs_0 represents the initial absorbance of β-carotene.

II.2.7. Evaluation of anti-inflammatory activity (*in vitro*)

II.2.7.1. Hemolysis Assay

The biosafety and biocompatibility of the samples evaluated in this study were determined using human erythrocytes by a hemolytic assay, as outlined by Iqbal *et al.* (2021). The author voluntarily contributed the blood sample. Precisely 1 mL of freshly collected red blood cells was acquired and preserved in a falcon tube containing EDTA. Erythrocytes were obtained using centrifugation at 1000g for ten minutes. The supernatant was discarded, and the solid residue was repeatedly washed with phosphate-buffered saline (pH 7.4). Erythrocyte suspensions at a 10% concentration were prepared by mixing 1 mL of erythrocytes with 9 mL of PBS. 100 µL of the erythrocyte suspension was treated with 1 mL of various quantities of test samples (AQEs, ZnO-NPs, and Diclofenac sodium as the reference). After treatment, the chemical mixture was placed in an incubator (37 °C/1 h) and centrifuged at 1000 rpm for 5 minutes. The hemoglobin concentration was quantified by assessing the supernatant's absorbance at 540 nm via spectrophotometry following centrifugation at 300 rpm for 3 minutes. The following equation **(Eq.7)** was utilized to estimate the approximate percentage of hemolysis inhibition:

$$\textbf{\textit{Hemolysis Inhibition}}\ (\%) = 100 - \frac{Abs_{sample}}{Abs_{control}} \times 100 \qquad \textbf{Eq. (7)}$$

II.2.7.2. Egg albumin denaturation assay

Inflammatory and arthritic conditions arise from protein denaturation, leading to the formation of autoantigens. Protein denaturation may transpire in particular arthritic situations within the body. Agents capable of inhibiting protein denaturation can be employed in formulating anti-inflammatory pharmaceuticals (Yesmin *et al.*, 2020). The reaction mixture (5 ml) was formulated by amalgamating 200 µl of fresh egg albumin with 2.8 ml of saline phosphate buffer (PBS, pH 6.4) and 2 ml of various sample concentrations (200-1000 µg/ml)—an equivalent volume of pure water served as the negative control. The incubation period was 15 minutes at 37 °C, after an additional heating duration of 5 minutes

at 70 °C. The absorbance was subsequently measured at 660 nm. Diclofenac sodium 50mg® served as a reference at identical final concentrations to the samples. The subsequent formula **(Eq.8)** was utilized to estimate the inhibition percentages of albumin denaturation:

$$\textit{Inhibition of egg albumin denaturation}(\%) = \frac{A_c - A_s}{A_c} \times 100 \quad \textbf{Eq. (8)}$$

Where; the absorbance of the control is represented by Ac and As is the absorbance of the sample.

II.2.8. Antibacterial activity testing

The vulnerability of the bacterial strains to the examined materials was assessed utilizing the agar well diffusion method. The antibacterial effectiveness of AQEs and ZnO-NPs was evaluated against six distinct human pathogenic microorganisms. The strains included *Bacillus subtilis* ATCC 6633 (S1), *Listeria innocua* CLP 74915 (S2), *Escherichia coli* ATCC 8737 (S3), *Pseudomonas aeruginosa* ATCC 6538 (S4), *Staphylococcus aureus* ATCC 6538 (S5), and *Salmonella typhimurium* ATCC 14028 (S6). The agar diffusion method previously described by Chavan *et al.* (2020) was employed for validation. Aseptic conditions were maintained throughout the whole testing process. Prior to use, the bacterial strains were cultured on nutrient agar for 24 hours at 37°C during the stationary growth phase. A further contributing factor is the suspension of bacterial cells, present at a concentration of 10^8 colony-forming units per milliliter (Optical density between 0.080-0.100 at 600nm). Sterilized swabs were utilized to apply the compounds to Petri dishes with Mueller Hinton agar. Subsequently, four holes, each measuring 6 mm in diameter, were made. Subsequently, 50 µl of test samples, all solubilized in DMSO (5%, v/v), were administered at varying concentrations (25, 50, 75, and 100 mg/ml for AQEs and 0.625, 1.25, 2.5, and 5 mg/ml for ZnO-NPs). Amoxicillin (10 µg/disk), Ciprofloxacin (30 µg/disk), and DMSO (5%) were utilized as the positive and negative controls. The created plates were placed in an incubator at 37°C for 24 hours. Subsequent to incubation, the diameter of the inhibitory zones was measured in millimeters using a scale.

II.2.9. Evaluation of gastroprotective activity *in vivo*

II.2.9.1. Acute toxicity testing for aqueous extracts AQEs and their ZnO-NPs

An acute toxicity investigation was conducted on the aqueous extracts of plants and their ZnO nanoparticles, manufactured following the traditional acute toxic approach by OECD rules (OECD/OCDE, 2001). Male albino rats were utilized for the acute toxicity assessment. The animals were subjected to an overnight fast, receiving only water, after which the various samples examined in this investigation were delivered via oral gavage as follows: aqueous extracts at a dosage of 2000 mg/kg body weight (AQE-JP, AQE-PG and Mixture of AQEs). ZnO nanoparticles were also evaluated at 100 mg/kg of body weight (ZnO-JP/ZnO-PG). Three animals were utilized for each dosage. Animals were monitored for two weeks. The doses used in this test were selected by the author based on previous research indicating that both plants are non-toxic. This preliminary assessment was conducted to confirm safety before proceeding to evaluate their gastroprotective properties against NSAID-induced gastric lesions.

II.2.9.2. Experimental design for the antiulcer study

Gastroprotective Properties of our samples were also Evaluated using an animal model of Gastric ulcers generated by NSAIDs in rats. The Indomethacin-induced gastric lesions model is frequently employed to examine the pathophysiology of stomach ulcers and assess the gastroprotective effects of several pharmaceuticals and natural substances. All samples in the present investigation were freshly prepared in distilled water (10 ml/kg body weight). The ZnO-NP sample was ultrasonicated for one hour using a DSA-SK1-2.8L sonicator to achieve optimal dispersion. After ultrasonication, the ZnO-NPs solution was vortexed for 60 seconds before delivery to each rat. The experimental protocol comprises 40 rats, categorized into eight groups of 5 each, as depicted in **(Fig. II.2.)**.

- Group 1 and 2 serves as the standard negative (normal control group) and positive control (Ulcer group) respectively, wherein the animals received only distilled water.

- Group 3: These animals were administered Omeprazole® as the typical anti-ulcer medication (20 mg/kg b.w).
- Group 4 and 5: These animals were administered AQE-JP and AQE-PG (200 mg/kg b.w) respectively.
- Group 6: The animals were administered a mixture of (AQE-JP+PG) at 200 mg/kg body weight.
- Group 7 and 8: The animals were administered ZnO-JP and ZnO-PG (10 mg/kg body weight) respectively.

All pretreatments were given once daily for 15 days. In the day 16. All animals were fasted for 18 hours then given the last dosage, after 30 min, ulceration was induced by the administration of Indomethacin (50mg/kg b.w in 2% of Na_2CO_3) for all animals (G2-8) (Aiyeola & Oluwole, 2024; Gomaa *et al.*, 2018; Nabil *et al*., 2021; Turkyilmaz *et al.*, 2019). Six hours after Indomethacin administration, the animals were sacrificed with cervical dislocation after slight anesthesia with chloroform and blood was gathered in heparinized tubes for liver function tests (LFT) and renal function tests (RFT).

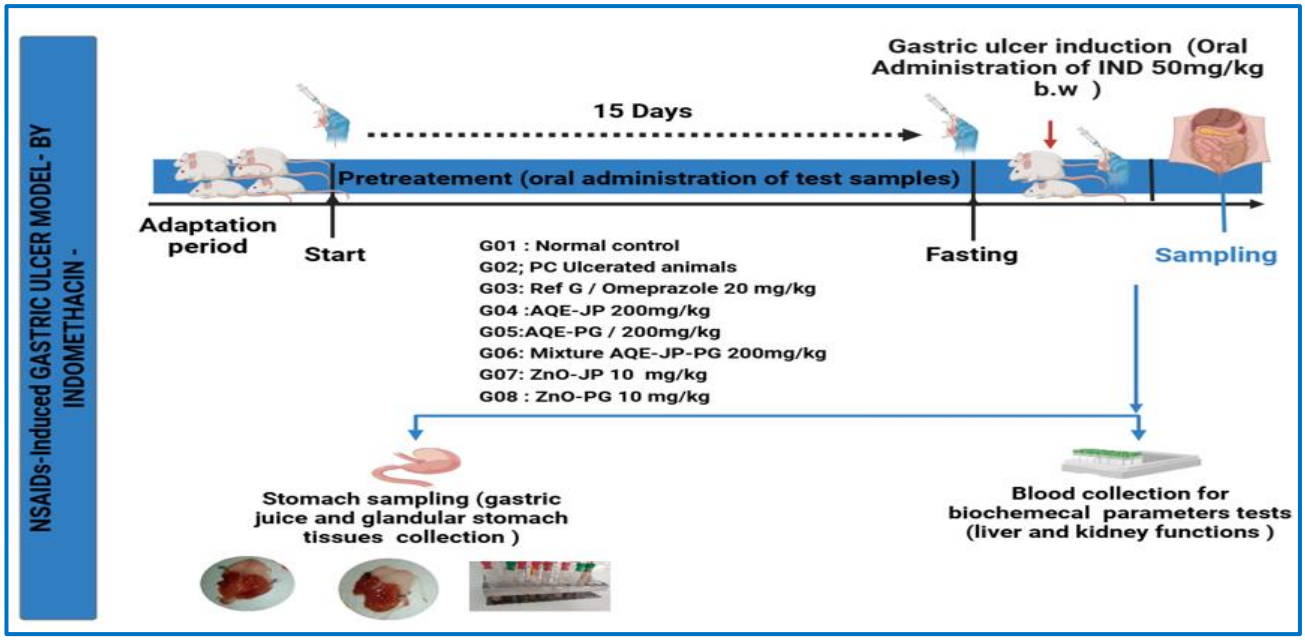

Figure.II.2. Experimental design of the gastroprotective evaluation

II.2.9.3. Gastric juice collection and pH measurement

The gastric juice collected from each rat was quantified in mL per 100 g of body weight and centrifuged at 3000 rpm for 10 minutes. A digital pH meter (WTW-PH7110) was employed to ascertain the pH of the supernatant.

II.2.9.4. Macroscopic and Microscopic evaluation of gastric tissues

The rats' stomachs were incised along the greater curvature. The gastric juice was collected, and the stomach tissues were rinsed with cold saline (0.9% NaCl) and photographed. Subsequently, macroscopically assessed for hemorrhagic lesions occurring in the glandular mucosa. The parameters utilized for assessing the lesion index included mucosal color, loss of mucosal folds and mucus, edema, petechiae, and ulcer count, adhering to the standard grading outlined in **Table II.1**, as outlined by (Elnashar & Abduljawad, 2018; Zhoua *et al.*, 2020)**.** Ulcer index (UI) and Ulcer inhibition rate (%) was calculated as follows Abdeen *et al.* (2019); Harakeh *et al.* (2022)**.**

$$\textbf{Ulcer Index (UI)} = \textbf{(UN + US + UP) X 10 - 1} \quad \textbf{Eq. (9)}$$

Where: UI; Ulcer Index, UN; Average of number of ulcers per animal US; Average of severity score and UP; Percentage of animal with ulcer.

$$\textbf{Protective rate (\%)} = \frac{\textbf{Ulcer Index}_{\textbf{Control}} - \textbf{Ulcer Index}_{\textbf{Treated}}}{\textbf{Ulcer Index}_{\textbf{Control}}} \times \textbf{100} \quad \textit{Eq.}\,\textbf{(10)}$$

Table II.1. Scale by attribution of scores for degree of ulceration.

Parameters		Scores
Petechiae	Light	1 point
	moderate	2 points
	intense	3 points
Thickening of the ulcer		(1 point/mm2)
Oedema		1 point
Hyperemia		1 point
Ulcers	not perforated	1 point/mm2
	perforated	2 points/mm2
Hemorrhagic lesion		3 points

II.2.9.5. Histopathological examinations

Representative tissue samples (stomach, liver, and kidney) were previously fixed in 10% formalin for microscopic examination. Dehydrated with escalating concentrations of ethanol, cleared in xylene utilizing a tissue processor (SLEE, MTP, K190016), and embedded in paraffin (SLEE, MPS/P1). Sections of 4 µm in thickness were produced using a conventional microtome (Thermo Scientific Microm-HM325) and subsequently stained with hematoxylin and eosin (HE). The tissue sections were analyzed and photographed using light microscopy (Optika B-293).

II.2.10. Evaluation of *in vivo* antioxidant activity

II.2.10.1. Preparation of homogenate

Right after the sacrifice, the stomachs of each animal were excised, rinsed with ice-cold saline, and the glandular portion was extracted, weighed, and homogenized in Tris-buffered saline (Tris; 50 mM, NaCl 150 mM, ice-cold PBS; pH 7.4) to achieve a 10% (w/v) homogenate. Subsequently, the homogenate was centrifuged at 3000 g for 15 minutes, and the supernatant was collected and stored at -20 °C for subsequent biochemical analyses: total protein content, lipid peroxidation (MDA), reduced glutathione (GSH), and catalase (CAT) (Abdeen *et al*., 2019).

II.2.10.2. Estimation of gastric total proteins content

The tissue proteins were identified using a colorimetric approach with a spectrophotometer, employing Coomassie blue as a reagent that reacts with the proteins' amine group (NH2) to form a blue complex. The intensity of the blue hue correlates with the protein concentration, and its manifestation reflects the ionization level of the acidic medium (Bradford, 1976). In summary, 100 mg of Coomassie blue should be dissolved in 50 mL of 95% ethanol, and the solution must be agitated for two hours in darkness before adding 100 mL of 85% orthophosphoric acid (H_3PO_4). Furthermore, distilled water was employed to achieve a total volume of 1 liter, after which filter, paper was utilized to cleanse the resulting solution. Subsequently, 1 ml of Bradford's reagent was combined with 200 µl of the tissue homogenate or standard (bovine serum albumin), and the resultant mixture was

incubated at room temperature for 5 minutes. The absorbance was subsequently measured at 595 nm. The protein concentration is evaluated against a standard range of bovine serum albumin (0.1-0.2-0.4-0.6-0.8-1 mg/mL) conducted under identical conditions **(Refer to Appendix N°:4)**.

II.2.10.3. Lipid peroxidation (LPO) estimation

Lipid peroxidation in stomach tissue was evaluated by quantifying malondialdehyde (MDA) production using the method established by Ohkawa *et al.* (1979). approach is based on the interaction of MDA with thiobarbituric acid (TBA) under acidic conditions and elevated temperature (100°C) to produce a pink MDA-$(TBA)^2$ complex. The TBA reagent consists of TCA at 20% w/v, TBA at 0.375% w/v, and BHT at 0.01% w/v, dissolved in 25 ml of 1N HCl, with the final volume adjusted to 100 ml using distilled water and subsequently heated at 40°C until TBA is fully dissolved. In summary, 0.2 ml of tissue homogenate was combined with 0.8 ml of TBA reagent. The solution was incubated at 100 °C for 15 minutes, rapidly cooled in an ice bath, then centrifuged at 3000 rpm for 15 minutes. The absorbance of the transparent pink supernatant was spectrophotometrically measured at 532 nm relative to a blank sample (Rathee *et al.*, 2006). The data were presented as µmol/mg of stomach tissue proteins. The concentration of thiobarbituric acid reactive compounds (TBARS) was determined using the molecular extinction coefficient of MDA (å= 1.53.105 $M^{-1}.cm^{-1}$). The results were expressed as nmol/mg of proteins **(Eq. 11)**.

$$\boldsymbol{MDA}\ (\text{nM/mg of prot}) = \frac{\boldsymbol{OD\ Sample}}{\boldsymbol{1.53 \times 10^5\ (mg\ of\ prot)}} \qquad \boldsymbol{Eq.(11)}$$

II.2.10.4. Assessment of reduced glutathione (GSH)

Reduced glutathione (GSH) was quantified using the Ellman method (1959) (Ellman, 1959). The assay relies on the oxidation of glutathione (GSH) by 5,5'-dithiol-bis (2-nitrobenzoic acid) (DTNB), known as Ellman's reagent. DTNB and GSH undergo a reaction to produce 2-nitro-5-thiobenzoic acid (TNB), characterized by a vivid yellow color and a peak absorbance at 412 nm. In this experiment, 800 µL of homogenate samples

are mixed with 200 µL of salicylic acid (0.25%). The mixture was then centrifuged for five minutes at a speed of 1000 rpm. Additionally, 25 µL of DTNB (0.01M) and 500 µL of supernatant were combined with 1000 µL of tris buffer (tris 0.4mol, 0.02mol NaCl, pH = 8). After 5 min of incubation, the absorbance of the reaction medium is measured at 412 nm and the content of GSH in tissue homogenate was quantified in micromoles per milligram of protein tissue **(Eq.12)**.

$$GSH\ (\text{nM/mg of prot}) = \frac{OD\ Sample \times 1 \times 1.525}{13133 \times 0.8 \times 0.5 \times (mg\ of\ prot)} \times D \qquad Eq.(12)$$

Where; OD: Optical Density. 1.525 mL: total volume of the blend; 13133: absorption constant of SH groups at 412 nm; 0.5 mL: volume of the supernatant; 1 mL: volume of the protein mixture; 0.8 mL: volume of the homogeneous solution devoid of protein in 1 mL.

II.2.10.5. Estimation of catalase (CAT) activity

Catalase activity was assessed in accordance with Aeb (1984) established with minor modifications. This assay operates on the idea of hydrogen peroxide decomposition facilitated by catalase, as illustrated by the following reaction: 20 µL of homogenized tissue was combined with 780 µL of PBS (0.1 M, pH 7.5) and 200 µL of H_2O_2 (0.030 M). The breakdown rate of H_2O_2 in the presence of CAT was spectrophotometrically measured at 240 nm immediately and after 1 minute; enzymatic activity was quantified as IU/min/g of protein **(Eq.13)**.

$$CATs\ (\text{UI/Min /g of prot}) = \frac{(2.3033/T).(Log\ A1/A2)}{DF \times (g\ of\ prot)} \qquad Eq.(13)$$

Where: A1 denotes absorbance at the first minute, A2 signifies absorbance at the second minute, and T represents the time interval in minutes.

II.3. Statistical data analysis

The statistical analysis was conducted using SPSS software (version 22 for Windows). All in vitro tests were conducted in triplicate, and the data are presented as mean ± standard

deviation (SD). IC50 values are determined using a linear regression method based on the curve [% inhibition = f(concentrations)]. The distinction between the control and various tests is assessed using the ONE-WAY ANOVA test, succeeded by the DUNNETT post hoc test. Pharmacological tests were reported as mean ± standard error of the mean (SEM) based on five repetitions. In all instances, p values ≤ 0.05 are deemed statistically significant. Analysis of Principal Components (APC) was also conducted to assess the relationships between study parameters. Finally, Graphs were generated using Origin Pro 2024.

Results & Discussions

Conclusion & Future Prospects

1. Conclusion

In this study, we conducted a comprehensive exploration into the therapeutic potential of tow medicinal species largely used by Algerian population for various purposes. *J. phoenicea* leaves and *P. granatum* peels. Our investigation encompassed a wide range of biological activities, focusing on antioxidant, anti-inflammatory, Antibacterial, and gastroprotective properties. Aqueous extracts of the selected species prepared using decoction procedures revealed a rich array of bioactive compounds, prominently including phenolic compounds. These compounds are known for their antioxidant and anti-inflammatory properties, which are critical in combating oxidative stress and inflammatory responses within biological systems.

The green synthesis of ZnO-NPs utilized the aqueous extract of the two medicinal species, ensuring an environmentally friendly approach. Characterization using UV-Vis spectrophotometry showed distinct absorption peaks at 302 nm for ZnO-JP NPs and 361 nm for ZnO-PG NPs, indicating their nanoparticulate nature suitable for biomedical applications. Additional analyses via FTIR, XRD, and SEM/EDS confirmed the crystalline structure, morphology, and surface characteristics of these nanoparticles. SEM images revealed nanoparticulate nature of our prepared ZnO-NPs with average diameters of 30.16± 5.20 nm for ZnO-JP NPs and 34.08± 7.44 nm for ZnO-PG NPs.

In vitro experiments demonstrated that both Aqueous extracts and their biogenic synthesized ZnO-NPs possess robust antioxidant potential as evidenced by their IC50 values in various antioxidant assays especially for our prepared AQEs (DPPH Test; 44.42 ± 0.140 μg/mL and 71.034 ± 0.340/ FRAP Test; 17.88±1.84 μg/mL and 23.67±4.86 μg/mL/ TAC; 265.36 ± 3.69 and 232.09 ± 1.02 mg Eq AA/g Dw./ BBC test; 607.88 ± 4.43 μg/mL and 206.04 ± 4.36 μg/mL for AQE-PG and AQE-JP respectively). While ZnO-NPs were more potent in safeguarding β-carotene bleaching as evidenced by their IC50 values (141.99 ±1.17 µg/ml and 265.006 ± 2.79 µg/ml for ZnO-JP and ZnO-PG NPs respectively). Furthermore, the anti-inflammatory effects observed in the *in vitro* tests highlight the potential of these substances in managing inflammatory conditions evidenced by their ability to stabilize membrane of HRBCs and protect egg albumin denaturation.

In vivo gastroprotective study of our prepared samples was assessed using NSAIDs-induced acute gastric ulcer model in male rats with Oral administration of single dose of Indomethacin 50 mg/kg of b.w. In this experience eight groups with five rats in each were received our tested samples as follow; normal control animals and Ulcer animal receiving distilled water, Omeprazole group; receiving standard drug Omeprazole 20mg, AQEs groups; receiving 200mg/kg of AQE-JP and AQE-PG respectively, group receiving the mixture of the two AQEs; Mixt AQE-JP/PG 200 mg/kg, and finally ZnO-NPs groups; receiving 10mg/kg of ZnO-JP and ZnO-PG NPs respectively. All animals were pretreated with these samples once for 15 days before they were supplemented with Indomethacin in the day 16. several parameters such as volume and pH of gastric juice, weight of the stomach tissue, Ulcer Index, Protective rate, Liver and kidney function Test, oxidative stress markers, and histopathological examination were assessed in this work.

research results from the *in-vivo* experiment highlight the intriguing potential for our prepared AQEs especially when they administered as a mixture in treating stomach ulcers confirming the traditional uses. Concerning Zinc oxide NPs, a potent gastroprotective capacity was observed as evidenced by the protective rate of stomach against the aggression of Indomethacin 94.8 % and 97.4 % compared the standard drugs Omeprazole ^{20mg} 83.11% and their effect on reducing lipid peroxidation and enhancing GSH content and Catalase activity in stomach tissues. while suggesting the possibility of supplementary effects related to the delivered dosage. Consequently, further in-depth investigations are required, mainly to judge the effectiveness of various dosages for stomach ulcer therapy and to examine the broader impacts of these nanomaterials on other organs.

2. Future Works

This research marks a significant advancement in the fields of Ethno-pharmacology and Nano-therapy by harnessing the bioactive constituents of *J. phoenicea* and *P. granatum* extracts, along with the unique properties of ZnO-NPs, for the management of gastric ulcers. The findings offer promising opportunities for further exploration and development. Future work will aim to expand upon this study, establishing a comprehensive framework to enhance its scientific and clinical relevance while broadening its potential impact.

- Evaluate the anti-urease activity of the extracts or nanoparticles to assess their potential in reducing *H. pylori*-induced gastric inflammation.
- Investigate the efficacy of the studied plant extracts and/or synthesized ZnO nanoparticles in inhibiting *Helicobacter pylori* growth.
- Conduct comprehensive toxicity studies on additional organs (e.g., liver, kidney, and lungs) using histopathological and biochemical analyses to ensure the safety of the tested Nanoparticles.
- Test different doses of the extracts or nanoparticles to establish a safe therapeutic window and determine the maximum tolerated dose.
- Explore the synergistic potential of combining plant extracts or nanoparticles with standard antibiotics to enhance efficacy and overcome antibiotic resistance in *H. pylori*.
- Evaluate the long-term effects of the samples on the gastrointestinal tract and their potential to restore microbiota balance.
- Investigate the anti-inflammatory effects of the plant extracts or nanoparticles in models of gastric inflammation to assess their broader therapeutic potential.

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Appendixes

تحقيق حول النباتات او العلاجات التقليدية المستعملة لدى سكان (الوادي -المغير- جامعة -ورقلة - غرداية) في التداوي ضد القرحة المعدية .

في اطار التحضير لنيل شهادة الدكتوراه في الطور الثالث LMD تفضلا ومساهمة منكم ارجو ملء هذه الاستمارة الموجهة لكافة فئات المجتمع خصيصا كبار السن ومن لديهم خبرة في مجال التداوي بالأعشاب.

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I. البيانات الشخصية :

- **تاريخ اجراء التحقيق :** .....
- **السن :** .....
- **الجنس:** ☐ ذكر ☐ انثى
- **مكان الاقامة :** .....
- **الحالة الاجتماعية:** ☐ متزوج ☐ اعزب ☐ مطلق ☐ ارمل
- **المؤهل الاكاديمي:** ☐ غير متعلم ☐ المتوسط او الثانوي ☐ جامعي ☐ دراسات عليا
- **هل انت ?** ☐ بائع الاعشاب

  ☐ مداوي بالأعشاب (وصف الاعشاب للمريض)

  ☐ مستعمل للأعشاب (حدد مهنتك) :.....
- **هل تستعمل العلاجات التقليدية بالنباتات الطبية في علاج الامراض التي تصيبك ?**

  ☐ نعم ☐ لا

II. حول العلاجات التقليدية المستعملة في التداوي ضد القرحة المعدية :

- **مصدر معلوماتك حول العلاجات التقليدية :**

☐ الصيدلي ☐ العشاب (العطار) ☐ الكتب ☐ عن طريق الخبرة من الغير

- **النبتة الاساسية المستعملة (يمكنكم ذكر الاسم المعروف لها في منطقتكم)**

.....

- **هل توجد استعمالات اخرى لهذه النبتة :**

.....

.....

- **نبتة او مواد اخرى مضافة (عسل مثلا او اعشاب اخرى ....) :**

.....

.....

- **الجزء المستعمل كعلاج :**

☐ (النبتة كاملة: الجزء الهوائي+ الجذور) ☐ الجزء الهوائي ككل (أوراق +سيقان +أزهار)

☐اوراق ☐ أوراق+ سيقان ☐أزهار ☐ الجذور

☐ قشور ☐ ثمار ☐البذور

- **استعمال النبتة:**

☐ طازجة ☐ جافة

- **من اين تحصلتم على هذه النبتة ؟**

☐عن طريق اقتنائها من محلات العطارة ☐ عن طريق جمعها من اماكن نموها

- **فصل جمع النبتة (اذا كنتم قد تحصلتم عليها عن طريق جمعها من اماكن نموها):**

.....

- **طريقة الاستعمال :**

☐غلي ☐ نقع في الماء الساخن ☐ نقع في الماء البارد ☐ غبرة او بودرة (بلع مباشرة مع الماء) ☐ او طريقة اخرى .....

- **مدة العلاج:**

☐ يوم ☐اسبوع ☐ شهر ☐الى غاية التحسن

- **وقت الاستعمال :**

☐على الريق (مرة واحدة في اليوم) ☐ قبل الوجبات (مرتين في اليوم)

☐ بعد كل وجبة (مرتين في اليوم) ☐قبل النوم (مرة واحدة في اليوم) ☐عشوائيا

- **الجرعة المستعملة :**

☐كاس شاي من منقوع او مغلي النبتة ☐ كاس ماء من منقوع او مغلي النبتة ☐ملعقة من بودرة النبتة مع كاس ماء ☐استعمال عشوائي

وجود أعراض جانبية : ☐ نعم ☐ لا

.....

Appendix 2(A): Plants used only as a treatment for gastric ulcers.

Plants species	Used parts	Mode of use	Dose of use	Time of use	Duration of treatment	FC		RFC
Punica granatum L	**(P)**	**Powder**	A Spoonful Of Plant	On An Empty Stomach Before Sleeping Before Meals After Meals Randomly	Until Improvement For Days For Weeks	**39**	**60**	**0.2**
		Decoction	A Glass Of Water A Cup Of Tea	Randomly On An Empty Stomach Before Sleeping Before Meals After Meals	Until Improvement For Weeks	**13**		
		Infusion	A Glass Of Water A Cup Of Tea	On An Empty Stomach Before Meals	Until Improvement For Days For Weeks For Month	**7**		
		Maceration	A Glass Of Water	On An Empty Stomach	Until Improvement	**1**		
Juniperus phoenicea L	**(L+S)** **(L)**	**Powder**	A Spoonful Of Plant Powder	Randomly On An Empty Stomach Before Sleeping Before Meals After Meals	Until Improvement For Days	**24**	**30**	**0.1**
		Infusion	A Cup Of Tea	On An Empty Stomach	Until Improvement	**4**		
		Decoction	A Cup Of Tea	Randomly On An Empty Stomach	For Weeks	**2**		
Artemisia herba alba Asso	**(Ap)** **(L+S)**	**Powder**	A Spoonful Of Plant Powder	Randomly On An Empty Stomach	Until Improvement For Days	**10**	**23**	**0.07**

	(L)			Before Sleeping After Meals				
		Decoction	A Glass Of Water A Cup Of Tea	On An Empty Stomach Before Sleeping Randomly	For Weeks For Days Until Improvement	**9**		
		Infusion	A Glass Of Water A Cup Of Tea	On An Empty Stomach Before Sleeping Randomly	Until Improvement For Days	**4**		
Glycyrrhiza glabra L	**(R)**	**Infusion**	A Glass Of Water	After Meals Before Meals Before Sleeping	Until Improvement For Weeks For Days	**3**	**7**	**0.02333**
		Decoction	A Glass Of Water	Before Meals	Until Improvement	**1**		
		Powder	A Spoonful Of Plant Powder	On An Empty Stomach	For Days	**1**		
		Maceration	A Glass Of Water	Randomly	For Weeks	**1**		
		Other Methods	Others Method Of Use	Randomly	For Days	**1**		
Thymus vulgaris L	**(L)** **(L+S)** **(Ap)**	**Decoction**	A Glass Of Water	Randomly After Meals An Empty Stomach Before Sleeping	Days For Weeks	**4**	**7**	**0.02333**
		Infusion	A Glass Of Water	Before Sleeping Randomly	Until Improvement	**3**		
Pimpinella anisum L	**(S)**	**Decoction**	A Glass Of Water	Before Sleeping Randomly	Until Improvement For Weeks	**2**	**5**	**0.0166**
		Infusion	A Glass Of Water	Before Meals	Until Improvement	**2**		

				After Meals	For Days			
		Powder	A Spoonful Of Plant Powder	On An Empty Stomach	Until Improvement	**1**		
Artemisia campestris L	**(L) (Ap) (L+S)**	**Decoction**	A Glass Of Water A Cup Of Tea	Randomly After Meals	Until Improvement For Weeks	**3**	**5**	**0.0166**
		Infusion	A Glass Of Water	After Meals	Until Improvement	**1**		
		Powder	A Spoonful Of Plant Powder	On An Empty Stomach	For Month	**1**		
Trigonella foenum-graecum L	**(S)**	**Powder**	A Spoonful Of Plant Powder	On An Empty Stomach Before Meals	Until Improvement For Days	**4**	**4**	**0.0133**
Tetraclinis articulata	**(L) (Rsn)**	**Decoction**	A Glass Of Water A Cup Of Tea	On An Empty Stomach Randomly	Until Improvement For Days	**2**	**4**	**0.0133**
		Chewing gum	Fist Of Fingers Of Resin	On An Empty Stomach	Until Improvement	**1**		
		Maceration	A Glass Of Water	On An Empty Stomach	Until Improvement	**1**		
Teucrium polium L	**(L)**	**Powder**	A Spoonful Of Plant Powder	On An Empty Stomach Randomly	Until Improvement For Days	**2**	**4**	**0.0133**
		Decoction	A Glass Of Water	Before Meals	For Weeks	**1**		
		Infusion	A Glass Of Water	On An Empty Stomach	Until Improvement	**1**		
Zingiber officinale Rosce	**(R)**	**Infusion**	A Glass Of Water	Before Sleeping Before Meals	For Weeks For Days	**2**	**3**	**0.01**
		Decoction	A Glass Of Water	On An Empty Stomach	For Weeks	**1**		
Lawsonia inermis L	**(L)**	**Maceration**	A Cup Of Tea A Glass Of Water	On An Empty Stomach Before Meals	For Days	**3**	**3**	**0.01**
	(L)	**Decoction**	Cup Of Water	Before Sleeping	For Weeks	**1**	**2**	**0.0066**

Rosmarinus officinalis L	**(Ap)**	**Powder**	A Spoonful Of Plant Powder	Randomly	Until Improvement	**1**		
Curcuma longa L	**(R)**	**Powder**	A Spoonful Of Plant Powder	On An Empty Stomach	For Days	**1**	**1**	**0.0033**
Mentha spicata L	**(L)**	**Decoction**	A Cup Of Water	A Randomly	For Days.	**1**	**1**	**0.0033**
Ziziphus lotus L	**(L)**	**Decoction**	A Cup Of Water	On An Empty Stomach	Until Improvement	**1**	**1**	**0.0033**
Matricaria chamomilla L	**(Fl)**	**Infusion**	A Cup Of Water	Before Sleeping	Until Improvement	**1**	**1**	**0.0033**
Sesamum indicum L	**(S)**	**OtherMethods**	Other Method	Randomly	Until Improvement	**1**	**1**	**0.0033**
Cicer arietinum L	**(S)**	**Powder**	Spoonful Of Plant Powder	Randomly	Until Improvement	**1**	**1**	**0.0033**
Citrus limon L	**(P)**	**Powder**	Spoonful Of Plant Powder	On An Empty Stomach	For Days	**1**	**1**	**0.0033**
Daucus carota L	**(Raw)**Fresh Fruit Of Carrot			Randomly	Until Improvement	**1**	**1**	**0.0033**
Erythrea Centaurium L	**(Ap)**	**Infusion**	A Cup Of Tea	Before Sleeping	For Weeks		**1**	**0.0033**
Ceratonia siliqua L	**(Fr)**	**Powder**	A Spoonful Of Plant Powder	On An Empty Stomach	Until Improvement		**1**	**0.0033**
Ocimum basilicum L	**(L)**	**Decoction**	A Cup Of Tea	Before Meals	Until Improvement		**1**	**0.0033**
Onopordum maracanthum L	**(L)**	**Decoction**	A Cap Of Water	Before Sleeping	For Days		**1**	**0.0033**
Solanum tuberosum	**(T)**	**Juice**	Fresh Juice Of Potato	On An Empty Stomach	Until Improvement		**1**	**0.0033**
Acacia Senegal (L.) Willd	**(Rsn)**	**Decoction**	A Cup Of Tea	On An Empty Stomach	Until Improvement.		**1**	**0.0033**
Arthrospira platensis	**(Wp)**	**Powder**	A Spoonful of Plant Powder	Randomly	For Weeks.		**1**	**0.0033**
Salvia hispanica	**S**	**Decoction**	A cup of water	Randomly	Until improvement		**1**	**0.0033**

Triticum durum Desf	**S**	**Powder**	A spoonful of plant powder	Randomly	For weeks.		**1**	**0.0033**
Total (176)								**58.66%**
L; Leaves / LS; Leaves +Steam / Fl; Flowers / Ap; Arial parts / S; Seeds / R; Roots / P; Peels Fr; Fruits / RSN; Resin / Wp; Whole plant / T; Tuber FC; Frequency of citation TFC; Total frequency of citation								

Appendix2(B): Set of declared herbal mixtures used as traditional remedies for gastric ulcers.

Traditional remedies				
Principal plant	**Associated plants**	**Mode of use**	**FC**	**RFC**
Punica granatum L	***Juniperus phoenicea L (LS)***	**Powder / Decoction / Infusion**	**30**	**0.1**
	Tetraclinis articulata ***(L)***	Powder	8	0.0266
	Juniperus phoenicea L ***(LS)*** *+ Tetraclinis articulata****(L)***	Powder	6	0.02
	*Teucrium polium L****(L)***	Powder / Decoction	3	0.01
	Juniperus phoenicea L ***(LS)*** *+ Artemisia campestris L* ***(LS)***	Powder / Infusion	2	0.0066
	Juniperus phoenicea L ***(LS)*** *+ Artemisia herba-alba Asso* ***(Ap)***	Powder	2	0.0066
	Juniperus phoenicea L ***(LS)*** *+ Artemisia herba-alba asso* ***(LS)*** *+ Artemisia campestris L* ***(LS)***		2	0.0066
	Juniperus phoenicea L ***(LS)*** *+ Foeniculum officinale L* ***(S)*** *+ Pinus halepensis****(P)*** *+ Vicia faba L* ***(S)***	Powder	2	0.0066
	Juniperus phoenicea L ***(LS)*** *+ Artemisia herba-alba asso* ***(LS)*** *+ Tetraclinis articulata* ***(L)*** *+ glycyrhhiza glabra L* ***(R)***	Powder	1	0.0033
	Trigonella foenum-graecum L ***(S)***	Powder	1	0.0033
	*Trigonella foenum-graecum L****(S)*** *+ Mentha spicata L****(L)***	Infusion	1	0.0033
	Artemisia herba-alba Asso ***(Ap)*** *+ Lowsonia inermis L* ***(L)***	Decoction	1	0.0033
	Ceratonia siliqua L ***(Fr)***	Powder	1	0.0033

	*Curcuma longa L**(R)**+ Matricaria chamomilla L**(Fl)***	Infusion	1	0.0033
	*Foeniculum officinale L **(S)***	Powder	1	0.0033
	*Trigonella foenum-graecum L**(S)** + Thymus vulgaris L **(LS)***	Infusion	1	0.0033
	*Juniperus phoenica L **(LS)** + Artemisia campestris L **(LS)** + Teucrium polium L**(L)***	Powder	1	0.0033
	*Juniperus phoenicea L (**LS**) + Lowsonia inermis L **(L)***	Powder	1	0.0033
	*Juniperus phoenica L **(LS)** + Tetraclinis articulata **(L)** + Teucrium polium L**(L)***	Powder	1	0.0033
	*Matricaria chamomilla L**(Fl)** + Foeniculum officinale L **(S)***	Infusion	1	0.0033
	*Olea europaea**(L)** + Tetraclinis articulata **(L)** + Hordeum vulgare L**(S)***	Decoction	1	0.0033
TOTAL			**68**	**0.226**
Juniperus phoenica L	***Punica granatum L (P)***	**Powder Decoction Infusion**	**9**	**0.03**
	*Artemisia herba-alba asso **(Ap)***	Decoction	2	0.0066
	*Artemisia herba-alba Asso **(Ap)** + Artemisia campestris L **(LS)***	Decoction / Powder	2	0.0066
	*Artemisia herba-alba asso **(Ap)** + Mentha spicata L**(L)***	Powder	2	0.0066
	*Punica granatum L (**P**) + Laurisnobilis L**(L)***	Infusion	2	0.0066
	*Artemisia campestris L **(Ap)** + Teucrium poliumL **(L)***	Infusion	1	0.0033
	*Artemisia herba-alba asso **(Ap)** + Lauris nobilis L **(L)** + Olea europaea**(L)***	Decoction	1	0.0033
	*Foeniculum officinale L **(S)***	Powder	1	0.0033
	*Rosmarinus officinalis L **(L)** + Teucrium polium L**(L)***	Decoction	1	0.0033
TOTAL			**21**	**0.07**
***Artemisia herba-alba* Asso**	*Juniperus phoenicea L **(LS)** + Matricaria chamomilla L **(Fl)** + Zingiber officinale **(R)***	Infusion /Decoction	4	0.01
	*Trigonella foenum-graecum **(S)***	Powder Decoction Infusion	3	0.01
	*Mentha spicata L**(L)** + Thymus vulgaris L **(Ap)***	Decoction	2	0.0066
	*Juniperus phoenicea L **(LS)***	Decoction	1	0.0033
	*Foeniculum officinale L **(S)***	Powder	1	0.0033
	*Juniperus phoenicea L **(LS)** + Artemisia campestris L **(LS)***	Infusion	1	0.0033

	*Mentha spicata L**(L)***	Other Methods	1	0.0033
	*Rosmarinus officinalis L (L) + Trigonella foenum-graecum L**(S)***	Decoction	1	0.0033
	*Thymus vulgaris L **(LS)***	Powder	1	0.0033
	*Trigonella foenum-graecum L**(S)** + Matricaria chamomilla L**(Fl)***	Infusion	1	0.0033
TOTAL			**16**	**0.053**
***Glycyrrhiza glabra* L.**	*Curcuma longa L**(R)***	Infusion	3	0.01
	*Pimpinella anisumL **(S)***	Infusion		
	*Trigonella foenum-graecum L**(S)***	Infusion		
***Thymus vulgaris* L.**	*Syzygium aromaticum**(S)** + Zingiber officinale **(R)***	Powder	3	0.01
	*Mentha spicata L**(L)***	Decoction		
	*Syzygium aromaticum**(S)***	Infusion		
Trigonella foenum-graecum L.	*Mentha spicata L**(L)***	Decoction	2	0.0066
***Mentha spicata* L**	*Thymus vulgaris L **(LS)***	Infusion	2	0.0066
	*Trigonella foenum-graecum L **(S)***	Infusion		
***Matricaria chamomilla* L.**	*Mentha spicata L **(L)***	Infusion	2	0.0066
	*Foeniculum officinale L **(S)***	Decoction		
Zingiber officinale	*Mentha spicata L**(L)***	Infusion	1	0.0033
***Teucrium polium* L.**	*Punica granatum L **(P)** + Vicia faba L **(F)***	Infusion	1	0.0033
***Pistacia lentiscus* L.**	*Olea europaea **(EssO)***	Essentiel Oils	1	0.0033
***Salvia officinalis* L.**	*Origanum majorana **(L)***	Infusion	1	0.0033
***Lauris nobilis* L.**	*Citrus simensis **(P)** + Rosa damascena **(Fl)***	Decoction	1	0.0033
***Cuminum cyminum* L.**	*Foeniculum officinale L **(S)***	Infusion	1	0.0033
Total 124 (41.33%)				
L; Leaves / LS; Leaves +Steam / Fl; Flowers / Ap; Arial parts / S; Seeds / R; Roots / P; Peels Fr; Fruits / EsseO; Essential Oil /				

Appendix 02 C. Some traditional uses of plant species declared by interviewed people

Plant Species	Others Traditional uses
P. granatum	Anti-Diarrheic, Antidiabetic, Antiseptics for vaginal infections, Hemorrhoids, and Cosmetic preparations
L. inermis	Wound Healing, Hair Loss, Eczema, Headache
J. phoenicea	Anti-diarrheic, For the Chest, Lung, Liver, and Bladder, Very Diuretic, Diaphoretic
T. articulata	Hair Fungi Infection
A. herba alba	Analgesic, Colds, and Flu, Anti-Vomiting, applicable in cases of Poisoning, Anti-Diabetics, Hypoglycemic, Aperitif, and its Infusion is used against Colic, Anthelmintic, and Having for Coffee
A. campestris	For all internal diseases, as it is an Analgesic for Colic, its infusion is helpful in cases of Poisoning, Adjusting Blood Pressure, and Diabetes
M. chamomilla	Calmative, applicable in cases of Insomnia
O. maracanthum	Uterine Cleaning
R. officinalis	Hepatic Disorders, Irregularity of menstrual cycle, Antidiabetic
T. vulgaris	Colds, Influenza
T. polium	Antiseptic, Wounds Healing
M. spicata	Calmative, Menstrual Cramps, Anxiety
S. Officinalis	Antiseptic for wounds, Antiperspirant, Hypoglycemic, opening to block the Liver, Anti-Asthmatic, Treatment of cases of high Prolactin Hormone
O. majorana	Hormonal Regulation, Infertility, Menstrual Cramps
O. basilicum	Calmative, Gas Repellent, Uterine Cleaning
S. hispanica.	Weight Loss

G. glabra	Asthma, Liver Disorders
T. foenum-graecum	Diuretics, Aperitifs, For Weight Gain, Tonics for the stomach and nerves, Asthma and Shortness of breath, Hypoglycemics, Anti-Tumors, and Lack of Mother's Milk.
C. arietinum	Anemia: Their dried powder is helpful for Skin Burns
C. siliqua	Anti-diarrheic, Anemia, Skin Spot
A. Senegal	Maceration of its resin was helpful i n Ulcerative Colitis
P. anisum	Calmative, Hormonal Regulation, Gain Body Weight,
D. carota	Adjusting Blood Pressure, Reinforcing Eyesight
C. cyminum	Gas Repellent
Z. officinale	Diuretic, Colds, Influenza, Obesity,
C. longa	Analgesic, Anti-Inflammatory, Skin Disorders
L. nobilis	Mouthwash With Lavender,
S. indicum	Anemia
P. lentiscus	Wound Healing
C. limon	Anti-acne, Colds and Influenza, Anxiety, Adjusting for blood pressure
Z. lotus	/
S. tuberosum	Gain Weight It's fresh juice is beneficial for Skin Eczema.
A. platensis	Food Supplement, Face Mask
T. durum	Kidney Diseases, Growth,
E. Centaurium	Fever, Anthelmintic, Aperitif, Blood Purifier For Skin Diseases and wound healing. Their Essential Oils are helpful for Rheumatism

Appendix N° 03

Certificate of the Ethics approval

People's Democratic Republic of Algeria

Ministry of Higher Education and Scientific Research

University of El Oued

Faculty of Life and Natural Sciences

The Scientific Council

El Oued: 16/04/2023

N°: 19/S.C/F.L.N.S/E.U/2023

CERTIFICATE OF ETHICS APPROVAL

The head of the Scientific Council admits that the experimental protocol used in the study conducted by **Naoual Zemmouli** and his co-authors is in accordance with the requirements and guidelines of the Local Ethical Committee. The study is registered under the reference **11/2023.**

The approval was done at scientific council meeting No. 07/2022-2023, held on 22/03/2023.

Study Title:

The antiulcer proprieties of some plants and their nano-formulation against acute ulcer un rats.

Reference Study Number: (11/2023)

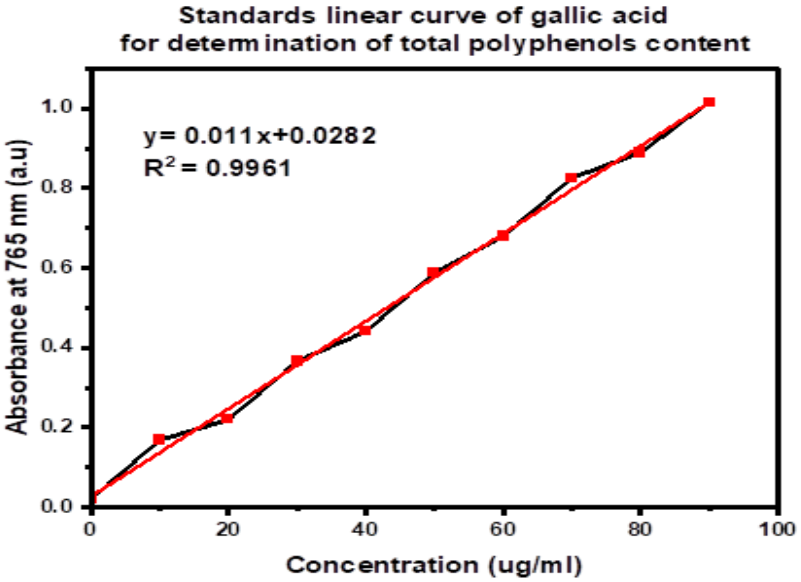
The head of the Scientific Council

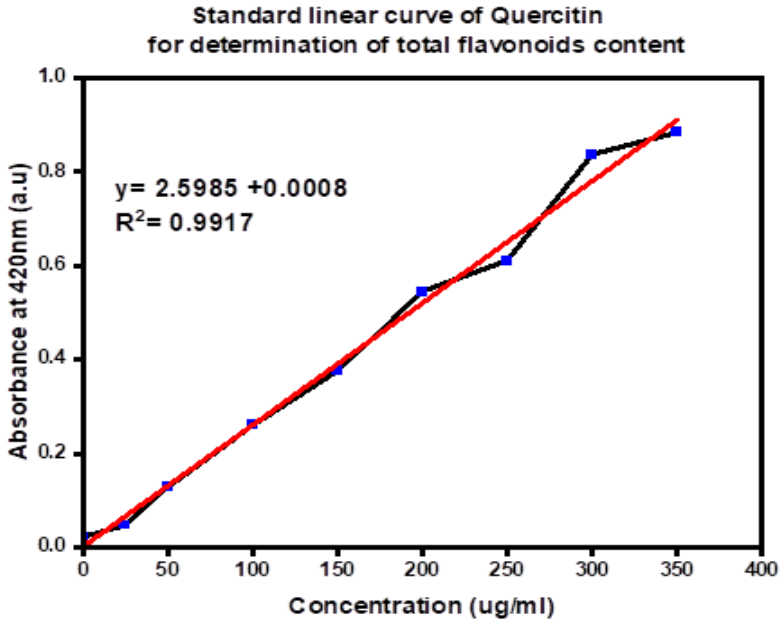
رئيس المجلس العلمي لكلية العلوم الطبيعية والحياة

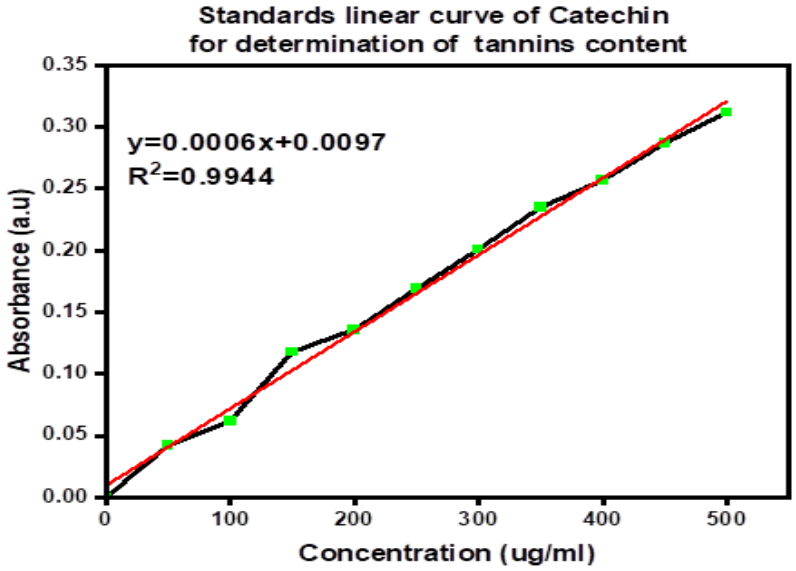
د/خزاني بشير

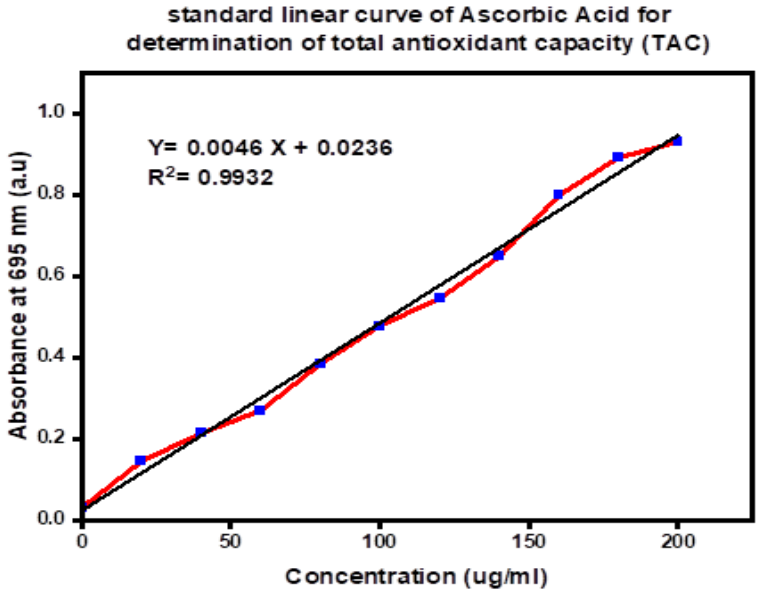
Appendix 04

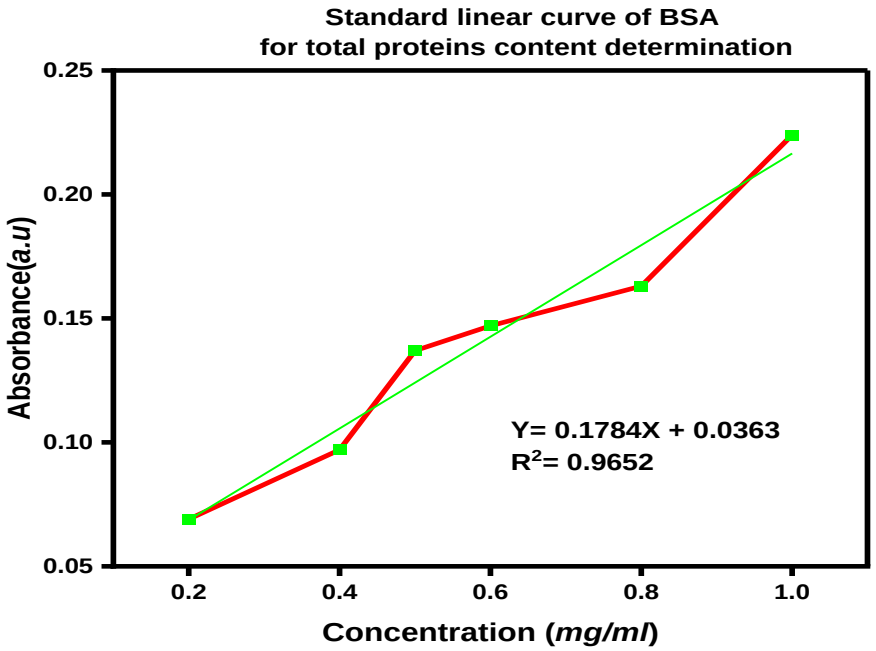
Standards linear curves used in the experimental part






Standards linear curve of Catechin
for determination of tannins content
y=0.0006x+0.0097
R2=0.9944
Absorbance (a.u)
Concentration (ug/ml)
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
100
200
300
400
500


standard linear curve of Ascorbic Acid for
determination of total antioxidant capacity (TAC)
Y= 0.0046 X + 0.0236
R2= 0.9932
Absorbance at 695 nm (a.u)
Concentration (ug/ml)
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200


Standard linear curve of BSA
for total proteins content determination
Absorbance(a.u)
0.25
0.20
0.15
0.10
0.05
0.2
0.4
0.6
0.8
1.0
Concentration (mg/ml)
Y= 0.1784X + 0.0363
R2= 0.9652

Name and formula

Reference code: 96-900-4181

Mineral name: Zincite
Compound name: Zincite
Common name: Zincite

Chemical formula: $Zn_{2.00}O_{2.00}$

Crystallographic parameters

Crystal system: Hexagonal
Space group: P 63 m c
Space group number: 186

a (?): 3.2490
b (?): 3.2490
c (?): 5.2040
Alpha (°): 90.0000
Beta (°): 90.0000
Gamma (°): 120.0000

Calculated density (g/cm^3): 5.68
Volume of cell (10^6 pm^3): 47.57

RIR: 5.25

Subfiles and quality

Subfiles: User Inorganic
User Mineral
Quality: User From Structure (=)

Comments

Creation Date: 03-02-2023 20:51:43
Modification Date: 03-02-2023 20:51:43
Publication title: Anharmonic thermal vibrations in ZnO Model: 3-c, at T = 293 K
COD database code: 9004180

References

Structure: Kihara, K., Donnay, G., *The Canadian Mineralogist*, **23**, 647 - 654, (1985)

Peak list

No.	h	k	l	d [A]	2Theta[deg]	I [%]
1	1	0	0	2.81372	31.777	55.1
2	0	0	2	2.60200	34.440	44.2
3	1	0	1	2.47510	36.266	100.0
4	1	0	2	1.91036	47.560	23.1
5	1	1	0	1.62450	56.612	30.4
6	1	0	3	1.47661	62.889	31.4
7	2	0	0	1.40686	66.396	4.0

8	1	1	2	1.37799	67.974	23.5
9	2	0	1	1.35811	69.109	10.8
10	0	0	4	1.30100	72.610	2.3
11	2	0	2	1.23755	76.989	3.6
12	1	0	4	1.18088	81.432	2.3
13	2	0	3	1.09267	89.654	8.0