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Theme

Comprehensive *In Vitro* Bioactivity Evaluation and Pharmacotoxicological Modeling of *Plantago psyllium*

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Abstract

This study aimed to evaluate the efficacy of *Plantago psyllium* seed ethanolic extract, which is rich in bioactive compounds such as flavonoids, polyphenols, and mucilage, in exhibiting multiple pharmacological activities including anti-inflammatory, antioxidant, antidiabetic, antiglycation, gastroprotective, and antibacterial effects.

Antioxidant activity was assessed using the DPPH assay, while anti-inflammatory potential was evaluated through inhibition of bovine serum albumin (BSA) denaturation using UV–Vis spectrophotometry, complemented by molecular docking simulations with COX-2. The study also investigated antidiabetic activity via α-amylase inhibition, antiglycation effects, and antibacterial activity against strains such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Furthermore, mucin protection assays were conducted to assess gastroprotective properties.

The results demonstrated significant antioxidant, anti-inflammatory, antidiabetic, antiglycation, and antibacterial activities, with IC_{50} and negative ΔG values indicating spontaneous and stable interactions with biological targets. Molecular docking confirmed the experimental findings, showing that ferulic acid—a major component—forms hydrogen bonds and hydrophobic interactions with enzymes and proteins. Antibacterial assays revealed stronger inhibition against Gram-positive bacteria compared to Gram-negative strains.

These findings highlight the therapeutic potential of *psyllium* as a natural source of bioactive compounds and open perspectives for its development into pharmaceutical or nutraceutical products, reinforcing its role as a safe and sustainable option in modern natural medicine.

Keywords: *Plantago psyllium*, molecular docking, COX-2, antioxidant, anti-inflammatory, antidiabetic, antiglycation, ferulic acid.

Résumé:

Cette étude visait à évaluer l'efficacité de l'extrait éthanolique des graines de *Plantago psyllium*, riche en composés bioactifs tels que les flavonoïdes, les polyphénols et les mucilages, dans la manifestation de plusieurs activités pharmacologiques, notamment les effets anti inflammatoires, antioxydants, antidiabétiques, antiglycation, gastroprotecteurs et anti-bactériens.

L'activité antioxydante a été évaluée par le test DPPH, tandis que le potentiel anti-inflammatoire a été étudié par l'inhibition de la dénaturation de l'albumine sérique bovine (BSA) à l'aide de la spectrophotométrie UV–Vis, complétée par des simulations de docking moléculaire avec COX-2. L'étude a également porté sur l'activité antidiabétique via l'inhibition de l'α-amylase, les effets antiglycation, ainsi que l'activité antibactérienne contre des souches telles que *Staphylococcus aureus* et *Pseudomonas aeruginosa*. De plus, des tests de protection de la mucine ont été réalisés pour évaluer les propriétés gastroprotectrices.

Les résultats ont montré des activités significatives antioxydantes, anti-inflammatoires, antidiabétiques, antiglycation et antibactériennes, avec des valeurs d'IC_{50} et de ΔG négatives indiquant des interactions spontanées et stables avec les cibles biologiques. Le docking moléculaire a confirmé les résultats expérimentaux, démontrant que l'acide férulique un composant majeur forme des liaisons hydrogène et des interactions hydrophobes avec les enzymes et protéines. Les essais antibactériens ont révélé une inhibition plus forte contre les bactéries Gram positives que contre les Gram négatives.

Ces résultats mettent en évidence le potentiel thérapeutique du *psyllium* comme source naturelle de composés bioactifs et ouvrent des perspectives pour son développement en produits pharmaceutiques ou nutraceutiques, renforçant son rôle comme option sûre et durable dans la médecine naturelle moderne.

Mots-clés : *Plantago psyllium*, docking moléculaire, COX-2, antioxydant, anti-inflammatoire, antidiabétique, antiglycation, acide férulique.

الملخص

هدفت هذه الدراسة إلى تقييم الفعالية البيولوجية لمستخلص بذور *Plantago psyllium* (لسان الحمل)، الغني بالمركبات النشطة حيويًا مثل الفلافونويدات، البوليفينولات، والمخاطيات، وذلك من خلال دراسة مجموعة من الأنشطة الدوائية شملت النشاط المضاد للأكسدة، المضاد للالتهاب، المضاد للسكري، المضاد للجليكيشن، المضاد للبكتيريا، إضافة إلى النشاط الواقي للمعدة.

تم تقييم النشاط المضاد للأكسدة باستعمال اختبار DPPH، بينما تم دراسة النشاط المضاد للالتهاب من خلال اختبار تثبيط تمسخ بروتين Bovine Serum Albumin (BSA) باستعمال مطيافية الأشعة فوق البنفسجية والمرئية، إلى جانب دراسة الإرساء الجزيئي (Molecular Docking) مع إنزيم Cyclooxygenase-2 (COX-2) كما شملت الدراسة تقييم النشاط المضاد للسكري عبر تثبيط إنزيم Alpha-amylase، إضافة إلى دراسة النشاط المضاد للجليكيشن والنشاط المضاد للبكتيريا ضد سلالات مختلفة مثل *Staphylococcus aureus* و *Pseudomonas aeruginosa* علاوة على ذلك، تم تقييم النشاط الواقي للمعدة من خلال اختبارات حماية واستقرار الميوسين المعدي.

أظهرت النتائج أن مستخلص البسيليوم يمتلك نشاطًا ملحوظًا مضادًا للأكسدة والالتهاب والسكري والجليكيشن إضافة إلى فعالية واضحة مضادة للبكتيريا، حيث سجل تثبيطًا أكبر للبكتيريا موجبة الغرام مقارنة بالبكتيريا سالبة الغرام.

كما بينت قيم IC_{50} و ΔG السالبة حدوث تفاعلات تلقائية ومستقرة مع المستهدفات البيولوجية المختلفة. وأكدت نتائج الإرساء الجزيئي توافقها مع النتائج التجريبية، حيث أظهر Ferulic acid، باعتباره أحد المركبات الرئيسية في المستخلص، قدرة على تكوين روابط هيدروجينية وتفاعلات كارهة للماء مع البروتينات والإنزيمات المستهدفة.

تؤكد هذه النتائج الإمكانات العلاجية الواعدة لـ *Plantago psyllium* كمصدر طبيعي غني بالمركبات الفعالة حيويًا، كما تفتح آفاقًا مستقبلية لتطوير منتجات صيدلانية أو تغذوية تعتمد على مستخلصاته، بما يعزز دوره كخيار آمن ومستدام ضمن تطبيقات الطب الطبيعي الحديث.

الكلمات المفتاحية: *Plantago psyllium*، الإرساء الجزيئي، Cyclooxygenase-2 (COX-2)، مضاد أكسدة، مضاد التهاب، مضاد سكري، مضاد جليكيشن، Ferulic acid.

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Nomenclature

Å :	Angström
A:	Absorbance
AC:	Absorbance of control
ADT:	AutoDockTools
AG:	Gallic acid
AINS:	Non-steroidal anti-inflammatory drugs (NSAIDs)
AIS:	Steroidal anti-inflammatory drugs
$AlCl_3$:	Aluminum chloride
ADME:	Absorption, Distribution, Metabolism, Excretion
At:	Absorbance of the sample
COX:	Cyclooxygenase
COX1:	Cyclooxygenase type 1
COX2:	Cyclooxygenase type 2
DMSO:	Dimethyl sulfoxide
DPPH:	2,2-diphenyl-1-picrylhydrazyl
EAG:	Gallic acid equivalent
EGTA:	Ethylene Glycol Tetraacetic Acid
ER:	Rutin Equivalent
FC:	Folin-Ciocalteu
g:	Gram
H:	Hydrogen
I%:	Percentage of inhibition
IC_{50}:	Half maximal inhibitory concentration
Kg:	Kilogram
mg:	Milligram
mgEAG/gES:	Milligrams of gallic acid equivalent per gram of dry extract
mgER/gES:	Milligrams of rutin equivalent per gram of dry extract
Ml:	Milliliter
mm:	Millimeter
PBS:	Phosphate-buffered saline
PDB:	Protein Data Bank
pH:	Potential of hydrogen
R:	Yield

Nomenclature

T°:	Temperature
TFC:	Total Flavonoid Content
TPC:	Total Polyphenol Content
°C:	Degrees Celsius
kJ:	kilojoule
Nm:	nanometre
UV-Vis:	Ultraviolet-visible spectroscopy
ΔG:	binding free energy
K:	binding constant

General Introduction

Medicinal plants have long been regarded as a fundamental pillar of traditional medicine and continue to attract increasing scientific interest due to their richness in bioactive compounds and their potential role in the prevention and treatment of chronic diseases. In recent decades, there has been a notable shift toward natural products as safer and more sustainable alternatives to synthetic drugs, owing to their diverse pharmacological properties such as antioxidant, anti-inflammatory, antidiabetic, anti-ulcer, antiglycation, and antimicrobial activities **(Shoaib *et al*., 2016; Franco *et al*., 2020).**

Among these plants, *Plantago psyllium* (*psyllium*) stands out as a promising candidate for pharmaceutical and nutraceutical applications. Traditionally used in the treatment of gastrointestinal and metabolic disorders, *psyllium* is distinguished by its high content of soluble fibers, mucilage, polyphenols, and flavonoids, which collectively contribute to its therapeutic potential **(Assi, Kalkan et Maskan, 2024)**. Modern studies have expanded the scope of investigation, employing advanced laboratory assays and computational techniques to elucidate its mechanisms of action and to identify the bioactive compounds responsible for its pharmacological effects.

The integration of experimental and computational methodologies has marked a significant advancement in the evaluation of natural compounds. The combination of in vitro biological assays with *in silico* molecular docking provides a powerful framework for predicting the interactions of phytochemicals with biological targets implicated in pathological processes **(Triastuti *et al*., 2022).** This dual approach not only validates traditional knowledge but also accelerates the discovery of novel therapeutic agents derived from medicinal plants.

In this context, the present study aims to investigate the phytochemical composition and biological activities of *psyllium* ethanolic extract. The research encompasses a bibliographic review of medicinal plants and *psyllium*, detailed experimental protocols for phytochemical screening and bioactivity assays, as well as molecular docking studies comparing *psyllium*-derived compounds with standard drugs such as acarbose, diclofenac, prednisolone, and amoxicillin. By integrating laboratory and computational evidence, this study seeks to highlight *psyllium's* potential as a natural source of bioactive compounds and to contribute to its valorization in pharmaceutical and therapeutic applications.

Accordingly, the central research question is:

- **Do ethanolic extracts of *Plantago psyllium* seeds contain bioactive compounds with a favorable pharmacological safety profile?**

To address this question, the research is structured into three main chapters:

- **Chapter I (Generalities):** Provides an overview of medicinal plants, secondary metabolites, and the botanical, phytochemical, and pharmacological background of *psyllium*.
- **Chapter II (Materials and Methods):** Describes the preparation of the ethanolic extract, phytochemical screening, quantitative analysis of phenolics and flavonoids, in vitro evaluation of biological activities (antidiabetic, anti-inflammatory, antioxidant, anti-ulcer, antiglycation, and antibacterial), and *in silico* methods (ADMET prediction and molecular docking).
- **Chapter III (Results and Discussion):** Presents and interprets the experimental and computational findings, comparing the extract's activities with standard drugs and validating the correlation between in vitro and *in silico* results.

This integrated methodology aims to provide a comprehensive scientific evaluation of the pharmacological potential and safety of *psyllium* ethanolic extract, thereby supporting its traditional use and opening perspectives for its development in pharmaceutical applications.

Chapter I: General Background and Literature Review

Medicinal plants have long been used as natural remedies for various diseases nand remain essential in traditional medicine. They contain bioactive compounds such as polyphenols and flavonoids, which exhibit important biological activities like antioxidant and anti-inflammatory effects.

Recently, interest in these plants has increased due to their therapeutic potential and low toxicity compared to synthetic drugs. However, the use requires scientific validation to ensure safety and effectiveness (**Lagos N.*et al*., 2025**).

I.1 Medicinal Plants and Secondary Metabolites

I.1.1. Definition of Medicinal Plants

Since the initial hunter-gatherer stage through various adaptation stages, plants have played an incredible role in human livelihoods, providing shelter, food, and medicines (**Beshah *et al*., 2020; Godeto *et al*., 2021; Abate *et al*., 2022; Asfaw *et al*., 2022**). Medicinal plants date back to early civilizations in China, India, and the Near East. Today, 60–80% of people worldwide rely on herbal medicine for primary healthcare (**Wanjohi *et al*., 2020**). Before pharmaceuticals, communities used traditional knowledge and natural resources to treat health issues (**Barata *et al*., 2016**). Nearly 80% of the world's population, especially in developing countries, depends on traditional medicine (**Mbuni *et al*., 2020; Abate *et al*., 2021**). About 25% of modern pharmaceutical medicines are derived from plants used in traditional systems (**WHO; Barata *et al*., 2016**). Medicinal plants are defined as those containing bioactive compounds with therapeutic effects, whose parts (leaves, seeds, roots, bark, flowers) are used in traditional or modern medicine. They are rich in primary metabolites secon (carbohydrates, proteins, lipids) and dary metabolites responsible for most biological activities (**Harborne, 1998).**

I.1.2. Major Groups of Secondary Metabolites in *Psyllium*

a-Phenolics

Phenols are aromatic chemical compounds with weakly acidic properties that are distinguished by a hydroxyl (OH) group linked directly to an aromatic ring (**Okigbo *et al*., 2009; Dai and Mumper 2010**). It was discovered that, in addition to their primary antioxidant activity, this group of chemicals has a wide range of biological roles, the majority of which are associated with carcinogenesis modulation (**Dai and Mumper 2010**).

Polyphenols represent a large and diverse group of secondary metabolites characterized by the presence of multiple phenolic structures. They are widely distributed in plants and are

known for their strong antioxidant properties. Polyphenols protect cells from oxidative stress by scavenging free radicals and chelating metal ions. They are associated with various biological activities, including anti-inflammatory, antimicrobial, anticancer, and cardioprotective effects. Their beneficial effects are mainly due to their ability to modulate enzymatic activity and cellular signaling pathways (**Cowan, M. M. 1999**).

b-Flavonoids

Flavonoids are a subclass of polyphenols and are among the most abundant plant secondary metabolites. Structurally, they consist of two aromatic rings connected by a three-carbon bridge.

Flavonoids exhibit multiple biological activities such as antioxidant, anti-inflammatory, antiviral, and anticancer properties. They can inhibit enzymes, modulate cell signaling pathways, and protect cells from oxidative damage. Their role in reducing oxidative stress makes them particularly important in preventing chronic diseases (**Cowan, M. M. 1999**).

c-Tannins

Tannins are high-molecular-weight polyphenolic compounds capable of precipitating proteins. They are commonly found in bark, leaves, and seeds. They exhibit antimicrobial, antioxidant, and anti-inflammatory properties. Tannins can inhibit microbial growth by binding to proteins and enzymes, thereby disrupting microbial metabolism. They also contribute to wound healing and protection against oxidative damage (**Cowan, M. M. 1999**).

Tannins are a type of polyphenol that can be divided into two categories: (1) condensed tannins (syn. proanthocyanidins), which are made up of flavan-3-of polymer subunits linked by 4-6 and 4-8 interflavan bonds, and (2) hydrolysable tannins, which are gallic acid esters with a central polyol, usually -D-glucopyranose (**Pott *et al.*, 2019**). Tannins have a wide range of effects, from decreasing protein and other nutrient availability, such as amino acids and minerals, to protecting ruminants from bloat, improving rumen bypass protein, improving meat quality, and reducing helminth infestation (**Makkar *et al.*, 2009**). Plant extracts containing tannins are employed as astringent, diuretic, anti-inflammatory, antiseptic, antioxidant, and haemostatic medicines and against stomach and duodenal tumours (**Saxena *et al.*, 2013**).

d-Alkaloids

Plants offer a large reservoir of active ingredients with substantial therapeutic uses such as antiviral, anticancer, analgesic, and antitubercular. Alkaloids are significant secondary metabolites that were identified and utilized as early as 4000 years ago and are widely known

for their medicinal potential. Alkaloids are categorized into many groups based on their heterocyclic ring system and biosynthetic precursors, such as indole, purine, quinoline, isoquinoline, tropane, and imidazole, among others. Alkaloids contain antiproliferative, antimicrobial, and antioxidant properties that can be exploited in medication development. Alkaloids' medicinal potential expands their industrial applicability. Numerous studies on the medicinal characteristics of various alkaloids derived from plants have been conducted. Alkaloids are naturally occurring chemical composites that often include basic nitrogen atoms. They could also have some neutral or mildly acidic substances in them. Several synthesized substances are also classified as alkaloids. Alkaloids, in addition to carbon, nitrogen, or hydrogen, may include sulfur and, in rare cases, bromine, phosphorus, or chlorine. The term "alkaloid" was coined in 1819 by German scientist Carl F. W. Meissner, who derived it from the Arabic name al-Qali, which is related to the plant from which soda was initially extracted. Alkaloids are low-molecular-weight compounds that account for around 20% of plant-based secondary metabolites. So far, over 12,000 alkaloids have been isolated from diverse plant species. Alkaloids are primarily solids that are found in higher plants. They are found in the following botanical families: Apocynaceae, Annonaceae, Amaryllidaceae, Berberidaceae, Boraginaceae, Gnetaceae, Liliaceae, Leguminoceae, Lauraceae, Loganiaceae, Magnoliaceae, Menispermaceae, Papaveraceae, Piperaceae, Rutaceae, Rubiaceae, and Ranunculaceae **(Návarová H *et al*., 2012).**

Alkaloids are nitrogen-containing compounds known for their strong pharmacological effects. Many well-known drugs are derived from alkaloids.

They exhibit a wide range of biological activities, including analgesic, antimicrobial, antimalarial, and anticancer effects. Alkaloids interact with various biological targets such as enzymes and receptors, making them important in drug development.

e-Terpenoids

Terpenes, also known as isoprenoids, are the most copious and diverse group of naturally occurring compounds. They are chiefly found in plants, but larger classes of terpenes, such as sterols and squalene are also common in animals. The natural aroma, flavour, and pigment of plants are all due to this group of compounds. Among various therapeutic applications, they are known for antiplasmodial activity, which is remarkable because their mode of action is analogous to that of the widely used antimalarial medication chloroquine **(Cox-Georgian *et al*., 2019).**

They possess diverse biological activities including antimicrobial, anti-inflammatory, and anticancer properties. Terpenoids also play a role in plant aroma and are widely used in pharmaceuticals and cosmetics.

f-Saponins

Biologically, saponins exhibit antimicrobial, anti-inflammatory, and immunomodulatory activities. They also have cholesterol-lowering effects and are used in various therapeutic applications.

Saponins are naturally occurring surface-active glycosides produced primarily by plants, some bacteria, and lower marine animals. The antidiabetic properties of saponins enabled physicians to discover new medications that are beneficial in treating diabetes mellitus **(Marrelli *et al*., 2016).** Saponins are amphiphilic compounds with carbohydrate, triterpenoid, or steroid aglycone moieties. Fungicidal, antibacterial, antiviral, anti-inflammatory, anticancer, antioxidant, and immunomodulatory properties are among their biological activities **(Alzandi *et al*., 2021).**

I.2. Overview of *Plantago psyllium*

I.2.1. Botanical Classification

Plantago psyllium, commonly known as *psyllium*, belongs to:

- **Kingdom**: Plantae
- **Division**: Magnoliophyta (Angiosperms)
- **Class**: Magnoliopsida (Dicotyledons)
- **Order**: Plantaginales
- **Family**: Plantaginaceae
- **Genus**: Plantago
- **Species**: *Plantago psyllium* L. **(Strkalj *et al* ..,2025)**

I.2.2. Morphological Description

1. Habit Annual herbaceous plant, small in size Belongs to the Plantaginaceae family Grows in dry and semi-arid regions **(Strkalj *et al*., 2025)**
2. Stem Short or almost absent stem non-woody structure Leaves arise in a basal arrangement
3. Leaves Narrow, linear to lanceolate leaves Arranged in a basal rosette Green in color, smooth or slightly pubescent Adapted to reduce water loss in dry environments

4. Inflorescence & Flowers Spike-like, slender inflorescence Flowers are very small and inconspicuous Mainly wind-pollinated (anemophilous plant)
5. Fruit is a small capsule containing 2–4 seeds.
6. Seeds: *Psyllium* seeds are ovoid-oblong in shape, about 2–3 mm long and 0.8–1.5 mm wide (Fig. 1). They are pinkish gray to brown in color with a convex dorsal surface and concave ventral surface with a deep groove running lengthwise along the center.

(Strkalj *et al*., 2025 ; Gülhan, 2025).

Figure 1: *Plantago psyllium* plant **(Myrtéa Formations, 2021).**

Figure 2: Morphology of *psyllium* seeds **(Madgulkar *et al*., 2014).**

I.2.3. Geographical Distribution

Ispaghul or blonde *psyllium* is a species of plantain native to the desert regions of North Africa, Southwest Asia, and the Southwestern United States. Today, this annual plant is mainly cultivated in India and to a very small extent in Pakistan, for its seed and the seed husk, which have laxative and emollient properties **(Sarfraz *et al*., 2017**).

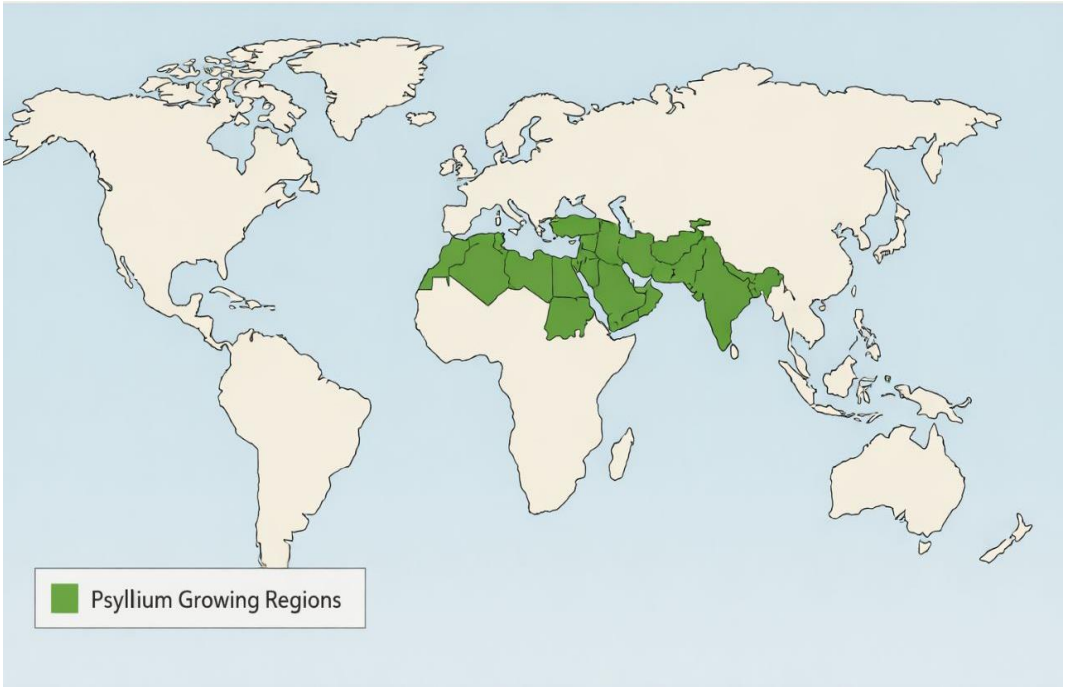

Figure 3: Geographical Distribution of *psyllium*

I.2.3. Traditional Uses and Ethnopharmacology

Psyllium seed husks (*Plantago*) have been employed since the 16th century in Asia and Europe as a remedy for chronic constipation. In traditional Chinese and Indian medicine, they were used as laxatives and to reduce risks of chronic diarrhea and dysentery. In Pakistan and India, *psyllium* seeds are considered diuretics, while in Iran aqueous extracts are applied externally for inflammation and orally for indigestion and biliary secretion disorders **(Rehana Khaliq *et al*., 2015).**

❖ **Hypocholesterolemic Effect:**

Viscous soluble fibers from *psyllium* husks are highly effective with minimal side effects. *Psyllium* significantly reduces plasma LDL cholesterol levels by 10–24%. Mechanistically, *psyllium* enhances bile acid synthesis by stimulating 7-hydroxylase activity, thereby converting cholesterol into bile acids and lowering serum cholesterol. In the small intestine, *psyllium* binds bile acids, preventing reabsorption and promoting new bile acid production from circulating

cholesterol. Clinical studies report LDL reductions of 8% and total cholesterol decreases ranging from 6% to 40% **(Baljit Singh, 2007; Shanti *et al*., 2017; Devesh *et al*., 2014).**

❖ **Diarrhea:**

Psyllium has shown benefits in patients suffering from diarrhea, particularly those fed via enteral nutrition. It increases stool bulk and normalizes stool consistency, reducing liquid stools. By increasing meal viscosity, *psyllium* delays gastric emptying and slows colonic transit, thereby improving diarrhea, including that caused by enterotoxigenic *E. coli* **(Baljit Singh, 2007).**

❖ **Constipation:**

Psyllium husks are widely recognized as bulk-forming laxatives. They increase stool frequency and weight, soften hard stools, and reduce painful defecation. Evidence suggests *psyllium* is more effective than sodium docusate. Its paradoxical effect lies in improving constipation by increasing stool mass, supported by multiple clinical studies **(Baljit Singh, 2007).**

❖ **Digestive Health:**

As a bulk-forming laxative, *psyllium* absorbs water, facilitating easier defecation without excessive flatulence. It acts as a prebiotic, supporting microbial fermentation into short-chain fatty acids such as butyrate, essential for colonic health. The mucilage forms a gel resistant to digestive enzymes, coating mucosa as a lubricant and absorbing intestinal toxins **(Baljit Singh, 2007; Devesh *et al*., 2014; Rehana Khaliq *et al*., 2015).**

❖ **Cardiovascular Health:**

Dietary fibers like *psyllium* are associated with reduced cardiovascular risk. *Psyllium* lowers blood pressure, improves lipid profiles, and strengthens cardiac muscle **(Baljit Singh, 2007).**

❖ **Diabetes:**

Psyllium fiber improves peripheral insulin sensitivity and reduces postprandial glycemic responses. It decreases appetite in type 2 diabetic patients and slows carbohydrate absorption, lowering post-meal glucose levels. Clinical and experimental studies confirm *psyllium's* role in stimulating insulin secretion, reducing inflammation, and lowering hyperglycemia in both type 1 and type 2 diabetes models **(Baljit Singh, 2007; Chris Iliades, 2021; Devesh *et al*., 2014; Rehana Khaliq *et al*., 2015).**

❖ **Satiety and Appetite Control:**

Administration of *psyllium* seed powder before meals significantly increases satiety and reduces fat intake, supporting its role in appetite regulation **(Devesh *et al*., 2014).**

❖ **Poultry Nutrition:**

In poultry diets, *psyllium* reduces cholesterol content in eggs, thereby improving their nutritional profile **(Shanti *et al*., 2017).**

❖ **Thickening Properties:**

Due to its mucilage, *psyllium* husk is used as a thickening agent in food industries (e.g., ice cream stabilization, gel production as agar substitute). It also finds applications in petroleum well acidification and as a pharmaceutical excipient in capsule formulation **(Devesh *et al*., 2014; Rehana Khaliq *et al*., 2015).**

I.3. Phytochemical Composition of *Plantago psyllium*

Psyllium (Plantago species) is widely recognized for its seed husks, which are rich in mucilagea natural polysaccharide primarily composed of arabinoxylans. Thisbiopolymer has attracted considerable attention due to its uniquephysicochemical properties and broad therapeutic potential **(Kumar *et al*., 2017).**

I.3.1. Mucilage and Polysaccharides

I.3.1.1. Definition and localization

A natural polysaccharide substance obtained from the husks of *psyllium* seeds, mainly composed of arabinoxylans (arabinose and xylose). It has the ability to absorb water and form a gel, which gives it important physicochemical properties useful in pharmaceutical and therapeutic applications. So, in simpler terms: mucilage is a **gel-forming fiber** from *psyllium* husks. Its water-binding capacity makes it valuable both for health benefits (like regulating digestion, lowering cholesterol, and controlling blood sugar) and for pharmaceutical uses (such as controlled drug release systems) **(Yu, L., Yakubov *et al*., 2017).**

Mucilage is the main component of *psyllium* seeds, located primarily in the seed husk (outer layer). It represents about 20–30% of the seed weight and is responsible for most of its physiological effects.

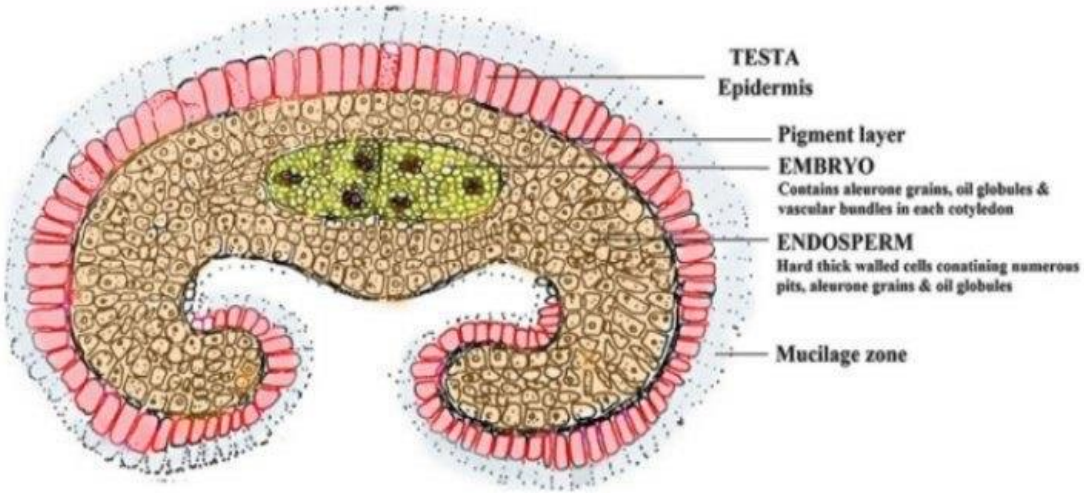

Figure 4: Transverse section of seeds of *Psyllium* ovate

(Madgulkar *et al*., 2014).

I.3.2.2. Chemical Composition of Mucilage

The chemical composition of mucilage extracted from the husks of *Plantago psyllium* seeds has been extensively studied:

Main Component: It is a neutral Arabinoxylan, composed primarily of the sugar units Arabinose (22.6%) and Xylose (74.6%) on a molar basis.

Degree of Branching: This arabinoxylan is characterized by a very high degree of branching, with approximately 35% of the sugar units being non-reducing terminal residues. This highly branched structure is what gives it its unique properties. · Detailed Structure: The main backbone consists of a chain of D-xylopyranosyl units linked by β-(1→4) bonds. Various side chains are attached to this main backbone, including trisaccharide branches with the sequence:

$$L - Araf - \alpha - (1 \rightarrow 3) - D - Xylp - \beta - (1 \rightarrow 3) - L - Araf.$$

Multi-layered Structure: Recent research has discovered that upon hydration, *psyllium* seeds secrete three distinct layers of mucilage, each containing arabinoxylans with different compositions and rheological (flow and viscosity) properties, despite their overall chemical similarity (**Guo, Q *et al*., 2021).**

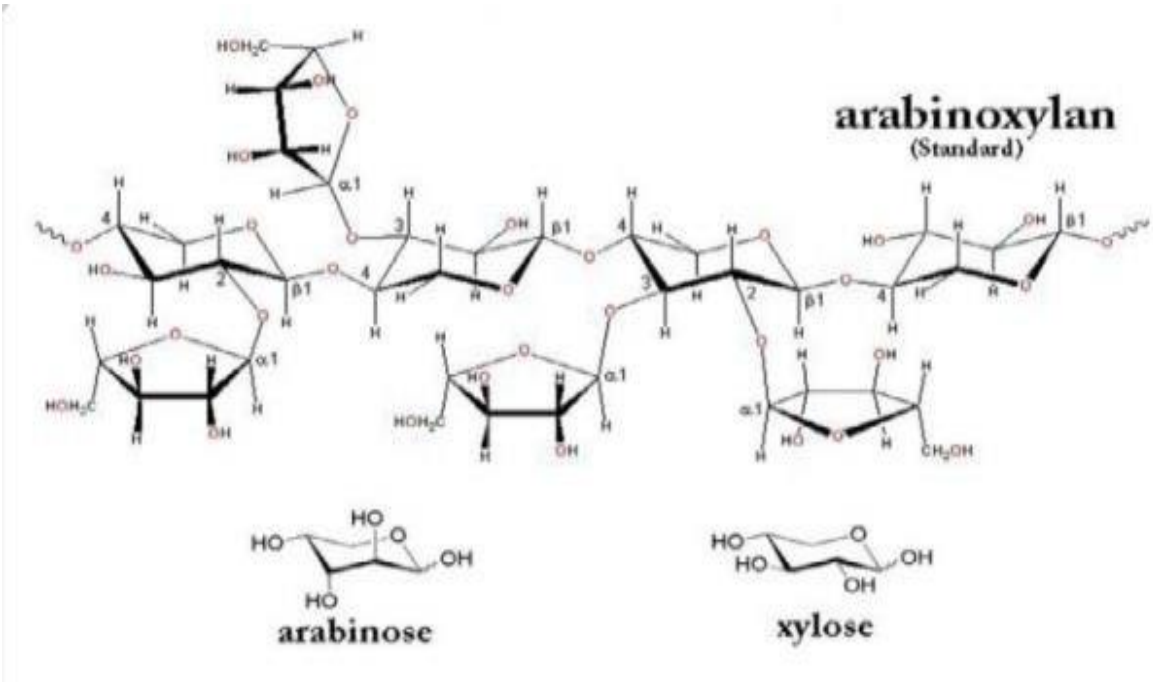

Figure 5: Structure of *Psyllium* mucilage

(Kumar *et al*., 2017).

I.3.2.3. Properties and Functions

Exceptional Water-Holding Capacity: *Psyllium* husk mucilage possesses an immense water-holding capacity, reaching over 40 grams of water per gram of fiber.

Gel Formation: Its ability to form a viscous gel relies primarily on hydrogen bonding and the distribution of side chains on the arabinoxylan molecules, leading to polymer entanglement and the formation of a three-dimensional network.

Applications: These properties are utilized in various fields: · Pharmaceutical: As a natural laxative for treating constipation, a cholesterol-lowering agent, a blood sugar regulator, and a binding agent in pharmaceutical tablets.

Food Industry: As a dietary fiber supplement, and as a stabilizer and thickener in products like ice cream and sauces.

Modern Applications: In the production of biodegradable edible films and coatings, which can extend the shelf life of food products **(J ovanovski *et al*., 2020).**

I.3.3. Phenolic Compounds

Phenolic Compounds in *Plantago psyllium* (Corrected) *Plantago psyllium* contains a variety of phenolic compounds, mainly represented by phenolic acids such as gallic acid, ferulic acid, caffeic acid, and p-coumaric acid. These compounds are generally present in relatively

low concentrations compared to the high mucilage content of the seeds, but they contribute significantly to the plant's biological activity.

Phenolic compounds in *psyllium* exist in both free and bound forms. Bound phenolics are often associated with cell wall components, particularly polysaccharides such as arabinoxylans in the seed husk. This association may affect their extraction efficiency, release during digestion, and overall bioavailability.

Among these compounds, gallic acid is widely used as a reference standard in the determination of total phenolic content using the Folin–Ciocalteu method. Therefore, the results are commonly expressed as mg gallic acid equivalents (mg GAE/g).

Phenolic compounds exhibit strong antioxidant activity through several mechanisms, including free radical scavenging, metal ion chelation, and inhibition of lipid peroxidation. Consequently, they play a key role in the protective effects of psylliu against oxidative stress and related diseases **(Shahidi *et al*., 2015).**

I.3.4. Flavonoids

In *psyllium*, flavonoids are mainly found in the seed coat (husk) and, to a lesser extent, in other aerial parts of the plant. Reported flavonoid compounds include derivatives of apigenin, luteolin, and quercetin, which contribute significantly to the pharmacological potential of the plant. These molecules act by scavenging free radicals and inhibiting oxidative stress, which is associated with many chronic diseases.

The presence of flavonoids in *psyllium* is also linked to its potential anti-inflammatory and antimicrobial effects. These activities enhance the traditional use of the plant not only as a laxative but also as a functional medicinal resource.

Overall, flavonoids represent an important bioactive fraction of *psyllium*, contributing to its health-promoting properties and supporting its use in both pharmaceutical and nutraceutical applications **(Samuelsen *et al*., 2000).**

I.3.5. Other Bioactive Constituents

In addition to mucilage and phenolics, *Plantago psyllium* contains:

- Proteins
- Lipids
- Iridoid glycosides
- Vitamins and minerals

These compounds contribute to the overall therapeutic potential of the plant **(Mudgil *et al*., 2013).**

I.4. Pharmacological Importance of *Plantago psyllium*

I.4.1. Anti-inflammatory activity

I.4.1.1 Inflammation

Is a complex biological response triggered by tissue damage or infection. It involves immune cells, signaling molecules, and vascular changes. While inflammation is essential for healing, it manifests as systemic symptoms (fever) and local ones (swelling, redness). Different tissues contribute uniquely to this process **(chekirou and Zeroual, 2023**).

I.4.1.2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs act by inhibiting cyclooxygenase enzymes (**COX-1** and **COX-2**), which are responsible for producing prostaglandins and thromboxanes.

- **COX-1**: Constitutively expressed, protects gastric mucosa, and supports platelet aggregation.
- **COX-2**: Inducible, mainly expressed during inflammation. Traditional NSAIDs inhibit both enzymes, while selective COX-2 inhibitors aim to reduce gastrointestinal side effects (**Mekenza et Medjmedj,2018).**

❖ **Diclofenac:**

Pharmacokinetics :

Diclofenac demonstrates distinctive pharmacokinetic properties, it is completely absorbed following oral administration; however, due to significant first-pass metabolism, only about 50% of the dose reaches systemic circulation. The drug is highly bound to plasma proteins (>99%) and distributes into synovial fluid, which enhances its therapeutic effect in joints. Hepatic metabolism produces five derivatives, one of which retains weak pharmacological activity. Elimination occurs mainly through the urine (approximately 65%) and to a lesser extent via feces, with a relatively short plasma half-life of 1.2–2 hours. Additionally, diclofenac undergoes enterohepatic recycling of about 35%, contributing to the prolongation of its therapeutic action **(Nagoudi, Bouchekima, and Oubira, 2023).**

Pharmacodynamics :

Diclofenac exerts its pharmacodynamic effects primarily through inhibition of cyclooxygenase (COX) enzymes, leading to a reduction in prostaglandin synthesis. This mechanism underlies its anti-inflammatory, analgesic, and antipyretic properties. In addition, diclofenac may also inhibit lipoxygenase (LOX) and phospholipase A2, further enhancing its therapeutic efficacy. Interestingly, its clinical benefits persist beyond its relatively short plasma

half-life, as the drug remains in synovial fluid for extended periods, thereby sustaining its anti-inflammatory action within joints **(Nagoudi, Bouchekima, and Oubira, 2023).**

I.4.1.3. Steroidal Anti-Inflammatory Drugs (SAIDs)

Derived from cortisol, SAIDs are powerful agents for chronic inflammation and autoimmune disorders. They suppress immune responses but carry risks of significant side effects with prolonged use.

❖ **Prednisone:**

- **Pharmacokinetics:**

Prednisone is rapidly absorbed following oral administration, with an approximate bioavailability of 80% and peak plasma concentrations occurring within 1–2 hours. Once absorbed, it undergoes hepatic conversion to its active metabolite, prednisolone. The drug is highly bound to plasma proteins (around 90%), which influences its distribution. Metabolism is mediated by enzymes such as 11β-hydroxysteroid dehydrogenase, and elimination occurs mainly via the urine. Its plasma half-life ranges between 1.5 and 3.5 hours, reflecting relatively quick clearance from systemic circulation **(Nagoudi, Bouchekima, and Oubira, 2023).**

- **Pharmacodynamics:**

Prednisone exerts its therapeutic effects by reducing the migration of inflammatory cells to sites of tissue injury, thereby limiting inflammatory responses. It also inhibits the production of vasoactive substances, which play a role in vascular permeability and inflammation. Furthermore, prednisone modulates immune cell activity, contributing to its immunosuppressive properties. Interestingly, plant-derived phytochemicals may mimic these mechanisms by targeting enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), nitric oxide synthase, and phospholipase A2, offering potential natural alternatives with fewer adverse effects **(Nagoudi, Bouchekima, and Oubira, 2023).**

I.4.2. Antioxidant Activity

I.4.2.1. Oxidative Stress and Antioxidants

Oxidative stress occurs when the production of free radicals exceeds the body's antioxidant defenses. During metabolic processes, free radicals are generated and can initiate chain oxidation reactions that damage cells and accelerate aging **(Dahel et Messaoudi,2019.)**

In biological systems, oxidative stress specifically refers to the imbalance between reactive oxygen species (ROS) and the antioxidant mechanisms that neutralize them **(Ait Yahia et Zemmoura, 2014).**

Free radicals, including ROS and reactive nitrogen species (RNS), are highly reactive molecules due to their unpaired electrons, which drive them to capture electrons from other molecules, destabilizing cellular structures **(M' cili et melghid, 2020.)**

I.4.2.2. Sources of Free Radicals

Free radicals can be produced by radiation, chemical reactions, and enzymatic processes. The mitochondrial respiratory chain is a major source of ROS, while NADPH oxidases contribute during inflammation and cytochrome P450 enzymes generate ROS during detoxification. Thus, mitochondria, plasma membranes, and the endoplasmic reticulum are key sites of ROS release. Excess ROS leads to biochemical damage of DNA, proteins, and lipids, triggering cytotoxicity and mutagenesis, particularly through lipid peroxidation (**M'cili et Melghid, 2020)**

I.4.2.3. Biochemical Consequences and Pathologies

Excessive ROS production causes severe damage to biomolecules and is implicated in diseases such as cancer, Alzheimer's, Parkinson's, diabetes, immune dysfunction, pregnancy complications, and rheumatic disorders. With aging, antioxidant defenses decline and mitochondrial dysfunction increases, enhancing free radical production (**Guillet-pichon et Verny, 2016).**

I.4.2.4. Definition of Antioxidants

Antioxidants are compounds that counteract oxidative processes. In food science, they prevent rancidity and delay lipid peroxidation without altering sensory or nutritional qualities. An ideal antioxidant is fat-soluble, effective at low doses, non-toxic, and stable during processing (**Hellal, 2011).**

I.4.2.5. Enzymatic Antioxidant Systems

The enzymatic defense system is the first line against oxidative stress:

- **Superoxide Dismutase (SOD):** Catalyzes the conversion of superoxide radicals into hydrogen peroxide and oxygen:

$$O2•−+2H+→H2O2+O2 \qquad \textbf{(Kabel, 2014)}$$

- **Catalase (CAT):** Found in peroxisomes, it decomposes hydrogen peroxide into water and oxygen at an extremely high rate:

$$2H2O2→2H2O+O2 \qquad \textbf{(Starlin et Gopalakrishnan, 2013).}$$

- **Glutathione Peroxidase (GPx):** Reduces hydrogen and lipid peroxides using glutathione:

$$2H_2O_2 + 2GSH \rightarrow 2H_2O + GSSG$$

$$ROOH + 2GSH \rightarrow ROH + GSSG + H_2O$$ **(Omodanisi *et al.*, 2017).**

- **Glutathione Reductase (GR):** Regenerates reduced glutathione from its oxidized form:

$$GSSG + NADPH \rightarrow 2GSH + NADP^+$$ **(Csiszár *et al.*, 2016).**

I.4.2.6. Non-Enzymatic Antioxidant Systems

Non-enzymatic antioxidants complement enzymatic defenses. Endogenous compounds include glutathione, uric acid, bilirubin, lipoic acid, and coenzyme Q10 (**Laraba, Serrat … et Ouassaa, 2016).**

Glutathione acts as a cofactor for antioxidant enzymes and interacts synergistically with vitamins C and E. Uric acid and bilirubin scavenge free radicals, while lipoic acid regenerates other antioxidants and chelates heavy metals (**David, 2015).**

Coenzyme Q10, present in cell membranes and mitochondria, is essential for ATP production and enhances vitamin E's antioxidant effect (**Canavy *et al.*, 2014).**

Exogenous antioxidants obtained from diet include vitamin E (tocopherols), vitamin C, and carotenoids such as beta-carotene, all of which neutralize ROS and protect cellular integrity (**Evans, 2000).**

I.4.3. Anti-Diabetic Activity

I.4.3.1. Definition and Diagnosis of Diabetes

Diabetes is a progressive metabolic disorder primarily characterized by hyperglycemia, or elevated blood glucose levels. Most cases are type 2 diabetes, which results from impaired insulin secretion by pancreatic beta cells combined with resistance of peripheral tissues to insulin. This dysfunction leads to persistent hyperglycemia and increases the risk of cardiovascular diseases such as coronary artery disease, myocardial infarction, and stroke. Maintaining blood glucose balance is therefore essential to prevent or delay vascular complications.

Therapeutic strategies include stimulating insulin secretion, enhancing glucose uptake by peripheral tissues, reducing hepatic glucose production, or limiting carbohydrate absorption in the intestines. Inhibiting the intestinal enzyme α-D-glucosidase, which breaks down carbohydrates, can slow glucose production and absorption, offering potential benefits in preventing diabetes and obesity (**Derbal and Benladjila,2021).**

I.4.3.2. Alpha-Amylase

- **Definition :**

Alpha-amylase is a globular protein enzyme widely distributed across living organisms. It functions as an endo-enzyme that randomly hydrolyzes α(1–4) glycosidic bonds in polysaccharides such as amylose, amylopectin, starch, and glycogen, except at terminal bonds. Hydrolysis produces glucose, maltose, et alpha-dextrins. Its molecular weight typically ranges between 40 and 70 kDa (**Sahraoui and Youmbai,2021).**

- **Nomenclature :**

- **Codified Name:** EC 3.2.1.1
- **Common Name:** alpha-amylase
- **Other Names:** glycogenase, endoamylase, Taka-amylase A, maxilase
- **Systematic Name:** 1,4-alpha-D-glucan-4-glucanohydrolase (**Schamburg et Slzmann, 1991 ;Dauter *et al.,* 1999 ;Nouadri., 2011).**

- **Types of Alpha-Amylase :**

In humans, alpha-amylase is produced mainly in the salivary glands (S-amylase) and the pancreas (P-amylase). These forms are encoded by different genes, Amy1 and Amy2A, located on calivaryhromosome 1. S amylase exists in two main types: type A, a glycosylated protein with a molecular weight of 62 kDa, and type B, a non-glycosylated protein with a molecular weight of 55 kDa (**Sahraoui and Youmbai,2021).**

- **Role of Alpha-Amylase :**

Starch digestion begins in the mouth with salivary alpha-amylase, which cleaves α(1–4) bonds in starch into smaller fragments. However, it cannot hydrolyze terminal bonds or those near branching points. Its activity ceases in the acidic environment of the stomach. Digestion resumes in the small intestine, where pancreatic alpha-amylase and beta-amylase further break down starch into disaccharides (maltose), trisaccharides (maltotriose), and oligosaccharides (dextrins with α (1–6) branches). Finally, intestinal enzymes convert these products into monosaccharides for absorption (**Voet.D et Voet.J., 2005).**

- **Hydrolysis reactions :**

α amylase

$(C_6H_{10}O_5)_n + H_2O \rightarrow$ Maltose ($C_{12}H_{22}O_{11}$) + Maltotriose + Dextrins

α-glucosidase

Maltose ($C_{12}H_{22}O_{11}$) → 2Glucose ($C_6H_{12}O_6$) (Janeček, Š., Svensson, B., et MacGregor, E. A. 2013).

- **Mechanism of Action of Alpha-Amylase :**

The catalytic mechanism of alpha-amylase depends on three essential amino acids in its active site: Asp231 (nucleophile), Glu261 (proton donor), and Asp328 (catalytic assistant). Its activity is strongly influenced by pH and temperature. Hydrolysis occurs in four steps:

- **Formation of the enzyme–substrate complex:** The enzyme binds to the starch chain.
- **Cleavage of the α (1–4) bond:** Protonated glutamic acid donates a proton to break the glycosidic bond, while aspartic acid forms a temporary covalent bond with one end of the chain.
- **Restoration of the enzyme:** A water molecule attacks the carbon atom bonded to aspartic acid, breaking the bond and releasing the first fragment.
- **Release of the second fragment:** Glutamic acid returns to its original state, freeing the second part of the chain **(Kolli *et al.*, 2015).**

I.4.4. Anti ulcer-gastric Activity

I.4.4.1. Gastric Ulcer

A gastric ulcer, also referred to as a gastroduodenal ulcer, is a progressive and destructive condition that damages the mucosal and submucosal layers of the stomach and duodenum. This process results in a partial loss of digestive wall tissue that may extend into the muscular layer. Healing typically occurs with scar formation, which distinguishes ulcers from superficial erosions, abrasions, or excoriations that do not penetrate the muscular layer and usually resolve without scarring **(Afrit, 2022).**

Ulcers are not confined solely to the stomach, which is why the broader term **Equine Gastric Ulcer Syndrome (EGUS)** is used; lesions may also involve the esophageal or duodenal mucosa **(Marguet, 2009)**. From a pathological standpoint, gastroduodenal ulcers are characterized by mucosal and muscular destruction, often accompanied by vascular injury and neuronal hypertrophy **(Labayle *et al.*, 2001; Calop *et al.*, 2008).**

The development of gastric ulcers is explained by an imbalance between protective factors of the gastric mucosa—such as mucus secretion, bicarbonate production, mucosal blood flow, and cytoprotection—and aggressive agents including hydrochloric acid, pepsin, and gastrin. This reflects the constant interplay between aggression and defense. When this equilibrium is disrupted, either through increased aggressiveness or reduced mucosal resistance, ulcer formation can occur **(Gimenez *et al*., 2000; Sherwood, 2006; Calop *et al*., 2008).**

I.4.4.2. Mechanism of Ulcer Formation

Ulcer formation is a complex pathological process that results from a disruption in the balance between **defensive factors** of the gastric mucosa and **aggressive factors** present in the stomach.

❖ **Defensive Factors:**

The gastric mucosa is normally protected by several mechanisms:

- **Mucus secretion**, which forms a physical barrier against acid and pepsin.
- **Bicarbonate secretion**, which neutralizes acid at the epithelial surface.
- **Adequate mucosal blood flow**, ensuring oxygen and nutrient supply and removal of toxic metabolites.
- **Prostaglandins**, which stimulate mucus and bicarbonate production and maintain mucosal integrity.
- **Cellular regeneration and cytoprotection**, which repair minor injuries and sustain epithelial resistance **(Sherwood, 2006).**

❖ **Aggressive Factors:**

On the other hand, several agents can damage the mucosa:

- **Hydrochloric acid (HCl)**, secreted by parietal cells, is corrosive if unbuffered.
- **Pepsin**, a proteolytic enzyme, digests mucosal proteins when the barrier is compromised.
- **Gastrin**, a hormone, stimulates acid secretion and increases mucosal exposure.
- **Helicobacter pylori infection**, which disrupts the mucosal barrier, induces inflammation, and increases acid secretion **(Li *et al*., 2024).**
- **Non-steroidal anti-inflammatory drugs (NSAIDs)**, which inhibit prostaglandin synthesis, reducing mucus and bicarbonate secretion **(Joshi *et al*., 2024).**

❖ **Pathophysiological Sequence:**

- **Imbalance between defense and aggression**: either increased aggressiveness (acid hypersecretion, pepsin activity, *H. pylori*) or reduced defense (mucus depletion, prostaglandin inhibition).
- **Disruption of the mucosal barrier**: acid and pepsin penetrate deeper into the epithelium.
- **Inflammation and vascular injury**: reduced perfusion impairs healing capacity and promotes necrosis **(Labayle *et al*., 2001; Calop *et al*., 2008).**
- **Extension of damage**: lesions spread into the submucosa and muscularis, causing pain and bleeding.
- **Ulcer formation**: a chronic lesion develops, which heals with scar tissue, unlike superficial erosions that resolve without scarring **(Afrit, 2022; Marguet, 2009).**

Gastric ulcers are the consequence of a **shift in the aggression–defense equilibrium**, where either excessive aggressiveness or weakened mucosal resistance initiates progressive tissue destruction and ulceration **(Gimenez *et al*., 2000).**

I.4.4.3. Mechanism of Anti-Ulcer Agents

Anti-ulcer agents act by restoring the balance between **defensive factors** of the gastric mucosa and **aggressive factors** such as acid, pepsin, and *Helicobacter pylori*. Their mechanisms can be grouped into several categories :

Acid Secretion Inhibitors :

Proton Pump Inhibitors (PPIs) such as omeprazole and lansoprazole block the H^+/K^+-ATPase enzyme in parietal cells, suppressing gastric acid secretion at its final step **(Shin et Kim, 2013; Saha *et al*., 2021).**

H_2-Receptor Antagonists such as ranitidine and famotidine inhibit histamine-stimulated acid secretion by blocking H_2 receptors on parietal cells. Both classes reduce gastric acidity, creating favorable conditions for mucosal healing **(Sung *et al*., 2020).**

Cytoprotective Agents :

Sucralfate forms a protective coating over ulcerated mucosa by binding to proteins at the lesion site. **Prostaglandin analogues** such as misoprostol stimulate mucus and bicarbonate secretion, enhance mucosal blood flow, and inhibit acid secretion. These agents strengthen mucosal defenses and accelerate recovery (**Wallace, 2008; Saha *et al*., 2021).**

- **Antacids :**

Antacids neutralize existing gastric acid (HCl), providing rapid symptom relief. They also raise gastric pH, thereby reducing pepsin activity. Their effect is immediate but short-lived (**Sung *et al*., 2020).**

- **Anti-Helicobacter pylori Therapy :**

Combination regimens of antibiotics (clarithromycin, amoxicillin, metronidazole) with PPIs eradicate *H. pylori*. Removing infection eliminates a major cause of chronic ulceration and recurrence (**Malfertheiner *et al*., 2022).**

- **Other Protective Mechanisms :**

Additional agents act by enhancing epithelial regeneration, reducing back-diffusion of hydrogen ions, and improving mucosal blood flow. Prostaglandins, for example, restore perfusion and oxygen delivery to damaged tissue (**Wallace, 2008).**

- **Pathophysiological Impact :**

By either reducing aggressors (acid, pepsin, *H. pylori*) or enhancing defenses (mucus, bicarbonate, blood flow), anti-ulcer agents re-establish the aggression–defense equilibrium. This allows the mucosa to recover, prevents further necrosis, and promotes scar-free healing in many cases (**Saha *et al*., 2021).**

- **Standard Anti-Ulcer Drugs :**

Several well-established drugs are widely used in the management of gastric and duodenal ulcers. Their mechanisms of action complement the general categories of anti-ulcer agents described earlier **(Saha *et al*., 2021; Lanas et Chan, 2017).**

- **Omeprazole :**

Omeprazole is a **proton pump inhibitor (PPI)** that irreversibly blocks the H^+/K^+-ATPase enzyme in gastric parietal cells. By inhibiting the final step of acid secretion, it produces profound and long-lasting suppression of gastric acid output. This reduction in acidity allows the mucosa to heal and prevents recurrence of ulcers (**Shin et Kim, 2013; Saha *et al*., 2021).**

- **Lanzomed (Lansoprazole) :**

Lanzomed, a commercial name for **lansoprazole**, is another PPI with a similar mechanism to omeprazole. It binds to and inactivates the proton pump, thereby reducing gastric acid secretion. Lansoprazole is often preferred for its rapid onset of action and effective ulcer healing rates (**Shin et Kim, 2013).**

Alginate Formulations :

Alginate-based drugs (e.g., sodium alginate) act differently: they form a **viscous gel or raft** that floats on the gastric contents. This physical barrier reduces reflux of acid into the esophagus and protects the gastric mucosa. Alginate therapy is particularly useful in patients with gastroesophageal reflux disease (GERD) and can provide symptomatic relief in ulcer patients by shielding the mucosa (**Leiman *et al*., 2017).**

Clinical Impact :

These standard drugs: Omeprazole, lansoprazole (Lanzomed), et alginate formulations represent the cornerstone of modern ulcer therapy. PPIs provide strong acid suppression, while alginates offer mechanical protection. Their combined use restores the aggression defense balance, promotes mucosal healing, and reduces recurrence rates (**Sung *et al*., 2020; Saha *et al*., 2021).**

Natural Product (Flaxseed) :

- **Mechanism of Action:**
  - Flaxseed (*Linum usitatissimum*) is a traditional medicinal plant that has gained attention for its **anti-ulcer properties**. Its activity is attributed to several bioactive compounds, mainly **mucilage, lignans, omega-3 fatty acids, and antioxidants**. **Mucilage content**: forms a protective layer over the gastric mucosa, reducing irritation from acid and pepsin **(Singh *et al*., 2011).**
  - **Antioxidant activity**: lignans and polyphenols scavenge free radicals, decreasing oxidative stress that contributes to mucosal injury **(Prasad, 2000).**
  - **Anti-inflammatory effect**: omega-3 fatty acids modulate inflammatory pathways, lowering cytokine-mediated damage **(Kajla *et al*., 2015).**
  - **Cytoprotective role**: enhances mucus secretion and supports epithelial regeneration, strengthening mucosal defenses **(Goyal *et al*., 2014)**
- **Pathophysiological Impact:**

By combining **mechanical protection** (mucilage), **antioxidant defense**, and **anti-inflammatory activity**, flaxseed helps restore the aggression–defense balance in the stomach. This natural product reduces ulcer severity, promotes healing, and may complement standard pharmacological therapy (**Dugani *et al*., 2008)**

I.4.5. BSA Interaction Activity

Protein–ligand interactions are essential for biological regulation and drug action. They rely on non-covalent forces such as hydrogen bonds, hydrophobic contacts, and electrostatic attractions, which allow proteins to recognize and bind specific molecules with high affinity. These interactions influence enzymatic activity, receptor signaling, and pharmacokinetics (**Redhair et Atkins 2021)**

I.4.5.1. Bovine Serum Albumin (BSA)

Is a globular protein of about 66.5 kDa, derived from bovine blood plasma and structurally similar to human serum albumin. Thanks to its stability, solubility, and ability to bind a wide range of ligands, it is extensively used in biochemical, pharmaceutical, and medical research. Functionally, BSA plays multiple roles: it maintains osmotic pressure to regulate fluid balance in blood circulation, transports fatty acids, hormones, bilirubin, and drugs, stabilizes blood pH through its buffering capacity, and exhibits antioxidant activity by scavenging free radicals and binding toxic compounds. In addition, it serves as a model protein in studies of protein–ligand interactions, drug binding, and pharmacokinetics, while in laboratory practice it is widely applied as a stabilizer in enzyme assays, a blocking agent in immunoassays such as ELISA and Western blot, and a nutrient reservoir in cell culture **(Dungrela, 2024)**

I.4.5.2. Mechanisms of Interaction (Binding Interactions)

Protein–ligand interactions are stabilized by a combination of non-covalent forces, including hydrogen bonds, van der Waals contacts, electrostatic complementarity, and hydrophobic effects. Hydrogen bonds provide specificity and directionality, while van der Waals forces contribute to shape complementarity and close molecular packing. Electrostatic interactions often drive initial recognition between charged groups, and hydrophobic effects enhance stability by clustering nonpolar regions away from solvent. Together, these forces define the affinity and selectivity of protein–ligand complexes, which are fundamental for understanding drug binding and rational design in pharmaceutical research **(Madushanka *et al*., 2023; Grassmann *et al*., 2023).**

I.4.5.3. Spectroscopic Analysis (UV–Vis) of BSA

UV–Visible spectroscopy is a simple and effective method to study **Bovine Serum Albumin (BSA)** interactions. BSA exhibits a strong absorption peak near **280 nm**, mainly due to aromatic amino acids (tryptophan, tyrosine, phenylalanine). Monitoring changes in this bet allows detection of **ligand binding**, **conformational changes**, and **structural stability**. Shifts

in wavelength or variations in absorbance intensity (hypochromic/hyperchromic effects) provide evidence of binding events and protein rearrangements. UV–Vis titration can also be used to estimate **binding constants** and stoichiometry of BSA–ligand complexes **(Singh et Kumar, 2024)**

I.4.5.4. Importance of BSA Interaction Studies

The study of **Bovine Serum Albumin (BSA) interactions** is highly important because it provides a reliable **model protein** for understanding drug binding and transport in blood, clarifies the role of **non-covalent forces** such as hydrogen bonds, van der Waals, electrostatic, and hydrophobic interactions in stabilizing complexes, and offers insights into **protein conformational changes and stability**. These investigations also support **drug design, toxicology, and nanomedicine** by predicting how compounds interact with serum proteins, while enhancing **biotechnological applications** where BSA is widely used as a stabilizer, carrier, or blocking agent **(Singh et Kumar, 2024)**

I.4.6. Antiglycation Activity

I.4.6.1. Glycation

Is a non-enzymatic chemical reaction in which reducing sugars (such as glucose or fructose) covalently bind to proteins, lipids, or nucleic acids. This process leads to the formation of **(AGEs) Advanced Glycation End Products**, which alter the structure and function of biomolecules. The accumulation of AGEs is strongly associated with **aging** and the development of chronic diseases such as **diabetes, cardiovascular disorders, and neurodegenerative conditions (Uceda *et al*., 2024).**

I.4.6.2. Antiglycation Mechanism

Antiglycation agents exert their protective effects by inhibiting multiple stages of the glycation process, thereby preventing the formation of harmful Advanced Glycation End Products (AGEs). These compounds interfere with the initial interaction between reducing sugars and protein amino groups, thus limiting the formation of Schiff bases. They also act by trapping reactive carbonyl species, which reduces the generation of intermediate glycation products. In addition, their antioxidant properties enable them to scavenge reactive oxygen species (ROS), thereby decreasing oxidative stress associated with glycation. Furthermore, antiglycation agents inhibit the progression of Amadori products into irreversible AGEs and may chelate metal ions involved in oxidation reactions. Collectively, these mechanisms

contribute to the protection of protein structure and the preservation of their biological function **(Long *et al*., 2025)**

I.4.6.3. BSA Model System

Bovine Serum Albumin (BSA) is commonly used as a model protein to study glycation *in vitro* and to evaluate the inhibitory effects of compounds on AGE formation (**Long *et al*., 2025)**

I.4.7. Antibacterial Activity

Bacteria are responsible for various infections in living organisms. Researchers once hoped to eradicate certain diseases with the discovery of antibiotics. Unfortunately, the widespread use of these drugs has led to a growing resistance of bacteria against antibiotics. In this context, there has been great interest in the search for new biologically active and effective substances as alternatives derived from natural resources **(Fatteh, 2019).**

I.4.7.1. Antibacterial Agents

An antimicrobial agent is broadly defined as any chemical, physical, or biological substance capable of inhibiting the growth or survival of microorganisms. Within this category, chemotherapeutic agents are distinguished by their ability to suppress or eliminate pathogenic targets while remaining non-toxic to the host organism. This group encompasses antibiotics, antifungal compounds, and antiviral drugs **(Dahel et Messaoudi, 2019).**

I.4.7.2. Antibiotics

These are chemical substances prouced by microorganisms. They possess the ability to inhibit the growth or development of other microorganisms, into which they penetrate by disrupting metabolism or by specifically acting on an essential stage of it. Importantly, they are devoid of toxicity toward other human or animal cells **(Rahimi et Refice, 2021).**

I.4.7.3. Mode of Action of Antibiotics

Unlike antiseptics and disinfectants, antibiotics generally act in a highly specific manner on certain structures of the bacterial cell. This marked specificity of action explains why antibiotics are effective at very low concentrations**.** Antibiotics may act on the bacterial cell wall, the cell membrane, DNA, the bacterial ribosome, and other targets **(Asselineau *et al*., 1973).**

I.4.7.4. Antibiotic Resistance

Bacterial resistance is defined as the ability of bacteria to withstand the effects of antibiotics or biocides intended to control or eliminate them. This resistance may be either natural or acquired **(Mégraud, 2017)**

I.5. *In Silico* Pharmacokinetic and Toxicological Studies

This research focuses on a bioactive compound isolated from a medicinal plant, aiming to evaluate its anti-inflammatory activity under controlled *in vitro* conditions. Ultraviolet-Visible (UV-Vis) spectroscopy will be employed to characterize the compound, while computational methods will be utilized to analyze its physicochemical properties and predict its interactions with selected drugs and the cyclooxygenase enzyme. These *in silico* investigations are designed to provide theoretical support and complement the experimental outcomes.

I.5.1. Principle of Ultraviolet-Visible Spectroscopy

Electronic transitions within molecules that occur in the ultraviolet-visible (UV-Vis) spectral region correspond to some of the highest energy processes in chemistry, typically ranging from 13,000 to 50,000 cm^{-1} (160–665 $kJ \cdot mol^{-1}$). These energy values are comparable to molecular bond dissociation energies, which explains why UV-Vis radiation can occasionally induce bond cleavage. More commonly, however, absorption of UV-Vis radiation promotes electrons to higher energy states, resulting in transitions between distinct molecular orbitals and energy levels (**Baudouin, 2012).**

1.5.2. Beer-Lambert Law

The absorbance of monochromatic radiation is directly proportional to the length of the absorption path (ℓ) and the concentration of the species in the medium (C). The concentration is generally expressed in moles per litter ($mol\ L^{-1}$) and the length in centimeters (cm), resulting in the following relationship**:**

$$A = log(I0/I) = \varepsilon lC$$

Where:

A: Absorbance, formerly called optical density (O.D.) (unitless)

ε: Molar extinction coefficient ($mol^{-1}.cm^{-1}.L$)

C: Concentration (mol/L) l: Path length of the cuvette (cm)

I0: Intensity of the irradiation energy arriving at the sample (incident light)

I: Intensity of the radiation that has passed through the sample (transmitted light) **(Aouiche, and Beggas, 2021).**

I.5.3. Molecular Docking

Molecular docking is a computational technique employed to predict the interaction between two molecules, typically a ligand and a target protein. By simulating the binding process, this method provides valuable information regarding the spatial orientation of the ligand within the protein's active site as well as its binding affinity. Through the analysis of these interactions, molecular docking facilitates the identification of candidate compounds with the potential to bind selectively to specific proteins, thereby contributing to drug discovery, rational design, and mechanistic investigations **(Shende *et al*., 2024)**

I.5.3.1. Types of Molecular Docking

Molecular docking methods differ in complexity, particularly in how they account for the flexibility of interacting molecules.

- **Rigid docking** is the simplest and fastest approach, treating both the ligand and the protein as fixed structures. It is often applied in protein–protein interaction studies but may overlook conformational changes.
- **Semi-flexible docking** allows the ligand to adopt different conformations while the protein remains rigid. This method is commonly used in protein–ligand interactions, though its accuracy can be limited when significant protein flexibility is involved.
- **Flexible docking** is the most advanced and computationally demanding technique. It considers the flexibility of both the ligand and the protein, applying constraints to balance computational efficiency with predictive accuracy. This approach provides a more realistic representation of molecular interactions **(Lebbad, 2016)**

I.5.3.2. Principle

Molecular docking is founded on computationally modeling the association of two or more molecules to form a stable complex. The method aims to predict the optimal binding orientation of a ligand within the active site of a target protein by evaluating spatial complementarity and interaction energies. In essence, docking seeks the lowest-energy configuration that reflects the most favorable molecular fit **(Asses,2011; Lanez,2016).**

I.5.3.3. Steps of Molecular Docking

The docking process is iterative, and each calculation step is divided into two stages:

1.5.3.3.1. Molecular Docking with Auto Dock Tools

In molecular docking, the ligand is computationally positioned within the active site of the target protein, and a range of conformations, orientations, and binding poses are systematically explored. The software evaluates these possibilities based on scoring functions that estimate binding affinity, ultimately selecting the most favorable configurations. AutoDockTools, as a widely used platform, plays a critical role in biology, pharmacy, and medicine by facilitating the identification of drug candidates capable of interacting with specific biological targets **(EL Hadj,2016; Lanez,2016).**

I.5.3.3.2. Modeling of Energy Potential

AutoDock estimates the free energy of a ligand–receptor complex by combining classical force field terms with additional entropy-related contributions. The binding free energy is expressed as:

$$\Delta G = \Delta Gvdw + \Delta Ghbond + \Delta Gelec + \Delta Gconform + \Delta Gtor + \Delta Gsol$$

Where :

- ΔGvdw: van der Waals dispersion/repulsion energy
- ΔGhbond: hydrogen bond energy
- ΔGelec: electrostatic interaction energy
- ΔGconform: energy due to deviations from covalent geometry
- ΔGtor: torsional entropy term reflecting restrictions in ligand rotation and translation upon complexation
- ΔGsol: solvation-related entropy term accounting for desolvation during binding

To relate complex structures with binding free energy, AutoDock employs an empirical QSAR-type model based on multiple linear regression of these energy terms. Each term is weighted by coefficients derived from a large dataset of receptor–inhibitor complexes with known inhibition constants (Ki). The relationship between binding free energy and the inhibition constant is given by:

ΔG=-RTlnK **(Azeb et Azza,2023).**

1.5.4. Swiss ADME

SwissADME is a free and user-friendly web tool that offers rapid and reliable predictive models for evaluating crucial properties of molecules in drug discovery. These include physicochemical properties, pharmacokinetics ADME), drug-likeness, and medicinal

chemistry friendliness. Both experts and non-specialists can easily use it to quickly obtain predictions that support their research **(Daina *et al.*, 2017).**

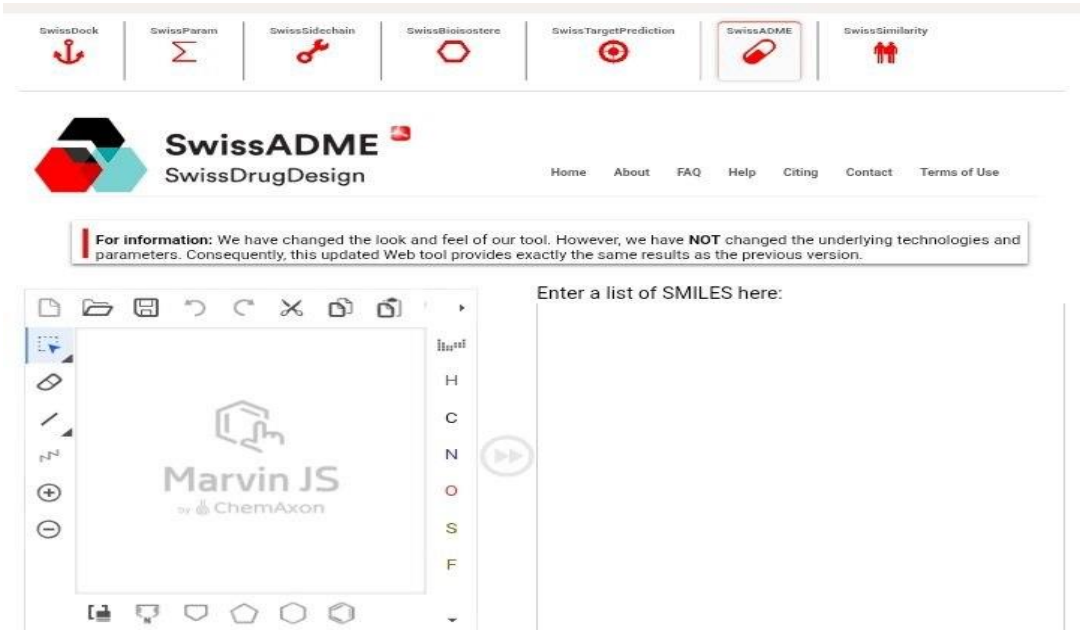

Figure 6: Homepage of the swiss ADME server.

I.5.5. Protox

The free web server ProTox-II (http://tox.charite.de/protox_II) enables efficient prediction of chemical compound toxicity based on their 2D structure. It provides detailed results with confidence measures, a summary of overall toxicity, and identifies similar compounds with known acute toxicity **(Dara, Zarei, et Saha, 2023)**

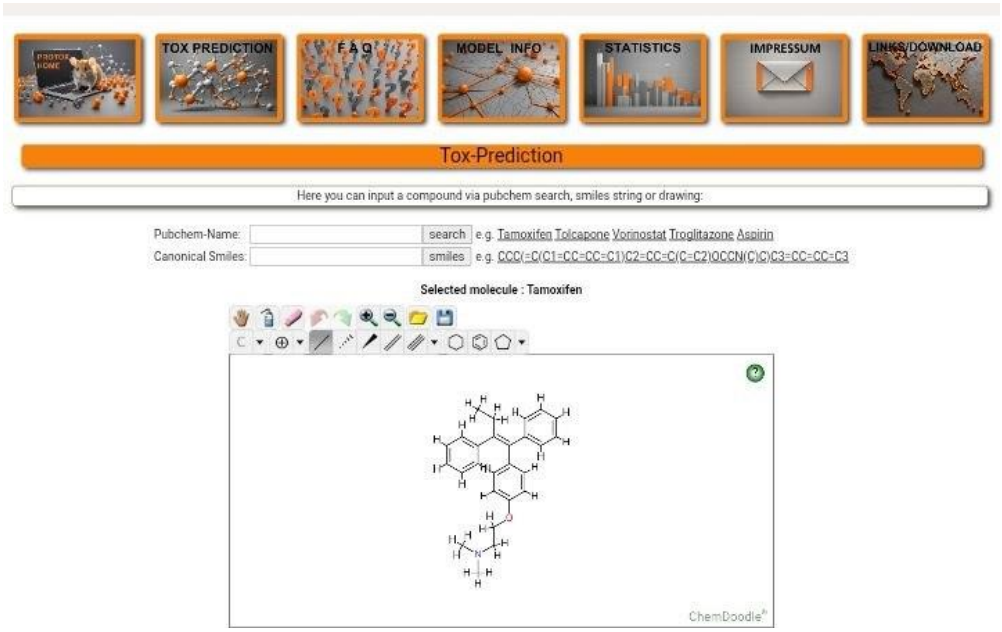

Figure 7: Homepage of the protox server

I.5.6. PubChem

PubChem is a major and free chemical database launched in 2004, offering comprehensive information on small and large molecules (like drugs and biomolecules) to scientists, students, and the general public through its website and programming services. This information includes chemical structures, physical and chemical properties, biological activities, toxicity data, and much more **(Trad, 2020).**

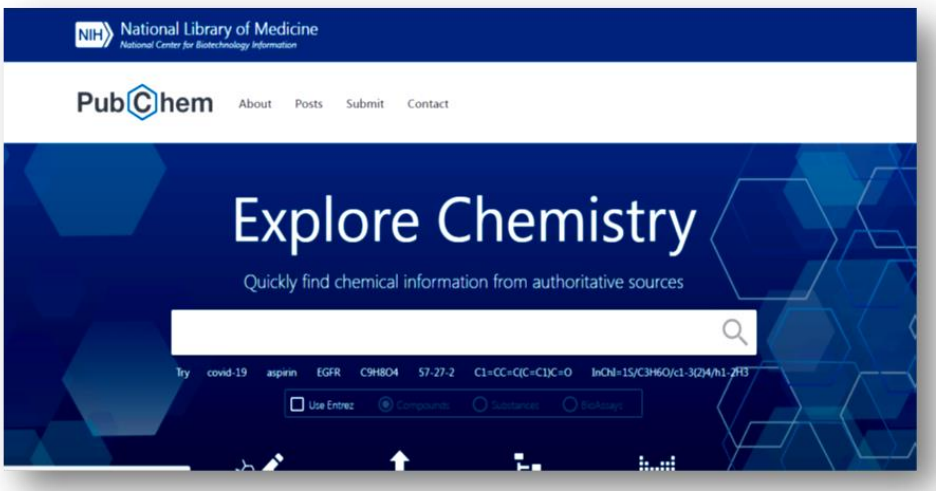

Figure 8: Home page of the PubChem database server**.**

I.5.7. Protein Data Bank

The Protein Data Bank (PDB) is the unique worldwide online repository of molecular structures (https://www.rcsb.org/). The archive has grown to more than 180,000 three-

dimensional structures of biologic macromolecules determined experimentally (Figure) **(Burley *et al*., 2022).**

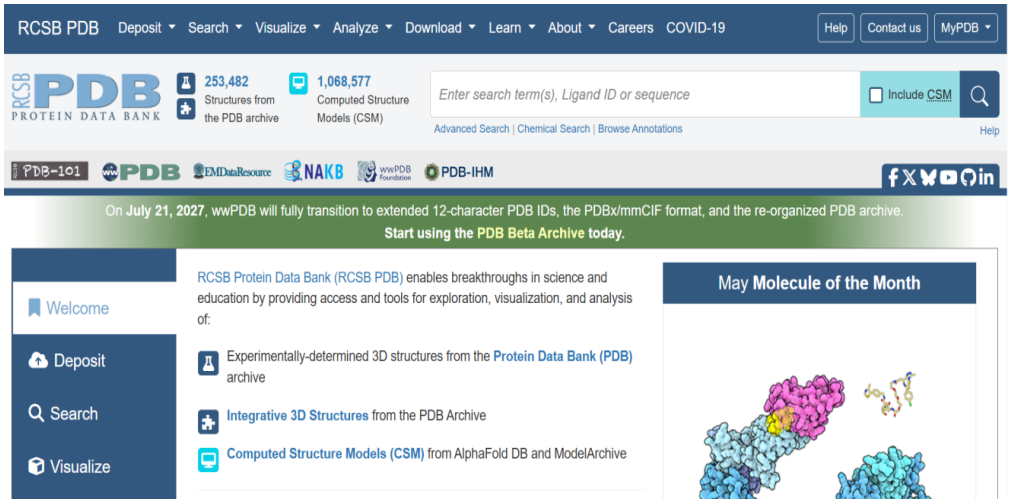

Figure 9: Home page of the PDB database server**.**

Chapter II: Materials and Methods

General Conclusion

The findings of this study confirm that the ethanolic extract of *Plantago psyllium* seeds is a rich source of bioactive compounds, particularly phenolics and flavonoids, which demonstrated significant biological activities including antioxidant, anti-inflammatory, antidiabetic, antiglycation, gastroprotective, and antibacterial effects. These activities were consistently supported by experimental assays, while computational analyses further validated the molecular mechanisms underlying these effects, highlighting the role of non-covalent interactions in stabilizing bioactive complexes.

The integration of *in vitro* and *in silico* evidence not only substantiates the traditional use of *psyllium* but also opens new perspectives for its development as a natural therapeutic agent with a promising safety profile. This research contributes to bridging a knowledge gap regarding the pharmacological value of *psyllium* and supports the global trend toward safer, sustainable alternatives to synthetic drugs.

Accordingly, this study represents an important step toward the valorization of *psyllium* in pharmaceutical applications. Future in vivo and clinical investigations are strongly recommended to confirm its efficacy, optimize dosage regimens, and establish its therapeutic potential, thereby paving the way for its incorporation into modern treatment strategies based on natural and sustainable medicine.

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