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END-OF-STUDY DISSERTATION

Submitted in partial fulfillment of the requirements for the Academic Master's Degree
in Biological Sciences
Specialty: Biodiversity and plant physiology

THEME

pharmaceutical prédiction and biological activities of *Solenostemma argel* in vitro and in silico study

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Dedication

With deep love, respect, and gratitude, we dedicate this modest work to our beloved parents, whose sacrifices, prayers, and continuous support have been the source of our strength and motivation throughout our academic journey.

We also dedicate this work to our dear brothers and sisters, for their encouragement, affection, and constant support.

To all our family members, who stood by us with love and patience, we express our sincere gratitude and appreciation.

Finally, we dedicate this work to everyone who believed in us, supported us, and encouraged us during the completion of this dissertation.

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List of Abbreviations

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ADME: Absorption, Distribution, Metabolism, and Excretion

BSA: Bovine Serum Albumin

COX: Cyclooxygenase

COX-2: Cyclooxygenase-2

CYP: Cytochrome P450

DNS: 3,5-Dinitrosalicylic Acid

FT-IR: Fourier Transform Infrared Spectroscopy

GI: Gastrointestinal

HPLC: High-Performance Liquid Chromatography

IC50: Half-Maximal Inhibitory Concentration

K: Binding Constant

LD50: Median Lethal Dose

LOX: Lipoxygenase

NO: Nitric Oxide

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

OD: Optical Density

PLA2: Phospholipase A2

PLIP: Protein–Ligand Interaction Profiler

ProTox: Prediction of Toxicity of Chemicals

QSAR: Quantitative Structure–Activity Relationship

RBCs: Red Blood Cells

SAIDs: Steroidal Anti-Inflammatory Drugs

S. argel: *Solenostemma argel*

UV-Vis: Ultraviolet–Visible Spectroscopy

VTRS: Valorization and Technology of Saharan Resources

ΔG: Gibbs Free Energy

λmax: Maximum Absorption Wavelength

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Abstract

This study aimed to evaluate the pharmaceutical prediction and biological activities of *Solenostemma argel* using both in vitro and in silico approaches. The work focused on the extraction, phytochemical screening, characterization, and biological evaluation of the plant extract, with particular attention to its anti-inflammatory, anti-hemolytic, and antidiabetic potential.

Phytochemical screening revealed the presence of several secondary metabolites, mainly alkaloids and cardiac glycosides, with weaker detection of flavonoids and tannins. The extract was characterized using UV-Visible spectroscopy and HPLC, which confirmed the presence of alkaloid-related compounds. The anti-inflammatory activity was evaluated through the

inhibition of BSA denaturation. The results showed a concentration-dependent inhibitory effect, with inhibition increasing from 30.736% to 60.833%. The IC50 value of *Solenostemma argel* extract was 0.432 µM, indicating a measurable anti-inflammatory activity, although lower than that of the reference drugs diclofenac and prednisolone.

The anti-hemolytic test showed that the extract improved red-blood-cell protection as concentration increased, but its effect remained lower than that of aspirin. In addition, the extract showed promising antidiabetic activity through α-amylase inhibition, with an IC50 value of 0.1867 µM compared with 0.2091 µM for acarbose. The in silico study supported the experimental results. SwissADME prediction indicated acceptable physicochemical and pharmacokinetic properties, while ProTox results suggested no predicted hepatotoxicity, carcinogenicity, mutagenicity, or cytotoxicity. Molecular docking also showed a negative binding energy with cyclooxygenase-2, suggesting a possible interaction with this inflammatory target.

Overall, *Solenostemma argel* demonstrated promising biological potential, particularly as a natural source of anti-inflammatory and antidiabetic bioactive compounds. However, further studies are required to isolate the active molecules, confirm their mechanisms of action, and evaluate their safety and efficacy in vivo.

Keywords: *Solenostemma* argel, alkaloids, anti-inflammatory activity, anti-hemolytic activity, antidiabetic activity,

الملخص

هدفت الدراسة إلى تقييم التنبؤ الصيدلاني والأنشطة البيولوجية لنبات *الارقل* ***Solenostemma argel*** اعتمادًا على مقاربتين: الدراسة المخبرية **in vitro** والدراسة الحاسوبية **in silico.** وقد ركزت الدراسة على استخلاص المستخلص النباتي، والكشف الفيتوكيميائي، والتوصيف، وتقييم النشاط البيولوجي، خاصة النشاط المضاد للالتهاب، والمضاد لانحلال كريات الدم الحمراء، والمضاد للسكري.

أظهر الكشف الفيتوكيميائي وجود عدة مركبات أيضية ثانوية، خاصة القلويدات والغليكوزيدات القلبية، مع ظهور أضعف لكل من الفلافونويدات والعفص. كما أُجري توصيف المستخلص باستعمال مطيافية الأشعة فوق البنفسجية والمرئية **UV-Visible** وتقنية**HPLC** ، حيث أكدت النتائج وجود مركبات مرتبطة بالقلويدات. تم تقييم النشاط المضاد للالتهاب من خلال اختبار تثبيط تمسخ ألبومين مصل البقر**BSA** ، وأظهرت النتائج تأثيرًا تثبيطيًا مرتبطًا بزيادة التركيز، إذ ارتفعت نسبة التثبيط من

30.736% إلى 60.833%. كما بلغت قيمة **IC50** لمستخلص ***Solenostemma argel*** حوالي 0.432 ميكرومول، مما يدل على وجود نشاط مضاد للالتهاب، لكنه بقي أقل من فعالية الأدوية المرجعية مثل الديكلوفيناك والبريدنيزولون.

أما اختبار الحماية من انحلال كريات الدم الحمراء، فقد أظهر أن المستخلص حسّن نسبة الحماية بارتفاع التركيز، غير أن فعاليته بقيت أقل من الأسبرين. بالإضافة إلى ذلك، أظهر المستخلص نشاطًا واعدًا مضادًا للسكري من خلال تثبيط إنزيم-**α amylase**، حيث بلغت قيمة **IC50** للمستخلص 0.1867 ميكرومول مقارنة بـ 0.2091 ميكرومول بالنسبة للأكاربوز. كما دعمت الدراسة الحاسوبية هذه النتائج؛ إذ أظهرت نتائج **SwissADME** خصائص فيزيائية-كيميائية وحركية دوائية مقبولة، بينما أشارت نتائج **ProTox** إلى عدم التنبؤ بسمية كبدية أو سرطانية أو طفرية أو خلوية. كما أظهر الالتحام الجزيئي **docking**طاقة ارتباط سالبة مع إنزيم**cyclooxygenase-2** ، مما يشير إلى إمكانية وجود تفاعل مع هذا الهدف المرتبط بالالتهاب.

بشكل عام، أظهر نبات ***Solenostemma argel*** قدرة بيولوجية واعدة، خاصة كمصدر طبيعي لمركبات فعالة مضادة للالتهاب ومضادة للسكري. ومع ذلك، تبقى هذه النتائج أولية وتحتاج إلى دراسات إضافية لعزل المركبات النشطة، وتأكيد آليات تأثيرها، وتقييم سلامتها وفعاليتها داخل الجسم الحي.

الكلمات المفتاحية: نبات الارقل ، القلويدات، النشاط المضاد للالتهاب، النشاط المضاد لانحلال الدم، النشاط المضاد للسكري،

General Introduction

General Introduction

Inflammation is a complex biological response of the body to different harmful stimuli, including physical, chemical, biological, and infectious agents. (Vane et Botting., 1987)

Although it represents an essential defense mechanism, excessive or persistent inflammation may contribute to the development of several pathological conditions. The current management of inflammation is mainly based on steroidal and non-steroidal anti-inflammatory drugs. However, despite their effectiveness, prolonged use of these drugs may lead to undesirable side effects, particularly gastrointestinal disorders, ulcers, and other toxic effects. Therefore, the search for new anti-inflammatory agents with fewer side effects remains an important field of scientific investigation. (Yamada et al., 1987)

In recent years, medicinal plants have received increasing attention as potential sources of bioactive molecules. Traditional medicine continues to play an important role in health care, especially in regions where medicinal plants are widely used by local populations. Plant-derived compounds, such as alkaloids, flavonoids, tannins, and other secondary metabolites, are known for their pharmacological activities and may represent promising alternatives to synthetic anti-inflammatory drugs. The study of these natural substances is therefore important not only for validating traditional uses but also for discovering new therapeutic agents.

Among these medicinal plants, ***Solenostemma argel*** is of particular interest. It is a perennial shrub belonging to the family **Asclepiadaceae** and is used in traditional medicine. Botanically, the plant is characterized by vigorous stems, opposite oval leaves, white flowers with a strong odor, and thick pyriform fruits containing pubescent seeds. Phytochemical studies have reported the presence of several bioactive compounds in this plant, including flavonoids, kaempferol, quercetin, rutin, flavonols, flavanones, chalcones, and alkaloids. These constituents suggest that *Solenostemma argel* may possess significant biological and pharmacological properties, especially anti-inflammatory potential. (Benhouhou, 2005; Abdel-Sattar & El-Shiekh, 2024)

Based on this background, the present work focuses on the extraction, characterization, and evaluation of the anti-inflammatory activity of bioactive compounds extracted from *Solenostemma argel*. The study aims to assess its potential inhibitory effect against inflammatory

processes, particularly through in vitro and in silico approaches. The experimental part may include phytochemical screening, extraction of total alkaloids, spectroscopic characterization, and evaluation of anti-inflammatory activity using suitable biological models. In parallel, molecular docking can be used to study the interaction between selected plant compounds and cyclooxygenase-2, an important enzyme involved in the inflammatory pathway.

Thus, this research seeks to contribute to the scientific valorization of *Solenostemma argel* as a medicinal plant and to explore its possible role as a natural source of anti-inflammatory agents. Through the combination of phytochemical, biological, and computational methods, this study may help provide a clearer understanding of the therapeutic potential of this plant and support its future use in the development of safer natural anti-inflammatory products.

Part I:

Bibliographic Synthesis

Chapter I:

Medicinal Plants and Secondary Metabolites, Alkaloids

I.1. Introduction:

Humans and plants have lived together for a long time. As a result, humans became accustomed to consuming different plant species, appreciating them for their taste, nutritional qualities, and medicinal properties. This explains why the human body may adapt better to plant-based treatments than to chemical treatments.

Thus, on every continent, different traditions and rituals using plants developed, and these practices were transmitted and enriched over time.

Algeria is known for its diversity of medicinal and aromatic plant species, most of which grow spontaneously and are widely used throughout the country. However, the 3,000 species of Algerian flora belong to several plant families, 15% of which are endemic, and there are still few phytochemical and pharmacological investigations (Triki and Ouled Cheikh, 2021).

I.2. Definition:

According to the definition of the French Pharmacopoeia: "Medicinal plants are plant drugs of which at least one part has medicinal properties. These medicinal plants may also have food, condiment, or hygienic uses" (Limonier, 2018).

At the international level, more than 35,000 plant species are used worldwide for medicinal purposes, representing the widest range of biodiversity used by human beings. Medicinal plants continue to meet an important need despite the growing influence of the modern healthcare system (Boumediou and Addoun, 2017).

I.3. Origin of Medicinal Plants:

Two origins of medicinal plants can be distinguished:

I.3.1. Wild Plants: In the past, wild plants were the only plants used, and today they still represent a significant percentage of the European market. Their distribution depends on the soil and, above all, on the climate (Grenez, 2019).

I.3.2. Cultivated Plants: This mode of production provides a sufficient quantity of raw material to meet needs, and the collected plant drugs are homogeneous in both appearance and chemical composition (Grenez, 2019).

I.4. Uses of Medicinal Plants:

For 150 years, medicinal plants have provided pharmacy with highly effective medicines. Today, many studies in the field of ethnopharmacology show that plants used in traditional medicine and tested experimentally are often effective in pharmacological models and, at the

same time, are almost free of toxicity.

Ethnopharmacology and ethnobotany aim both to understand practices and representations related to health and disease and to describe and therapeutically evaluate the plants used in traditional pharmacopoeias. The empirical use of different traditional plant preparations is therefore extremely important for their effective selection, since most of the secondary metabolites used in modern medicine were discovered through ethnobotanical investigations (Gheriani and Khemis, 2019).

I.5. Definition of Active Principles:

An active principle is a molecule contained in a plant drug or in a preparation based on a plant drug and used for the manufacture of medicines. This molecule has therapeutic, curative, or preventive value. It is obtained from fresh or dried plants. The parts used may include roots, bark, flowering tops, leaves, flowers, fruits, or seeds.

Plants contain secondary metabolites that may be considered indirectly essential substances for plant life, unlike primary metabolites, which are the main compounds involved in plant development and growth (Zerari, 2016).

Two classes of metabolites are distinguished: primary metabolites and secondary metabolites.

I.5.1. Primary Metabolites:

Primary metabolites are a type of metabolite directly involved in the growth, development, and normal reproduction of a cell or organism. These compounds generally have a physiological function in that organism, that is, an intrinsic function. Primary metabolites include carbohydrates, lipids, amino acids, and nucleic acids.

Primary metabolites include amino acids, lipids, carbohydrates, and nucleic acids (Benslama, 2016).

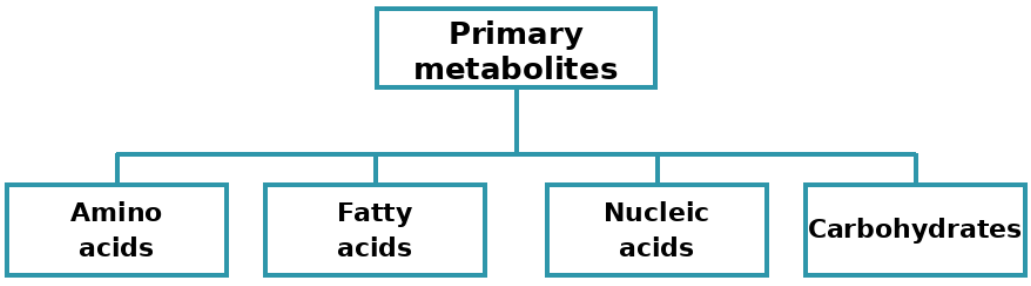


Figure 01: Diagram of primary metabolites in plants.

I.5.2. Secondary Metabolites:

Secondary metabolites can be divided into three classes: polyphenols, terpenoids, steroids, and alkaloids (Seghaouil and Zermane, 2017).

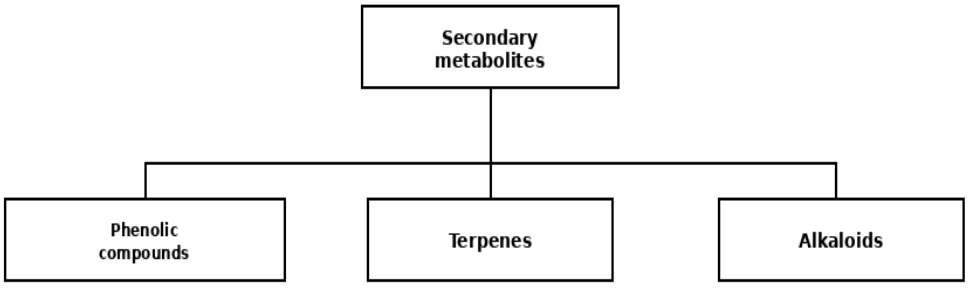


Figure 02: Diagram of secondary metabolites in plants.

I.5.2.1. Polyphenols:

Polyphenols, or phenolic compounds, form a large class of chemical products found in plants, mainly in superficial tissues. They are polyhydroxylated phytochemical compounds containing at least one aromatic ring with six carbon atoms. They are subdivided into main subclasses, including phenolic acids, flavonoids, lignins, tannins, and others (Chakou and Medjoudja, 2014).

Phenols have anti-inflammatory, antiseptic, and analgesic activities; aspirin is derived from salicylic acid (Guelmine, 2018).

I.5.2.2. Terpenes and Steroids:

Terpenoids are a vast family of natural compounds, including nearly 15,000 different molecules that are generally lipophilic. Their great diversity is due to the number of basic units forming the main chain with the formula $(C_5H_8)_n$. Depending on the value of n, these compounds include monoterpenes, sesquiterpenes, diterpenes, and triterpenes. These molecules occur in the form of essential oils, plant fragrances and flavors, pigments such as carotene, hormones such as abscisic acid, and sterols such as cholesterol (Guelmine, 2018).

I.5.2.3. Saponins:

The term saponosides is derived from the word soap. They are glycosylated terpenes and may also occur in aglycone form. They have a bitter and acrid taste (Hopkins, 2003). They exist in two forms: steroids and terpenoids (Guelmine, 2018).

I.5.2.4. Essential Oils:

Essential oils are highly complex mixtures of volatile aromatic substances obtained from plant raw material (Nahal Bouderba, 2016). They give the plant a characteristic odor and are found in secretory organs. They play a role in protecting plants against excessive light and in attracting pollinating insects (Guelmine, 2018).

I.5.2.5. Alkaloids:

Alkaloids are nitrogenous organic substances of plant origin, with alkaline properties and complex structures (Ounis and Boumaza, 2018). They are found in several plant families.

Most alkaloids are soluble in water and alcohol and have a bitter taste. Some are highly toxic. They have important pharmacodynamic properties at low doses and can be reproduced by synthesis. The molecular weight of alkaloids varies from 100 to 900 (Gaci and Lahiani, 2017).

I.5.2.5.1. Classification of Alkaloids:

The classification of alkaloids is based on several criteria: biological origin, biosynthetic pathway, and structure (Badiaga, 2011). Three major classes are distinguished depending on whether or not they have an amino acid as a direct precursor and whether or not they contain a nitrogen atom in a heterocycle.

I.5.2.5.1.1. True Alkaloids:

True alkaloids have a complex nitrogen-containing and basic structure, with nitrogen included in a heterocycle. They occur as salts. They are biosynthetically derived from amino acids and have significant pharmacological activity, such as nicotine, codeine, and morphine (Tidjani et al., 2016).

I.5.2.5.1.2. Pseudo-alkaloids:

Pseudo-alkaloids generally display most characteristics of true alkaloids. They are basic but are not derived from amino acids; examples include caffeine and solanidine (Muniz, 2006).

I.5.2.5.1.3. Proto-alkaloids:

Proto-alkaloids are simple amines whose nitrogen is not included in a heterocycle. They are basic and are produced in vivo from amino acids, such as adrenaline and dopamine (Bruneton, 1999; Maldonado, 2012).

Table 01: Main types of true alkaloids and their amino-acid precursors (Fettioune and Founas, 2015).

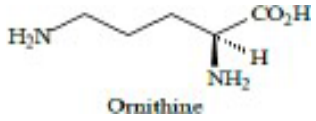
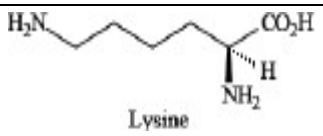
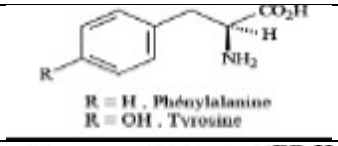
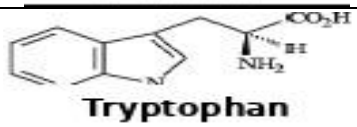
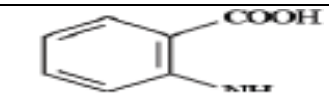
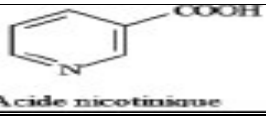
Precursors (amino acids)	Alkaloid group	Examples
 Ornithine	Pyrrolidines, Pyrrolizidines, Tropanes	Hygrine, Meteloidine Atropine, Cocaine
 Lysine	Piperidines, Quinolizidines, Indolizidines	Coniine, piperine, lupinine Swainsonine
 R = H , Phénylalanine R = OH , Tyrosine	Isoquinolines	Codeine, morphine
 Tryptophan	Indoles	Serotonin, tryptamine
 Anthranilic acid	Quinolines, Quinazolines, Acridines	Perforine, Peganine, Acronycine
 Arginine	β-carboline	Saxitoxin
 Histidine	Imidazoles	Histamine
 Acide nicotinique	Pyridines	Nicotine

Table 02: Main types of proto-alkaloids and their amino-acid precursors (Fettioune and Founas, 2015).

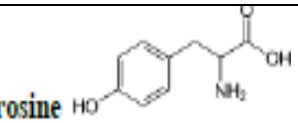
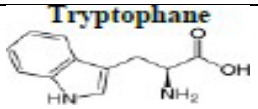
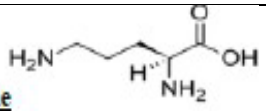
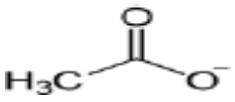
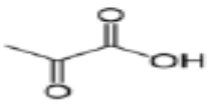
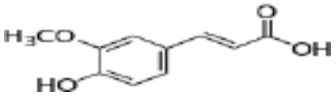
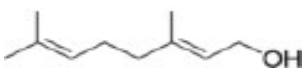
Precursors (amino acids)	Alkaloid group	Examples
Tyrosine 	Phenylethylamines	Adrenaline, dopamine
Tryptophane 	Indole terpene	Yohimbine
Ornithine 	Pyrrolizidine	Stachydrine

Table 03: Main types of pseudo-alkaloids and their amino-acid precursors

(Fettioune and Founas, 2015).

Precursors (amino acids)	Alkaloid group	Examples
Acétate 	Piperidine, sesquiterpene	Coniine, pinidine, worforine, evonine
Acide pyrovique 	Ephedra	Ephedrine, cathine
Acide férulique 	Phenyl	Capsaicin
Géraniol 	Terpenoid	Aconine, gentianine
Saponins	Steroids	Cholestane, solanidine

I.5.2.5.2. Distribution and Localization of Alkaloids:

Alkaloids are mainly found in the plant kingdom, particularly in angiosperms. They are also found in bacteria, such as pyocyanin from Pseudomonas aeruginosa, in fungi such as psilocin, and in animals, such as flustramine, saxitoxin, and samandarine (Singla et al., 2010).

I.5.2.5.3. Extraction of Alkaloids:

Alkaloids are organic compounds whose extraction is based on differences in their solubility in acidic and alkaline media, on the one hand, and on the nature of the solvent, on the other hand (Jean, 2009).

Depending on the pH of the medium, alkaloids occur as bases or salts. This property influences the type of solvent used during extraction. There are three general types of alkaloid extraction:

• Extraction with a non-polar organic solvent.

• Extraction with a polar organic solvent.

• Extraction with acidified water (Guessoumi, 2015).

I.5.2.5.4. Characterization of Alkaloids:

Alkaloid salts produce characteristic colored precipitates with iodinated complexes of heavy metals. The four most commonly used reagents are:

• Bouchardat reagent (iodine-potassium iodide solution): brown precipitates;

• Dragendorff reagent (potassium iodobismuthite solution): orange to vermilion-red precipitates;

• Valser-Mayer reagent (potassium mercuric iodide solution): whitish-yellow precipitate;

• Bertrand reagent (silicotungstic or phosphotungstic): whitish-yellow precipitate;

• Add 2 to 3 drops of Dragendorff reagent to 1 ml of the acidic aqueous solution of alkaloid salts (CHENNI. Mohamed, 2010).

I.5.2.5.5. Quantification of Alkaloids:

I.5.2.5.5.1. Quantification of Total Alkaloids:

• Gravimetric assay: this consists of weighing the residue of total alkaloids.

• Volumetric assay: this makes use of the basic character of alkaloids. The residue of total alkaloids is treated with a known excess quantity of standardized acid, and the acid excess is determined using a standardized base solution. The quantity of acid required to neutralize the alkaloids is then deduced.

• Colorimetric and spectrophotometric assay: certain alkaloids may produce more or less specific colored reactions that can be evaluated using a spectrophotometer.

I.5.2.5.5.2. Quantification of Specific Alkaloids:

Several methods are used: densitometry after semi-quantitative thin-layer chromatography, GC, HPLC, and UV-Visible spectroscopy (Guessoumi, 2015).

I.5.2.5.6. Biosynthesis of Alkaloids:

The origin of true alkaloids goes back to amino acids, including ornithine, lysine, phenylalanine, tyrosine, tryptophan, histidine, and anthranilic acid.

In all cases, the first step consists of decarboxylation of amino acids by specific decarboxylases. Tyrosine and phenylalanine, which are compounds at the origin of the aromatic nucleus, are the precursors of the important group of isoquinoline alkaloids. Their synthesis most often occurs at precise sites; they are then transported to their storage sites (Nacoulma, 2012).

I.5.2.5.7. Biological Activities and Therapeutic Interest of Alkaloids:

Alkaloids are particularly interesting substances because of their biological activities, which occur in a wide range of fields in mammals, including heart diseases, cancer, diabetes, hypertension, and Alzheimer's disease.

On the central nervous system: depressants such as morphine and scopolamine; stimulants such as caffeine and strychnine. On the autonomic nervous system: sympathomimetics such as ephedrine.

• Sympatholytics such as yohimbine and certain ergot alkaloids; parasympathomimetics such as eserine and pilocarpine; parasympatholytics such as atropine and hyoscyamine; ganglioplegics such as sparteine and nicotine. At the vascular level:

hypertensive agents such as ephedrine and hydrastine; hypotensive agents such as yohimbine; vincamine improves cerebral circulation. Other actions:

• Curare-like and local anesthetic effects, such as cocaine; antiarrhythmic effects, such as quinidine; antitumor effects, such as vinblastine and ellipticine; antimalarial effects, such as quinine; and amoebicidal effects, such as emetine.

They act at low doses and may present strong toxicity, sometimes even at very low doses, as in the case of aconitine (Bourgou et al., 2016).

I.6. Study of Biological Activities

I.6.1. Anti-inflammatory Activity

I.6.1.1. Inflammation and Anti-inflammatory Drugs

I.6.1.1.1. Inflammation

Inflammation is the response of vascularized living tissues to aggression. The role of this inflammatory response is to eliminate the aggressive agent and allow tissue repair. It therefore helps maintain the integrity of the "self" (Boudjida and Halit-Sahnoun, 2017).

Inflammation is usually a beneficial process: its aim is to mobilize the immune system in order to eliminate the pathogen and repair tissue lesions. Indeed, immune cells on guard automatically detect the invader, and a series of biochemical reactions is triggered to prevent the aggressive agent from spreading while initiating repair (Ibrahima, 2019).

I.6.1.1.2. Anti-inflammatory Drugs

Anti-inflammatory therapy is generally based on synthetic molecules such as non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs (corticosteroids), and morphine-like compounds.

I.6.1.2. Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs constitute one of the therapeutic classes with anti-inflammatory, antipyretic, and analgesic properties. This category includes many molecules such as diclofenac, ibuprofen, aspirin, and indomethacin (Erdogan et al., 2019; Hassan et al., 2019; Katsinelos et al., 2019). Their mechanism of action is largely based on the competitive inhibition, reversible or irreversible, of cyclooxygenase 1 and/or 2, an enzyme responsible for the production of prostaglandins from arachidonic acid (Zhao et al., 2021). This common property of NSAIDs leads to a 50% decrease in the production of prostaglandins, prostacyclins, and thromboxanes, which are important mediators of inflammation (Grandin, 2013; Katsinelos et al., 2019).

Unfortunately, NSAIDs are also associated with many deleterious effects, since prolonged use may cause gastrointestinal disorders and platelet dysfunction. Other side effects, such as hypertension associated with renal dysfunction, have also been reported (Mebirouk, 2017; Capet et al., 2001; Orliaguet et al., 2013).

I.6.1.2.1. Metabolism of Diclofenac

Pharmacokinetic Properties:

• Absorption: Diclofenac is completely absorbed after oral administration. However, because of first-pass hepatic metabolism, only about 50% of the absorbed dose is systemically available. Food has no significant effect on the extent of diclofenac absorption.

• Distribution: The volume of distribution of diclofenac is 1.4 L/kg. It binds more than 99% to plasma proteins, mainly albumin. Diclofenac diffuses into and out of synovial fluid according to the concentration gradient, although it is not clearly established whether this diffusion contributes to its efficacy.

• Metabolism: Five metabolites have been identified in plasma and urine. Diclofenac is hydroxylated in the liver before undergoing glucuronidation and sulfonation, followed by biliary excretion. Only one metabolite, 4'-hydroxy-diclofenac, retains pharmacological activity, although this activity remains very weak.

• Excretion: A very small amount of the unchanged form is eliminated in urine, along with 65% of the metabolites; the remainder is eliminated in feces. The plasma half-life of unchanged diclofenac ranges from 1.2 to 2 hours, and approximately 35% of the dose enters the enterohepatic cycle.

Pharmacodynamic Properties:

Mechanism of action: The action of a single dose lasts much longer than its half-life, which is partly explained by the high concentrations present in synovial fluid. The exact mechanism of action is not fully known, but it is similar to that of other NSAIDs, through the inhibition of prostaglandin synthesis by blocking cyclooxygenase (COX). COX inhibition reduces prostaglandin levels in the gastric epithelium, making it more sensitive to corrosion by gastric acidity. Diclofenac shows a slight preference for COX-2 inhibition, making it less aggressive than aspirin and indomethacin. It is apparently the only NSAID that also inhibits lipoxygenase (LOX), thereby reducing leukotriene synthesis, which are pro-inflammatory mediators. An action on phospholipase A2 is also suspected, contributing to its antipyretic, analgesic, and anti-inflammatory effects (S. Swarnalata, 2008).

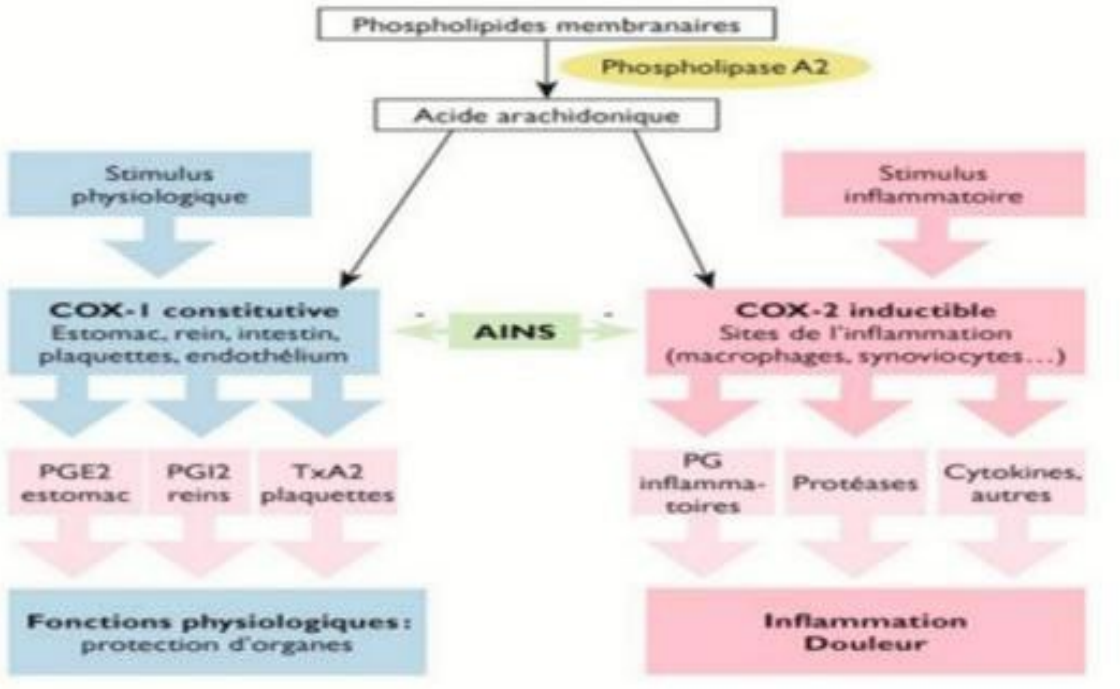


Figure 03: Mechanism of action and effects of non-steroidal anti-inflammatory drugs (Ferrer et al., 2019).

I.6.1.3. Steroidal Anti-inflammatory Drugs (SAIDs)

Steroidal anti-inflammatory drugs (SAIDs), or glucocorticoids, constitute a large family of medicines derived from cortisol. They represent the most effective treatment used for chronic inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel diseases, and autoimmune diseases. Examples include methylprednisolone, betamethasone, prednisone, and prednisolone. As with NSAIDs, the use of glucocorticoids is associated with many adverse effects. The risk of these adverse effects increases with prolonged treatment duration and higher dosage (Kessel et al., 2014; Danielson et al., 2018).

I.6.1.3.1. Metabolism of Prednisone

Pharmacokinetic Properties:

• Absorption: Digestive absorption of prednisone, mainly in the initial part of the jejunum, is rapid and reaches approximately 80% after a single oral dose. Peak plasma concentration is reached orally within 1 to 2 hours. The plasma half-life is 205 minutes (3.4 to 3.8 hours). After absorption, prednisone is converted into prednisolone, its active metabolite, by hepatic 11β-

hydroxylation. Prednisolone metasulfobenzoate (Solupred®), however, is less well absorbed than prednisone (Precortyl®), which gives it lower bioavailability. This therefore supports the preferential choice of prednisone in the treatment of inflammatory diseases.

• Protein binding: In plasma, glucocorticoids circulate mainly in bound form: 90% for prednisone and prednisolone, and 77% for methylprednisolone, bound to two transport proteins.

• Metabolism: The metabolic pathways of the different glucocorticoids are poorly understood. Prednisone metabolism is hepatic. The main enzymes involved in the hepatic elimination of prednisolone and methylprednisolone appear to be 11β-hydroxysteroid dehydrogenase and 20-ketosteroid reductases.

• Elimination: Elimination is urinary in the form of conjugated metabolites (80%) and unchanged prednisolone (20%). The plasma elimination half-life of corticosteroids is around 1.5 to 3.5 hours (Dramane and Kone, 2001).

Pharmacodynamic Properties:

Tissue mechanism of action: The action of SAIDs is analyzed at three levels:

• A decrease in the mobility of cells involved in inflammation.

• A decrease in the production of vasoactive substances involved in inflammatory phenomena.

• A decrease in the function of immunocompetent cells involved in chronic inflammation (Moulin and Coquerel, 2002).

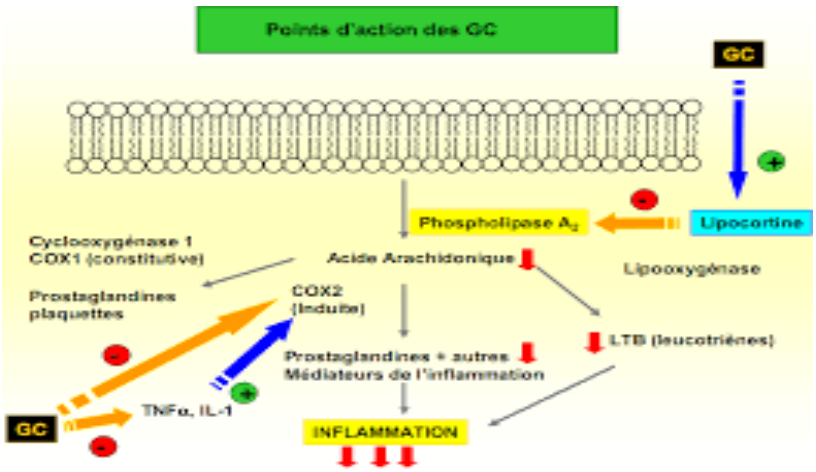


Figure 04: Mechanism of action and effects of steroidal anti-inflammatory drugs (Anonymous 03, 2023).

I.6.1.4. Natural Morphine-like Anti-inflammatory Agents

In vitro and in vivo studies have demonstrated the anti-inflammatory effect of phytochemical compounds derived from the plant kingdom. These compounds are numerous and display a wide range of biological activities (Dhingra et al., 2018). Such active substances can act at several levels of the inflammatory response, for example by inhibiting the activation of inflammatory cells and the synthesis of pro-inflammatory cytokines. Some of them possess anti-inflammatory activity and target COX-1 and COX-2, lipoxygenases (LOX), nitric oxide (NO), phospholipase A2 (PLA2), and others. These molecules are of crucial interest because they offer advantages over conventional anti-inflammatory drugs, with fewer side effects (Maroon et al., 2010; Mebirouk, 2017; Dhingra et al., 2018).

I.6.1.4.1. Metabolism of Morphine

Pharmacokinetic Properties:

It is a prolonged-release form that allows oral administration once daily.

• Absorption:

After oral administration of this 24-hour prolonged-release morphine formulation, the dose-normalized amount of absorbed morphine (AUC) is similar to that obtained after administration of morphine solution or other prolonged-release morphine forms. However, the rate of morphine absorption from this formulation is slower. The peak plasma concentration (Cmax), after administration of a 50 mg oral dose of this morphine formulation in 30 healthy subjects, is 8.1 mg/ml with a Tmax of 8.5 hours. Food slows the digestive absorption of morphine from this formulation (slightly longer Tmax) without changing the amount absorbed (AUC). This slowing has no clinical consequence, and this morphine formulation can be administered either with meals or between meals.

> The bioavailability of oral forms compared with subcutaneous administration is 50%, and compared with intravenous administration is 30%.

• Distribution: After absorption, morphine is bound to plasma proteins at a rate of 30%. Morphine crosses the blood-brain barrier and the placenta.

• Metabolism: Morphine is extensively metabolized into glucuronide conjugates that undergo enterohepatic circulation. Morphine-6-glucuronide and normorphine are two active metabolites of the parent compound.

• Elimination: The plasma half-life of morphine is variable, ranging from 2 to 6 hours.

The elimination of glucuronide conjugates occurs mainly through the urinary route, by both glomerular filtration and tubular secretion. Fecal elimination is low (< 10%).

Pharmacodynamic Properties:

Opioid analgesic (N: central nervous system).

• Action on the central nervous system: Morphine has a dose-dependent analgesic action. It may affect psychomotor behavior and, depending on dose and individual condition, may cause sedation or excitation.

At therapeutic doses, morphine exerts a depressant action on the respiratory centers and the cough center. The respiratory depressant effects of morphine decrease during chronic administration. Its action on the vomiting center, through the chemoreceptor trigger zone, which may be stimulated by pain, and through the cochleo-vestibular center, as well as its effect on gastric emptying, gives it variable emetic properties. Morphine also causes centrally mediated miosis.

• Action on smooth muscle: Morphine decreases the tone and peristalsis of longitudinal fibers and increases the tone of circular fibers, causing sphincter spasm, including the pylorus, ileocecal valve, anal sphincter, Oddi's sphincter, and bladder sphincter (Anonymous 04, 2023).

I.6.2. Anti-hemolysis Test

I.6.2.1. Hemolysis

Hemolysis (hemo: blood; lysis: disruption) is an irreversible phenomenon that leads to the rupture of the red blood cell membrane, causing the release of intra-erythrocytic elements into the plasma, particularly hemoglobin (Kato et al., 2017).

I.6.2.2. Physiological Hemolysis

Physiological hemolysis is characterized by the destruction of red blood cells after a lifespan of about 120 days due to aging. It is immediately compensated by the bone marrow and has no clinical or biological consequences. This phenomenon can be detected visually by the appearance of a pink to red color in the sample after centrifugation, or by measuring the optical density of the supernatant (hemoglobin) using spectrophotometry (Mezzour et al., 2006).

I.6.2.3. Mechanism of Action of Anti-hemolytic Agents Drugs:

The treatment of hemolytic anemia inevitably depends on treating its underlying causes. Therefore, there are almost as many treatments as there are causes. A number of anti-hemolytic drugs, substances capable of delaying or inhibiting the lysis of red blood cells, are available. Folic acid, iron supplementation, corticosteroids, and vitamin B supplements may be used to treat hemolytic anemia (Dubost and Dupuis, 2011).

I.6.3. Antidiabetic Activity

To overcome the side effects of antidiabetic treatments, scientific research has focused on 1,123 plants traditionally used against diabetes (Raccah, 2004). The minority of plants studied includes Momordica charantia, Catharanthus roseus, Trigonella foenum-graecum, Allium cepa, Allium sativum, and others (Al-Achi, 2005). Guanidines were first extracted from Galega officinalis, which constitutes a natural source for the semi-synthesis of biguanides that are less toxic than guanidines (Dey Lucey et al., 2002). Other plant compounds also show biological activity.

Table 04: Plant compounds with antidiabetic properties

Compound	**Chemical nature**	**Source**	**Possible mechanism of action**
Polypeptide	Polypeptide	Momordica charantia	Insulin-mimetic, administered subcutaneously in patients with type 1 diabetes (Marles and Farnsworth, 1994).
Charantin	Steroidal heteroside	Momordica charantia (Dey Lucey et al., 2002); Momordica foetida (Marles and Farnsworth, 1994)	The exact mechanism of action remains unknown. Studies have reported that: M. charantia juice may improve glucose tolerance in patients with type 2 diabetes (Ovaizu, 1986). The aqueous extract of M. charantia decreases postprandial blood glucose with a reduction in glycated hemoglobin levels (Srivastava et al., 1993). It increases hepatic glucose utilization and inhibits gluconeogenesis; it reduces insulin resistance by increasing the level of membrane glucose transporters (Al-Achi, 2005).
Ginsenosides	Steroidal heteroside	Panax ginseng	The plant causes an increase in the number of glucose transporters. Stimulation of insulin synthesis (Al-Achi, 2005).

Trigonelline	Alkaloid	Trigonella foenum-graecum (Marles and Farnsworth, 1994; Dey Lucey et al., 2002)	Crude extracts showed the following effects: Decrease in postprandial blood glucose. Decrease in glucagon, somatostatin, insulin, total cholesterol, and triglyceride levels. Increase in HDL cholesterol levels (Ribes et al., 1984). Resensitization of cells to the action of insulin (Al-Achi, 2005).

Generally, all these antidiabetic agents cause different side effects that vary according to the class and generation of the drug. More specifically, sulfonamides and insulin secretagogues can cause hypoglycemia. This effect is considered the main side effect, along with hyponatremia, hepatitis, hematological disorders, possible dermatological reactions, and weight gain caused by hyperinsulinemia (Marles and Farnsworth, 1994; Dey Lucey et al., 2002).

I.7. Molecular Docking

I.7.1. Types of Molecular Docking:

There are three types of molecular docking. The first is rigid docking, which is based on the "lock-and-key" model. Proposed in 1894 by Emil Fischer, this type of docking considers both the protein and the ligand as rigid bodies. This procedure is the simplest and fastest to perform because the search space is much smaller. However, if the ligand conformation is not correct, the probability of finding a complementary fit is lower. Nevertheless, it is still often used for protein-protein docking.

The second type is semi-flexible docking, which is often used for protein-ligand docking. In this case, the ligand is considered flexible while the protein is kept rigid. However, some proteins naturally have highly flexible regions that undergo considerable rearrangements in the presence of a ligand. In this case, neglecting protein flexibility may compromise the reliability of the docking results and requires the use of approaches capable of taking the flexibility of the whole system into account.

In contrast, the third class is flexible docking, which treats both molecules as flexible, although the allowed flexibility remains limited (Lebbad, 2016; El Hadji Said, 2016; Bouchagra, 2018).

I.7.2. Principle:

Docking is used to predict the structure of the intermolecular complex resulting from the association between at least two molecules. It also helps determine how a ligand, which is a

small molecule, interacts with a receptor, which is a macromolecule, and calculates the binding energy between them. It also helps identify which candidate ligand interacts best with a target receptor (Asses, 2011; Lanez, 2016).

I.7.3. Steps of Molecular Docking:

The docking process is iterative, and each calculation run consists of two steps:

I.7.3.1. Molecular Docking with AutoDock Tools:

This is the selection step, which consists of placing the ligand in the active site of the molecule and sampling possible conformations, positions, and orientations, known as poses, while retaining only those that represent the most favorable interaction modes. Docking software is therefore very useful in biology, pharmacy, and medicine, because most active principles are small molecules, or ligands, that interact with a biological target of therapeutic interest (El Hadj, 2016; Lanez, 2016).

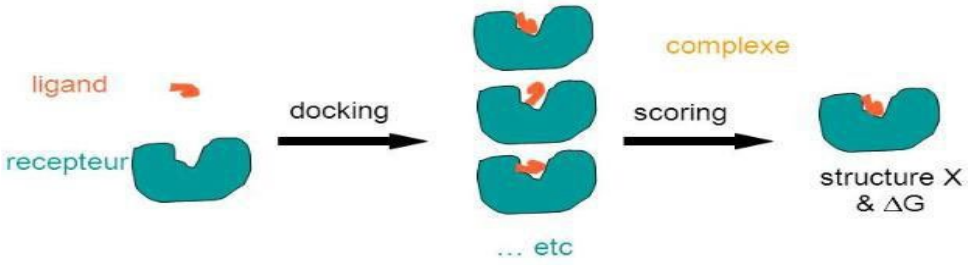


Figure 05: General principle of a docking program

I.7.3.2. Energy Potential Modeling:

To calculate the free energy of the ligand-receptor complex, AutoDock uses the terms of a traditional force field to which two entropy-related terms are added. The energy is given by the following equation:

$\Delta G = \Delta Gvdw + \Delta Ghbond + \Delta Gelect + \Delta Gconform + \Delta Gtor + \Delta Gsol$ (Garrett, M., et al., 1998)

ΔGvdw: dispersion/repulsion energy of atoms,

ΔGhbond: hydrogen-bond energy,

ΔGelec: electrostatic interaction energy,

ΔGconform: energy of deviations from covalent geometry,

ΔGtor: a term reflecting the increase in system energy caused by the restriction of the ligand's

free rotors and by the restriction of ligand rotations and translations during receptor complexation,

ΔGsol: another entropy-related term describing the energy variations of the system during ligand desolvation at the moment of receptor complexation.

Using an empirical QSAR-type relationship is necessary to connect the structure of the complexes with the free binding energy. The empirical model used in Auto Dock is a multiple linear regression of the different terms of the free-energy equation. Each term is therefore weighted by a coefficient derived from an extensive set of receptor-inhibitor complexes for which the inhibition constant Ki is known. The relationship between the inhibition constant and the free binding energy is given by the following equation:

$\Delta G = RT \ln K$

where R is the ideal gas constant (1.987 cal K-1 mol-1) and T is the absolute temperature (298.15 K) (Lanez, 2016).

CHAPTER II

Solenostemma argel

II.1. Description of the Asclepiadaceae Family

Plants belonging to the Asclepiadaceae family present highly diverse forms. Sometimes they are trees; in other cases, they are upright shrubs or perennial herbs (Ricardou, 1893; Watson, 1992), often climbing and then twining, rhizomatous, tuberous, or rooting, sometimes fleshy and cactus-like (Bosser et al., 2005), and often with white latex, sometimes colorless (Ping-tao et al., 1995).

The leaves of these plants have fairly diverse forms. They are simple, almost always opposite, sometimes whorled or isolated (Watson, 1992). The inflorescences are also varied; they may be lateral, axillary, or terminal, most often cymose but sometimes umbel-like, spike-like, or even paniculate (Bosser et al., 2005). The flowers are regular, hermaphroditic, and rarely functionally unisexual (Ping-tao et al., 1995). The calyx is usually composed of five free sepals or sepals fused at their base. These sepals are generally made up of green leaves ending in a tapered point (Carson, 1847). The corolla is most often gamopetalous, with a long or short tube and five lobes that are imbricate, twisted, or valvate in the bud (Watson, 1992). The stamens alternate with the petals. The gynoecium is generally formed of two carpels. These carpels are closed and free, but their styles fuse in the stigmatic region and enlarge into a pentagonal body (Carson, 1847; Bosser et al., 2005). Each ovary locule contains a large number of ovules arranged in several rows (Ping-tao et al., 1995; Bosser et al., 2005).

The fruit is composed of two distinct follicles. At maturity, it ruptures along a longitudinal line corresponding to the edges of the carpellary leaf and opens, revealing its placenta bearing seeds. These seeds almost always have, around the hilum and at their apex, a tuft formed by many silky hairs (Egelsfeld, 1847; Ricardou, 1893).

II.2. Definition

Solenostemma argel is a species of a monotypic genus belonging to the Asclepiadaceae family (Benzid, 2012). It is found mainly in tropical and subtropical regions (Endress and Bruyns, 2000), although some species are also present in temperate zones. It is used in traditional medicine (Benhouhou, 2005).

II.3. Botanical Classification:

Table 05: Botanical classification of S. argel (Burkill, 1985).

Kingdom	**Plants**
Division	Spermatophytes
Subdivision	Angiosperms
Class	Dicotyledons
Order	Gentianales
Family	Asclepiadaceae
Genus	Solenostemma
Species	S. argel (Delile) Hayne
Vernacular name	*Solenostemma argel*

Figure 06: Photograph of *Solenostemma argel* plant (Benchelah et al., 2004).

II.4. Geographical Distribution

Solenostemma argel is a tropical plant that spreads across the central Sahara, Sinai, and the southeastern desert (Benhouhou, 2005). It is a Saharan species found in the desert areas of Algeria, Libya, and Egypt (Figure 2) (Benhouhou, 2005; Gurib-Fakim and Schmelzer, 2013).

In Algeria, the species is widespread in the central Sahara, Tassili n'Ajjer, and the Hoggar Mountains (Benhouhou, 2005). It thrives mainly in rocky and sandy areas as well as in gravelly wadis, between 500 and 1600 m (Sahki, 2004; Gurib-Fakim and Schmelzer, 2013).

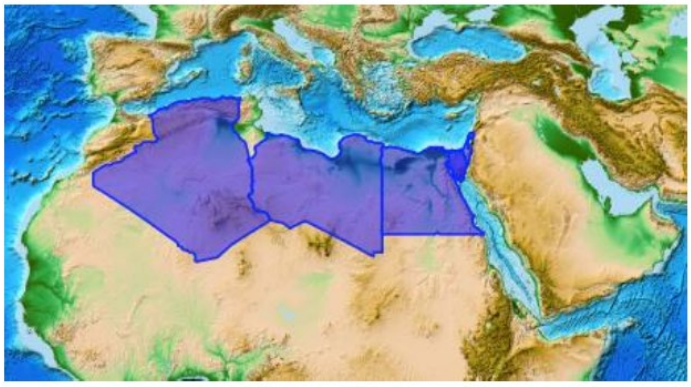


Figure 07: Geographical distribution of *Solenostemma argel* in North Africa and the Sahara region.

II.5. Morphological Description of S. argel (Del.)

S. argel (Del.) is a perennial shrub 60-100 cm high, with several vigorous stems (Figure 1) (Fawzy et al., 2008).

Leaves: They are oval, opposite, leathery, glaucous, and covered with fine hairs.

Figure 08: Stems and leaves of *Solenostemma argel*.

Flowers: The numerous flowers have white petals and a strong odor.

Inflorescences of S. argel: The inflorescences are dense umbels that give the plant an attractive appearance.

Figure 09: Flowers and inflorescences of *Solenostemma argel*.

Fruits: The fruits are thick, pear-shaped, 5 cm long and 1.5-2 cm wide, green with purple lines; they contain pubescent seeds.

Figure 10: Fruits of *Solenostemma argel*.

Seeds: The seeds appear black, oval, and covered with hairs (Abdel-Sattar and El-Shiekh, 2024).

Figure 11: Seeds of *Solenostemma argel* (Abdel-Sattar and El-Shiekh, 2024).

II.6. Ethnobotanical Uses

Throughout its geographical distribution area, the decoction of the aerial parts or leaves of S. argel is highly valued as a febrifuge and purgative, and also to treat colic, stomach pain, constipation, flatulence, urinary tract infections, kidney pain, and cough (Hocking, 1955; Hegazi

et al., 1994; Innocenti et al., 2005). The infusion of the aerial parts treats diabetes and jaundice, while the infusion of the leaves and flowers is indicated for purifying the blood and calming the nerves (Gurib-Fakim and Schmelzer, 2013). The bitter stem sap is used as eye drops during colds; one drop of this sap is said to help clear the sinuses (Benhouhou, 2005).

In Libya and Egypt, the leaf decoction is recommended for treating bronchitis, neuralgia, and sciatica (Jabeen et al., 1984). In the Hoggar, dried leaves reduced to powder are boiled in milk and sweetened with dates or sugar. The prepared decoction is drunk to treat rheumatism, gonorrhea, and hemoptysis. In Lebanon, dried leaves are imported and boiled in olive oil. This liquid is used as a rub against rheumatism (Gurib-Fakim and Schmelzer, 2013). The plant is also burned and its smoke inhaled to treat measles (Gurib-Fakim and Schmelzer, 2013). Fresh crushed leaves or powdered dried leaves are applied to wounds and burns to disinfect them. The plant proves highly effective as an antisyphilitic when used for an extended period ranging from 40 to 80 days (Boulos, 1983; Hammiche and Maiza, 2006). Moreover, the plant is also abortifacient (Sahki, 2004).

In traditional agriculture, small clumps of the plant are introduced into irrigation canals, streams, and ponds as an insecticide. The branches are used to disinfect water. Crushed plants are used as soap for cleaning the body and clothing (Benhouhou, 2005; Gurib-Fakim and Schmelzer, 2013).

II.7. Phytochemicals

The phytochemicals of S. argel have been studied by many researchers [6, 12, 13, 14]. They have been investigated from different parts of S. argel, including leaves, stems, and flowers, and have provided numerous ingredients and crystalline compounds [8, 15]. A previous study conducted by Cud (11) reported and classified the main chemical constituents of S. argel, including acylated phenolic glycosides, namely argelin and argeloside, choline, flavonoids, monoterpenes, pregnane glucoside, sitosterol, and a triterpenoid saponin [13]. Hamed (2001) described two types of stemnosides (A and B) as pregnane ester glycosides, and stemmin C as a polyhydroxylated pregnane.

In addition, leaf extracts contain quercetin, rutin, flavonoids, alkaloids, flavonols, and kaempferol [16, 17]. Murwan et al. (2010) reported that S. argel leaves are characterized by 64.8% carbohydrates and about 15% protein. They found that crude matter, moisture content, and ash were 1.6%, 4.4%, and 7.7%, respectively. They estimated minerals such as potassium at 0.54%, while calcium, magnesium, and sodium were 0.06%, 0.03%, and 0.01%, respectively.

Iron, zinc, and copper were estimated at low percentages: 0.001%, 0.002%, 0.001%, and 0.0001%, respectively. In addition, [9] fractionated S. argel leaves into different compounds, including albumin, non-nitrogenous proteins, prolamin, globulins, and glutelin. Furthermore, S. argel leaves contain anti-nutritional factors, namely phytic acid and tannins (Farah Khameis Farag Teia, 2008).

Conclusion and perspectives

Conclusion and perspectives:

The present study focused on the pharmaceutical prediction and the evaluation of the biological activities of *Solenostemma argel* using both in vitro and in silico approaches. This work aimed to contribute to the scientific valorization of this medicinal plant by investigating its phytochemical composition, its biological potential, and its possible interaction with selected therapeutic targets.

The obtained results showed that *Solenostemma argel* provided a crude extraction yield of 8.2%, indicating that the plant material contained a sufficient amount of extractable compounds for further chemical and biological analyses. The phytochemical screening revealed the presence of important secondary metabolites, mainly alkaloids and cardiac glycosides, with weaker signals for flavonoids and tannins. These compounds may contribute to the biological effects observed during the experimental assays.

The characterization of the extract by UV-Vis and HPLC confirmed the presence of alkaloid-related compounds. These findings support the interest of *Solenostemma argel* as a source of bioactive molecules. The anti-inflammatory evaluation, based on the inhibition of BSA denaturation, showed a concentration-dependent activity, with inhibition increasing from 30.736% to 60.833%. The IC50 value of the extract was 0.432 µM, confirming that *Solenostemma argel* possesses measurable anti-inflammatory potential. However, this activity remained lower than that of the standard drugs used for comparison, especially diclofenac and prednisolone.

The anti-hemolytic activity also showed that the extract was able to improve red-blood-cell protection as the concentration increased. Nevertheless, its protective effect remained lower than that of aspirin at all tested concentrations. Therefore, *Solenostemma argel* can be considered active in this assay, but it should not be described as superior to the reference standard.

Concerning the antidiabetic activity, the extract exhibited an interesting α-amylase inhibitory effect. Its IC50 value was estimated at 0.1867 µM, compared with 0.2091 µM for acarbose. This suggests that the extract may contain compounds capable of reducing α-amylase activity under the experimental conditions. This result is promising, but it must be confirmed by further assays, because crude plant extracts may contain several compounds acting together.

The in silico study supported the experimental observations. SwissADME results indicated a favorable physicochemical and pharmacokinetic profile, including high gastrointestinal absorption and no predicted inhibition of the studied CYP enzymes. ProTox prediction suggested no hepatotoxicity, carcinogenicity, mutagenicity, or cytotoxicity. In addition, molecular docking showed a negative binding energy with cyclooxygenase-2, suggesting a spontaneous and stable interaction between the selected active principle and the biological target.

Overall, the results of this work indicate that *Solenostemma argel* has promising biological potential, particularly as an anti-inflammatory, anti-hemolytic, and antidiabetic natural source. However, the findings remain preliminary and should be interpreted with scientific caution. The extract showed biological activity, but it cannot yet be considered a confirmed therapeutic agent without deeper phytochemical, pharmacological, and toxicological investigations.

As perspectives, future studies should focus on the isolation and purification of the active compounds responsible for the observed activities. Advanced analytical techniques such as LC-MS/MS, NMR, and GC-MS could be used to identify the major bioactive molecules more precisely. It would also be useful to compare different plant parts, extraction solvents, and harvesting periods in order to determine the best conditions for obtaining extracts with higher biological activity.

Further biological investigations are also required. In vitro assays should be repeated with additional concentrations, replicates, and reference standards. In vivo studies are necessary to confirm the anti-inflammatory and antidiabetic effects in biological systems. Toxicological studies should also be conducted to evaluate the safety of the extract, especially because some secondary metabolites may be active at low doses but toxic at high concentrations.

Finally, the in silico approach should be improved by using molecular dynamics simulations and additional biological targets related to inflammation and diabetes. This would provide a better understanding of the stability of ligand-target interactions. These future investigations may help confirm the therapeutic value of *Solenostemma argel* and support its possible use as a natural source for the development of safer bioactive compounds.

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