MINISTERE DE L'ENSEIGNEMENT SUPERIEUR ET DE LA RECHERCHE SCIENTIFIQUE
UNIVERSITE AKLI MOHAND OULHADJ – BOUIRA
FACULTE DES SCIENCES DE LA NATURE ET DE LA VIE ET DES SCIENCES DE LA TERRE
DEPARTEMENT DE BIOLOGIE

Réf : ……./UAMOB/F.SNV.ST/DEP.BIO/2024

MEMOIRE DE FIN D'ETUDES

EN VUE DE L'OBTENTION DU DIPLOME MASTER

Domaine : SNV **Filière** : Sciences Biologiques

Spécialité : Biotechnologie microbienne**.**

Présenté par :

BRAHIMI Chaima & BOUAOUINA Meriem

Thème

Evaluation in vitro et in vivo de l'activite anti-inflammatoire d'artemisia vulgaris et linum usitatissimum.

Soutenu le : 27 /06/2024 **Devant le jury composé de :**

Nom et Prénom	*Grade*		
Mme METIDJI Karima	*MAB*	*Univ. de Bouira*	*Président*
Mme MOURI-HADIDI Lila	*MCB*	*Univ. de Bouira*	*Promotrice*
Mme YALAOUI-GUELLAL Drifa	*MCA*	*Univ. de Bouira*	*Examinatrice*

Année Universitaire : 2023/2024

Ministry Of Higher Education and Scientific Research
Akli Mohand Oulhadj - Bouira University
Faculty of natural and life sciences and earth sciences
Department Of Biology

Ref: ……. /UAMOB/FSNVST/2024

END OF STUDIES DISSERTATION SUBMITTED FOR THE DEGREE OF MASTER SECOND CYCLE LMD

Domain: Nature and Life Sciences **Sector:** Biological Sciences
Option: Microbial Biotechnology

Presented by

BRAHIMI Chaima & BOUAOUINA Meriem

Title

In vitro* and *in vivo* assessment of anti-inflammatory activity from *artemisia vulgaris* and *Linum usitatissimum.

Supported on: 27/06/2024 **Member of the Jury:**

Last and first name	***Grade***		
Ms. METIDJI Karima	*MCB*	*Bouira university*	*President*
Ms. GUELLAL Drifa	*MCA*	*Bouira university*	*Examiner*
Ms. HADIDI Lila	*MCB*	*Bouira university*	*Supervisor*

Academic year: 2023/2024

Acknowledgements

First of all, we thank Almighty God for giving us strength,

courage, persistence and allowed us to exploit the means at our disposal to accomplish this modest work. We express our deepest gratitude and respect to our supervisor Madame LILA HADIDI for her guidance, advice and and sacrifices in order to give our best, and for her support during the preparation of our dissertation. Our thanks go to the members of the jury, Ms. METIDJI K. who did me the honor of agreeing to swear in our work. We would also like to express our sincere thanks to all our teachers who have contributed to our training over the years.

Finally, we would also like to express our deep gratitude to everyone from near and far, those who have encouraged us.

Dedications

My dearest mother FADILA, who has worked for my success through her love, her support, all the sacrifices she has made and her invaluable advice, for all her assistance and presence in my life, receives through this work, however modest it may be, the expression of my feelings and my eternal gratitude.

I dedicate this modest work: To the man in my life KHLIF my eternal example, my moral support and source of joy and happiness, the one who has always sacrificed to see me succeed, who lights my way and illuminates me with gentleness and love, may God keep you for us dad.

To my fiancé FATEH, who has given me so much encouragement throughout this work. Thank you for being so patient with me during the most stressful moments, thank you for your loyalty and kindness.

To those I love dearly, my brothers MOHEMED and YAHIA and my sisters-in-law CHAHINEZ and DONIA, who always supported me and were always at my side.

To all my friends, especially: NARIMEN, ROMIASSA, SOUHILA, ROGUIA

To my partner: BOUAOUINA MERIEM

To all the others I haven't mentioned but who are also in my thoughts.

To all my family

BRAHIMI CHAIMA

Dedications

As a token of love and affection, I dedicate this modest work with great pride to all those

pride to all those who are dear to me:

My dearest mother❤FATIHA❤you have always been my school of patience, of

confidence and above all hope and love. You are and you will remain for me my reference,

the light that illuminates my path.

My very dear father❤Mr. AREZKI❤who has worked for my success, through his love, his support, all the sacrifices he has made.

his love, his support, all the sacrifices he made and his invaluable advice, for all his

assistance and presence in my life.

To My eyes: Yacir and thislasse may God lend them all happiness.

To my dear brothers: Remdan, Zakaria, hamou and salah and my dear beautiful sisters Karima, Djamila, Amina and Naima may God give you health, happiness and success.

To my lovely partner Chaima. Thank you for your presence, support and for encouraging me to go further.

To all my dear friends: Celina, Reguia, Roumaissa, Souhila, Asma and Samia

To all the others I haven't mentioned but who are also in my thoughts.

To all my family

BOUAOUINA MERIEM

Table of contents

Table of contents

Part II: Experimental procedures

III. Materials and Methods.

List of tables

List of figures

List of Abbreviations

AA: Arachidonic acid

ALA: alpha-linolenic acid

NSAI: Non-steroidal anti-inflammatory

AIS: Anti-Inflammatory Steroid

ALCL3: Aluminum chloride

COX: Cyclo-Oxygenase

IL: Interleukin

INF-α: Interferons-α

LB: B Lymphocytes

LDL: Low Density Lipoprotéine

LT: T lymphocytes

pH: Hydrogen potential

AUG: Increase in paw volume

INH: Inhibition of edema

Mpdt: the average weight of the right paw.

Mpg: the average weight of the left paw.

SDG: secoisolariciresinol di-glucoside

Introduction

Inflammation is one of the most central processes in the defense of cells against certain microbial injuries or infections. The mechanism of inflammation represents a chain of organized and dynamic responses including cellular and vascular events with specific humoral secretions **(Abdulkhaleq et al., 2018).**

Inflammation is currently treated with steroid (AIS) and non-steroid (NSAID) anti-inflammatories. These molecules are used in the relief of inflammation. However, the clinical use of these drugs is accompanied by undesirable side effects and they cannot be administered for a long time. This is why the search for new anti-inflammatory drugs is essential with new agents having fewer side effects **(Ghorbani et Esmaeilizadeh, 2017; Sawadogo et al., 2008).**

The use of natural compounds from medicinal plants proves useful, since ancient times, the treatment of various diseases has been based on medicinal plants **(Jaradat et al., 2017).** Medicinal plants should be explored to ensure their safety, quality and effectiveness. These plants are rich in active phytochemicals that exhibit a diversity of biological activities. Researchers are showing keen interest in studying plants with a view to isolating new active drugs that could eventually replace synthetic drugs **(Nemudzivhadi et Masoko, 2014).**

In this study, we are interested on two medicinal plants widely used in the world and particularly in Algeria, namely *Artemisia vulgaris*, locally known as "Chih" and *linum usitatissimum* known as "linseed".

To enhance these plants, our study is focused on the *in vitro* and *in vivo* evaluation of the anti-inflammatory potential of methanolic and ethanolic extracts of *A. vulgaris* and *linum usitatissimum.*

Our work will be structured in three parts. The first part will consist of a bibliographical review, divided into two chapters. The first chapter will discuss generalities about inflammation, while the second chapter will be dedicated to herbal medicine and medicinal plants.

The second part will describe the materials and methods used in our study, including:

- ✓ Preparation of extracts from two selected plants.
- ✓ Phytochemical study of this plants through the spectrophotometric determination of different polyphenolic groups and flavonoids.
- ✓ *In vitro* evaluation of the anti-inflammatory activity of extracts of *A. vulgaris* and *L. usitatissimum* is carried out by testing the inhibition of protein denaturation and evaluating

the preventive effects of the extracts *in vivo* on acute inflammatory edema of the paw of mice induced by carrageenan.

Finally, the third part will be devoted to the presentation of the results obtained, followed by their discussion, and will conclude with a general conclusion as well as perspectives for future research.

Part I: Literature review

I.1. Definition of inflammation

Inflammation represents a natural and adaptive response of body to an attack such as infections, injuries or irritation by chemical products. Its main goal is to protect the body by eliminating aggressive agents and promoting the healing of damaged tissues **(Mitul et al., 2012).** It is therefore a defense mechanism, vital for the good health of the body which is an integral part of the immune reaction. This is a complex process that involves numerous cellular (blood or tissue resident), lipid and protein players **(Charpentière, 2020).**

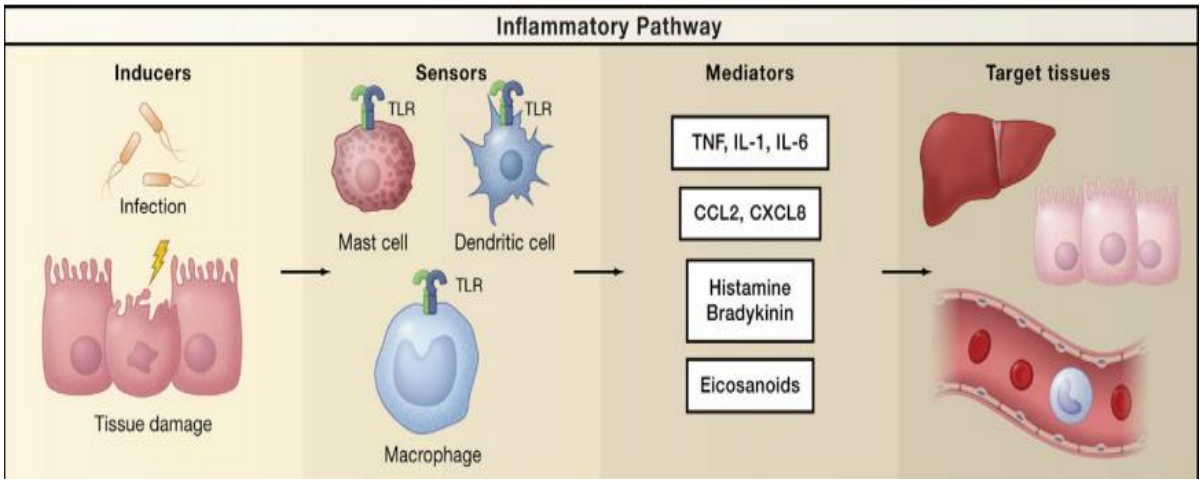


Figure 01: Different inflammatory pathways. **(Medzhitov, 2010).**

I.2. Manifestations of inflammation

Features traditionally associated with inflammation include swelling, redness, warmth, and pain. Swelling, usually results from edema, a buildup of fluid in the tissues. This phenomenon can arise from various mechanisms, including leaky blood vessels, which lead to increased capillary permeability.

Redness is the result of significant vasodilation, a process where blood vessels dilate to facilitate an increased flow of blood to the affected area. This phenomenon may be accompanied by an increase in local heat due to increased blood flow.

Pain results from the interaction of immune system activation with that of the peripheral sensory and autonomic nervous systems. Chemical mediators released during inflammation, such as prostaglandins and cytokines, play a crucial role in transmission. of the pain signal **(Bouhassira et al., 2009).**

I.3. Factors triggering inflammation

The elements that cause an inflammatory response are extremely diverse:

- Microorganisms such as bacteria, viruses, parasites or fungi can cause infection.
- Physical factors, such as wounds, tissue necrosis such as that observed during a heart attack, exposure to heat (burns) or cold (frostbite), as well as UV radiation (sunburn).
- Prostheses or silica particles present in the body.
- Substanceses chemicals, like toxins **(Dyckaets et al., 2003).**

I.4. The different types of inflammation

I.4.1. Acute inflammation

The acute inflammatory reaction is characterized by its rapid onset and relatively short duration. It is considered a defense mechanism of the body, to eliminate pathogens such as bacteria, while facilitating the regeneration of damaged tissues **(Iwalewa et al., 2007).**

Acute inflammation may be the body's first response to harmful stimuli. It is characterized by increased movement of plasma and leukocytes, particularly granulocytes, from the blood into injured tissues. This initial inflammatory reaction triggers a cascade of biochemical events that propagate and amplify the inflammatory response. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vasculature, the immune system and various cells of the injured tissue **(Sekhar et al., 2012).**

I.4.2. Chronic inflammation

Chronic inflammation, also known as long-term or slow inflammation, can last several weeks or even years. Persists even after the initial injury has healed, often due to the presence of a lingering aggressor factor **(Pahwa et al., 2018).**

Chronic inflammation is characterized by the prolonged presence of immune cells such as lymphocytes and macrophages in affected tissues. Their prolonged activity can lead to tissue damage, including scarring (fibrosis) and cell death (necrosis). This type of chronic inflammation may be a contributing factor in the development of various degenerative diseases and health conditions. Including multiple sclerosis, diabetes, as well as bacterial, fungal and parasitic infections, as well as cardiovascular disorders. It may promote tumor progression by

stimulating the growth of cancer cells and promoting angiogenesis (formation of new blood vessels to supply the tumor **(Iwalewa et al., 2007).**

I.5. Pathophysiology of inflammation

The inflammatory response is a dynamic process that takes place in several successive stages **(Yves, 2014).**

I.5.1. Vascular phase

During the vasculo-exudative phase of inflammation, the release of chemical mediators such as histamine and prostaglandins leads to vasodilation of arterioles and an increase in capillary permeability. This results in an increase in local blood flow, extravasation of plasma and inflammatory cells to surrounding tissues.

Increased microcirculatory blood flow partly contributes to the appearance of heat and redness. Plasma exudation induces edema by distending the tissues, which results in increased pressure on local nerve endings, thus explaining the sensations of swelling and pain. Complement proteins are part of the proteins attracted to damaged tissues, playing a major role in this inflammatory phase **(Weill et al., 2003).**

I.5.2. Cellular Phase

A stage follows the vascular phase, which consists of eliminating pathogenic microorganisms and damaged tissues by the mobilization of numerous cells **(Weill et al., 2003)**. Typically, (PNNs), also known as neutrophils, are the first cells to travel to the inflammatory site **(Nadji et al., 2019**), monocytes are involved in the inflammatory phase. These monocytes circulate in the blood and can be attracted to the site of inflammation by chemical signals released by inflamed tissues. Once in tissues, monocytes differentiate into macrophages, which are immune cells specialized in phagocytosis of bacteria, cellular debris, and other pathogens. Opsonizing substances such as IgG and C3b facilitate this process of phagocytosis resulting in the formation of cytoplasmic vacuoles called phagosomes, where enzymes play a role in breaking down the particles **(Pasquier, 1995).**

I.5.3. Resolution phase

It can be defined histologically as the period between the maximum infiltration of neutrophils and their disappearance from the body **(Nadji et al., 2019).** This process of resolving inflammation, highly regulated for tissue repair **(Marsolais et al., 2005).**

Resolution of inflammation varies depending on the level of tissue damage. Neutrophils eliminate attacking agents under the most favorable conditions, while macrophages phagocytize degradation products and cellular debris. Subsequently, macrophages produce cytokines and mediators that initiate the healing and tissue renewal phase **(weill et al., 2003).**

I.6. Mediators of inflammation

I.6.1. Cellular mediators

I.6.1.1. Vasoactive amines

Vasoactive amines, such as histamine and serotonin, play a crucial role in mediating inflammation. They are released by various cells, including mast cells, polymorphonuclear basophils, platelets and damaged capillaries **(Benloukil, 2015).** Histamine and serotonin are known to induce an increase in blood vessel permeability. The release of vasoactive amines by mast cells can cause serious and immediate consequences for sensitized organisms **(Medzhitov, 2008).**

I.6.1.2. Cytokines

Cytokines are soluble molecules, whether proteins or glycoproteins, produced by immune cells **(Moldoveneau et al., 2001).** They play a crucial role in communication between the different cells of the immune system (Table 01). These cytokines can be classified into two main categories: pro-inflammatory cytokines, such as interleukin (IL-1, IL-6), which promote inflammation, and anti-inflammatory cytokines, such as IL- 10, which function to limit the inflammatory response **(Degos et al., 2009).**

Table 01: Cellular Sources and Effects of the Main Inflammatory Mediators **(Rankin, 2004).**

Cytokine	Source	Main activities
IL-1	IL-1α: Macrophages, endothelial cells and fibroblasts. IL-1ß: NK cells, macrophages and monocytes	Generic name for two different proteins, IL-1a and IL-1ß are regulatory and inflammatory cytokines. Important in the up- and down-regulation of acute inflammation. IL-1 is associated with bone formation, appetite regulation, and fever induction
IL-10	T cells, monocytes and macrophages	Pleiotropic immunosuppressive and immunostimulatory cytokine. Inhibits the synthesis of IL-2 in T helpers. Inhibits the synthesis of cytokines in monocytes. Stimulates the production of IL-3 and IL-4.
IFN α	T cells, B cells, monocytes, macrophages and fibroblasts	Antiviral. Stimulates macrophages and NK cell activity. Anti-tumor properties
TGFß	Macrophages, lymphocytes, dendritic cells	TGFß belongs to a family of TGF proteins. Pleiotropic immunoregulatory functions. Autocrine and paracrine functions control the differentiation, proliferation and level of activation of immune cells. Chemotactic for leukocytes during the inflammatory response and inhibits the same cells once activated

I.6.1.3. Chemokines

Chemokines are small soluble proteins (cytokines) with chemoattractant activity that play a crucial role in the formation of an inflammatory infiltrate by inducing the recruitment of specific immunocompetent cells **(Murdoch et Finn, 2000).** Among these chemokines, interleukin-8 (IL-8) occupies a predominant place, mainly by attracting neutrophils to inflammatory sites, notably in smoke inhalation syndromes **(Ravat et al., 2011).**

Chemokines exert their action by binding to specific receptors present on the surface of cells, which activates the mobilization of integrin adhesion molecules. This recruitment mechanism is manifested by strong adhesion of circulating leukocytes to the inner wall of blood vessels, known as the vascular endothelium. Monitoring their migration through endothelial junctions and underlying tissues. Chemokines are clearly expressed at the inflammatory site and their action contributes to fueling the inflammatory process **(Marfaing-Koka, 1998).**

I.6.1.4. Lipid mediators

Lipid mediators, including prostaglandins, leukotrienes, and platelet activating factor (PAF), are associated with typical symptoms of inflammation. These symptoms include fever, edema (fluid accumulation in the tissues), and pain. These mediators are produced following the degradation of arachidonic acid, which comes from membrane phospholipids, by the enzyme phospholipase A2. This enzyme is mainly present in various cells, including leukocytes and platelets **(Zeghal et Sahnoun, 2013).**

Cytosolic phospholipase A2 is responsible for the production of arachidonic acid and lysophosphatidic acid. Arachidonic acid is transformed into eicosanoids by two main pathways: cyclooxygenases (COX1 and COX2), which produce prostaglandins and thromboxanes, and lipoxygenases, which generate leukotrienes and lipoxins. PGE2 and PGI2 act on the smooth muscle fibers of the vessels: vasodilation, increased permeability, edema.

- Lipoxins inhibit inflammation and promote resolution of inflammation.
- Thromboxane A2 causes vasoconstriction and promotes platelet agility **(Medzhitov, 2008).**

I.6.2. Mediators of plasma origin.

I.6.2.1. Coagulation/fibrinolysis system

Coagulation is an enzymatic cascade process in which activation of the first component, factor XII (Hageman), results in the release of thrombin, which converts fibrinogen to fibrin **(Danowski, 1991)**. This process is initiated by damage to blood vessels exposing components of the subendothelium, such as collagen and tissue factor (figure 02), which causes activation of platelets as well as circulating coagulation proteins **(Bezaud et al., 2001).**

The complex interactions between platelets, the vessel wall and adhesive proteins are responsible for the formation of a "platelet plug" during primary hemostasis **(Palta, 2014).** This process is followed by the aggregation of platelets and the simultaneous formation of a fibrin deposit (secondary hemostasis), from fibrinogen **(Spronk et al., 2003).**

The fibrinolytic system is characterized by the conversion of plasminogen, a proenzyme, to plasmin, an active enzyme, by factor XII, whose main role is to break down fibrin clots. This process is initiated when breakdown of fibrin deposits is required **(Alessi, 2002).**

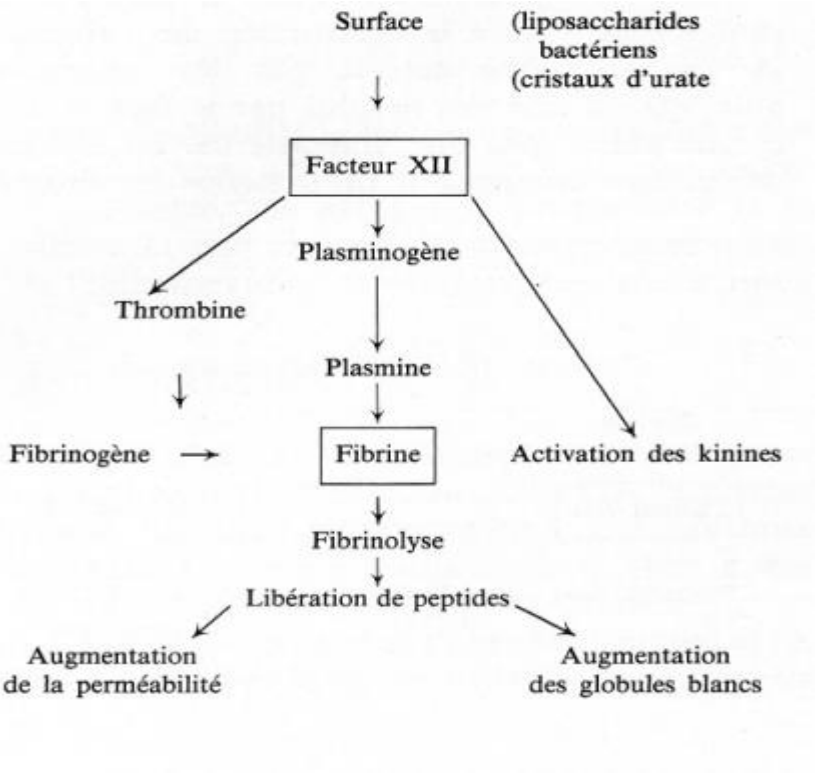


Figure 02: The coagulation system **(Danowski, 1991).**

I.6.2.2. The complement system

The complement system is a multiprotein system composed of around thirty proteins which contribute to the body's defense against infections by complementing the action of antibodies and inflammation (**Abbal et al., 2013**).

Proteins are involved in two distinct activation mechanisms: the first mechanism is triggered in the presence of foreign molecular structures (such as bacteria, viruses, tumor cells, etc.) on the surface of the target. The classic pathway depends on the specific recognition of the target by the antibody **(Ripoche et al., 1989).**

All pathways converge on C3, the most abundant complement protein in the blood, resulting in the formation of activation products such as C3a, C3b, C5a and the C5b-9 membrane attack complex **(Sarma et Ward, 2011**).

I.6.2.3. The kinins/ kallikrenia system

Kinins, such as bradykinin (BK), are natural peptides. The production of kinins involves a complex enzymatic cascade with kininogens and kallikreins, serine proteases, which cleave kininogens to release active kinins (**Bascands, 1996**).

Bradykinin acts on sensory neurons to cause pain and participates in inflammation by activating the alternative complement pathway (**Weill et al., 2003**). This process is crucial for the regulation of blood pressure and inflammatory reactions by increasing vascular permeability **(Golias et al.,2007; Campbell, 2001).**

I.7. Inflammation Cells

In an inflammatory focus, the proliferation of blood cells (polymorphonuclear cells, monocytes, lymphocytes) and local connective tissue cells (fibroblasts, mast cells, resident macrophages) is rapid **(Rousselet et al., 2005).**

I.7.1. Phagocytic cells

Phagocytic cells play a crucial role in the body's defense against pathogens **(Château, 1996).** These cells are blood monocytes and tissue macrophages. After their fixation in tissues, macrophages perform functions distinct from monocytes **(Revillard, 2001).** Their function is to capture and degrade pathogens, antigens and cellular debris, with the help of antibodies and complement. Additionally, macrophages can present antigens to lymphocytes **(David, 2015).**

I.7.2. Neutrophils

Polymorphonuclear cells (PMNs) play a crucial role in protecting against infections due to their potent microbicidal capacity. They represent a large portion of circulating granulocytes and are rapidly mobilized after tissue injury. Additionally, PMNs can produce pro-inflammatory cytokines, thereby contributing to the inflammatory response **(Kantari et al., 2008).**

I.7.3. Eosinophils

Eosinophils, which constitute 2% of leukocytes, can travel from blood vessels to tissues to carry out their functions there. These pro-inflammatory cells can release specific cytotoxic granulations. They are involved in the antiparasitic response and play a role in chronic allergic conditions such as asthma **(Carcelain, 2018).**

I.7.4. Lymphocytes

Lymphocytes play a central role in our immune system. About 20% of white blood cells are lymphocytes. They use antigen receptors to recognize and distinguish foreign elements **(Davide, 2015).**

There are two main types of lymphocytes: B cells produce antibodies against antigens **(Cooper, 1987).** While T lymphocytes promote the cellular immune response by destroying pathogens. T cells consist of two main types: cytotoxic T cells, which are responsible for killing host cells, and activating T cells, which stimulate other cells of the immune system **(O'connor et Nichol, 2015).**

I.7.5. Mast cells

Mast cells are tissue-resident cells, rich in granules and involved in allergic and non-allergic diseases **(Blank et Vitte, 2014).** They are distributed around blood vessels, in connective tissues and on mucosal surfaces **(Serhan, 2010).**

I.7.6. Basophils

Basophils, constituting the least common granulocytes, represent between 0.5% and 1.5% of leukocytes. They are studied for their role in parasitic and allergic diseases, as well as their similarity to mast cells **(Serhan, 2010).**

I.7.7. Platelets

Platelets, although not complete cells but cellular fragments, play a crucial role in hemostasis and immunity **(Davide et Roscoff, 2007).** They produce various soluble mediators and participate in coagulation **(Tariket, 2019).**

I.7.8. Fibroblasts

Fibroblasts are cells found in connective tissue. Their main role is the synthesis of extracellular matrix components **(Buckley et al., 2004).** Fibroblasts are also involved in wound healing and the inflammatory response. Additionally, they interact with other cell types, such as immune cells **(Naguib, 2014).**

I.8. Pathological implications of inflammation

Inflammatory diseases are clinical conditions defined by abnormal inflammatory responses, leading to chronic inflammation **(Ahmed, 2011).** This inflammation can lead to the

development of various human diseases (Table 02), such as autoinflammatory and autoimmune diseases **(Serhan, 2010).**

Pro-inflammatory cytokines play a crucial role in amplifying the inflammatory response by recruiting other immune cells to the site of inflammation. The maintenance of inflammatory cells at the site of inflammation is promoted by the production of cytokines and chemokines in various chronic diseases, such as rheumatoid arthritis and psoriasis **(Noack et al., 2018).**

Table 02: Examples of diseases linked to inflammation **(Nathan, 2002).**

Disorders in which the main pathogenetic role is played by inflammation
Asthma Rheumatoid arthritis Arteriosclerosis Osteoarthritis Hashimoto's Gout Thyroiditis Alzheimer's disease Systemic lupus erythematosus Eczema Crohn's disease Type I diabetes Ankylosing spondylitis
Diseases of infectious origin in which inflammation contributes to the pathology
Hepatitis C Influenza virus pneumonia Tuberculosis Bacterial dysentery Gastritis induced by Helicobacter pilory Tuberculosis
Diseases of various origins in which post-inflammatory fibrosis is the main cause of the pathology
Idiopathic pulmonary fibrosis Post-viral or alcoholic liver cirrhosis Bilharzia

I.9. Anti-inflammatories

The main goal of anti-inflammatory therapy is to regulate excess tissue inflammatory response to prevent progression to chronic inflammation **(Muster, 2005).** Anti-inflammatory drugs are classified into two main categories **(Buxeraud, 2008):**

I.9.1. Steroidal anti-inflammatories (AIS)

These medications include corticosteroids (Table 03), which mimic the action of natural steroid hormones produced by the adrenal glands **(Heymonet, 2013).**

They are widely used to treat chronic inflammatory diseases **(Payne et Adcock, 2001).** Due to their anti-inflammatory, antiallergic and immunosuppressive properties **(Guilpain et al., 2012).** These drugs can inhibit different stages of the inflammatory reaction, thereby controlling various aspects of inflammation such as vasodilation, edema and leukocyte migration **(Dejean et Richard, 2013).**

Table 03 : Main glucocorticoids (GC) **(Henzen, 2003).**

Glucocorticoid	Trade name
Cortisol (Hydrocortisone)	Hydrocortone, Solu-Cortef
Cortisone	Cortison CIBA
Prednisone	PrednisoneStreuli
Prednisolone	Spiricort, Ultracorten
Methylprednisolone	Urbason, Solu-Medrol
Triamcinolone	Kenacort, Ledercort
Betamethasone	Celestene, Diprostene
Dexamethasone	Fortecortin, Decadron

I.9.1.1. Mode of action

Glucocorticoids act by inhibiting prostaglandin synthesis, primarily by targeting phospholipase A2. They bind to glucocorticoid receptors in the cytoplasm (figure 03), then move to the nucleus to bind to glucocorticoid response elements (GREs) on genes. This process leads to increased transcription of genes that encode anti-inflammatory proteins, such as lipocortin, which inhibits phospholipase A2 and blocks the production of arachidonic acid **(Barnes,1998).**

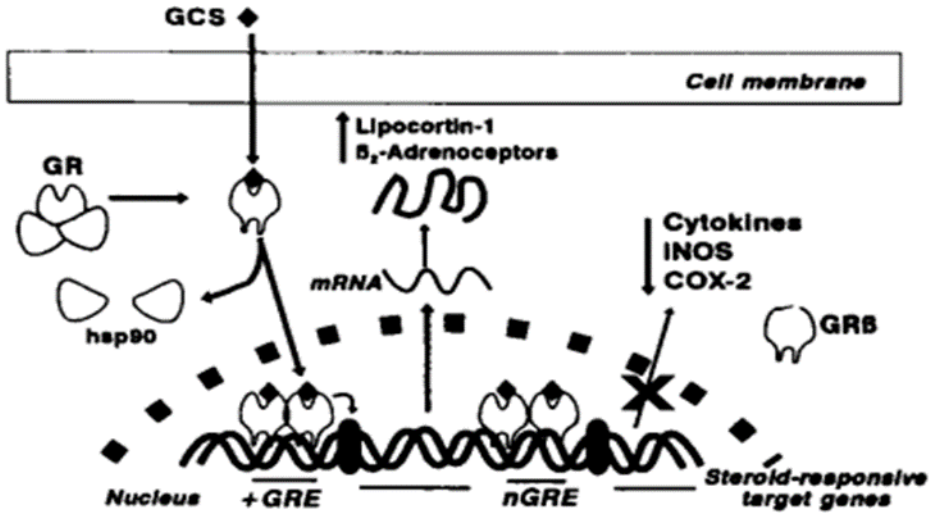


Figure 03: Mechanism of action of AIS. **(Barnes,1998).**

Indeed, just like NSAIDs, prolonged use of glucocorticoids can cause various side effects. These side effects include risks such as high blood sugar, psychiatric disorders, as well as digestive problems like peptic ulcers **(Viatte et al., 2007).**

I.9.2. Non-steroidal anti-inflammatory drugs (NSAIDs)

The most commonly used medications to treat pain and inflammation are nonsteroidal anti-inflammatory drugs (NSAIDs) **(Bidaut, 2001)** to treat pain and inflammation **(Wongrakpanich et al., 2018)**, which have therapeutics and common side effects. They have powerful anti-inflammatory, analgesic and antipyretic activity **(Orliaguet, 2013).**

Nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting the activity of the enzyme cyclooxygenase (COX), which impairs the synthesis of prostaglandins and thromboxanes, essential molecules in inflammatory processes (figure 04).

This discovery of the mechanism of action of NSAIDs by Vane showed that these drugs, despite their structural differences, share a common mode of action. Arachidonic acid is metabolized into eicosanoids, inflammatory mediators, thanks to COX, thus triggering the inflammatory process **(Bacchi, 2012).**

The COX pathway transforms arachidonic acid into prostaglandins and thromboxane. There are two forms of COX: COX-1 is a constitutional and ubiquitous isoenzyme which induces the formation of PG (PGE2 and PGI2) involved in physiological processes such as the protection of the gastric mucosa and the maintenance of renal blood flow. COX-2 is an isoenzyme present

in inflammatory cells. It leads to the release of PG (PGDf2 and PGF2) having a physiological (healing, kidney function) and pro-inflammatory (fever, pain, inflammation, cell proliferation) role **(Khandzian, 2019).**

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) work by blocking both COX-1 and COX-2, whereas COX-2-selective NSAIDs primarily focus on COX-2 that causes inflammation and pain, which reduces the risk of gastrointestinal side effects **(Blain, 2000).**

However, NSAIDs, in general, can cause side effects such as gastrointestinal ulcers, serious cardiovascular events, hypertension, acute renal failure, and worsening heart failure. It is essential to limit the dose and duration of treatment with NSAIDs to reduce these risks **(Vonkeman, 2010).**

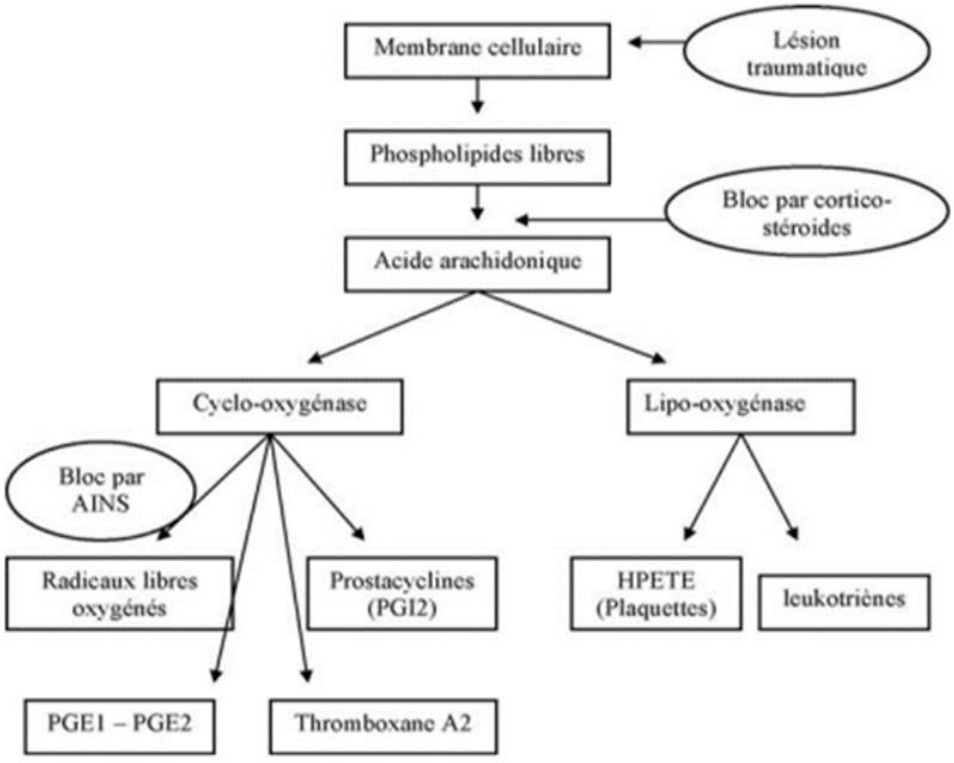


Figure 04: Modes of action of AIS, NSAIDs **(Ziltener, 2010).**

I.9.3. Anti-inflammatories of plant origin

Treatments based on medicinal plants or plant extracts are practiced by approximately 80% of the world's population. Currently, herbal products represent approximately 5% of the current drug market **(Soares-Bezerra, 2013).**

Plants contain a diversity of secondary metabolites, such as alkaloids, terpenes and phenolic compounds. These compounds may possess anti-inflammatory properties and are often used as active ingredients in herbal preparations. (Table 04).

It is fascinating how plants can act on the inflammatory response by inhibiting cytokine production and modulating the activity of various biochemical pathways such as cyclooxygenase (COX) and lipoxygenases (LOX), and phospholipase A2 **(Nunes et al., 2020).**

In this context, several examples of plants can be cited:

Pistacia vera, commonly known as pistachio, is an interesting example of a plant traditionally used to treat various ailments, such as asthma, stomach aches and hemorrhoids. Studies have revealed that the α-pinene contained in *Pistacia vera* has inhibitory activity on phospholipase A2, which may contribute to its beneficial effects **(Orhan et al., 2006).**

Baccharis trimera, or carqueja, is widely used in Brazil to treat various conditions, thanks to its diterpenoids which inhibit phospholipase A2, giving it anti-inflammatory properties **(Januário et al., 2004).**

Zingiber officinale, ginger, has long been recognized for its anti-inflammatory, antioxidant and digestive properties. Components like gingerols and curcumin present in ginger contribute to its beneficial effects by inhibiting the synthesis of prostaglandins and leukotrienes **(Setty et Sigal, 2005).**

Curcuma longa (turmeric), with its curcumin, has powerful anti-inflammatory effects by acting on various biological pathways. Curcumin inhibits nuclear factor kappa B, enzymes like cyclooxygenase 2 and lipoxygenase 5, and cytokines like interleukin 1 and interleukin 6. These mechanisms help reduce inflammation effectively **(Aggarwal et Sung, 2008).**

Table 04: Anti-inflammatory medicinal plants **(Setty et Sigal, 2005; Erdemoglu, 2003).**

Scientific name	**Part Used**	**Name common**	**Use**
Helleborus orientalis	roots	lenten-rose	edema, toothache, rheumatism
Rhododendron ponticum L.	Feuilles	Oleander	pain, headache
Nerium oleander L.	flowers	Oleander	pain, headache
Rubus sanctus Schreber	roots	brambles	rheumatic pain, kidney infections, hemorrhoids
Laurocerasus officinalis Roemer	Leaves	Laurel	fever, pharyngitis, stomach pain, hemorrhoids
Urtica dioica	Leaves roots	Nettle	allergic rhinitis, gout, eczema, rheumatic pain
Ocimum basilicum	leaves	Basil	Osteoarthritis
Oenothera biennis	Fruits Seeds	evening primrose biennial	sjogren's syndrome

Chapter I: General information about inflammation

Chapter II: Medicinal plants and inflammation

II.1. Phytotherapy

The word "phytotherapy" comes from the Greek words "phuton" and "therapeia", designating plant and treatment **(Limonier, 2018).**

Phytotherapy exploits the healing properties of plants to treat disorders or prevent diseases. Several medications are made from plant extracts, coming from various parts such as roots, leaves, bark or fruits, which contain the active ingredients **(Létard et al., 2015).**

II.1.1. The different types of herbal medicine

II.1.1.1. Gemmotherapy: Is an approach to natural medicine that uses the embryonic tissues of plants, such as buds and young shoots, for their therapeutic properties. The extracts obtained are often prepared in the form of glycerinated macerates, and they are used to treat various health disorders **(Andrianne, 2008).**

II.1.1.2. Aromatherapy: Aromatherapy has its origins in the Greek "aroma", which means smell, and "therapia", which means care. It is a natural skincare approach that uses "smells" and involves the use of essential oils obtained from various extraction processes **(Marinier et Lobstein, 2013).**

II.1.1.3. Pharmaceutical phytotherapy: Is the use of products of plant origin, a plant or plant-based preparation such as extracts, to produce medicines which are presented in different galenic forms: capsules, tablets, syrups, ointments, etc. **(Lehmann, 2013).**

II.1.2. Methods of preparation in herbal medicine

The techniques used to prepare herbal products in herbal medicine involve initial steps on the plant material, such as grinding, pressing and extraction, using various methods. Finished products can come in different forms such as powder, herbal tea, fluid, soft or dry extracts, mother tinctures, macerates, and more **(Ouedraogo et al., 2001).**

II.1.2.1. Dried plants and dry plant powders

The plants are first harvested, then dried before eventually being transformed into powder. These powders must be stored in airtight containers, protected from humidity and oxidation **(Fougère et Wynn, 2007).**

a. Capsules or tablets

Capsules or tablets are made from powders, and their quality generally improves with the fineness of the powder used. This powder is then inserted into capsules made of gelatin or plant material **(Chevallier, 2001).**

b. Dyeing

The tincture is obtained by macerating a plant in alcohol, promoting the dissolution of the active substances. This preparation can then be preserved in alcoholic form **(Chevalier, 2001).**

II.1.2.2. Herbal tea preparations

Herbal tea preparations refer to products made by infusing medicinal plants in boiling water **(Goetz, 2004),** from various plant parts such as flowers, leaves and seeds. It is a traditional and popular method for extracting active ingredients from plants, used for medicinal purposes **(Pohl et al., 2016).**

The different extraction processes for aqueous extracts of medicinal plants:

a. Infusions

Infusion is a preparation method that involves pouring boiling water over fresh or dried herbs, leaves, roots or bark, often in powder form. After an appropriate infusion time, usually around 15 minutes, the mixture is filtered to obtain an aromatic and possibly therapeutic drink **(Vernex, 2011).**

b. Decoction

The decoction is applied to the bark and roots, which release their active ingredients with difficulty. The plant material is first placed in cold water, brought to a boil for about 15 minutes, then left to steep for another 15 minutes. Then, the aqueous extract is decanted or filtered. This process results in a darker extract due to increased extraction of components **(Abayomi, 2010).**

c. Maceration

Maceration involves bringing the plant material into contact with the solvent at room temperature for a period of 30 minutes to 48 hours. This method allows for gentle extraction of active ingredients, particularly if they are sensitive to heat. Finally, simply filter the extract obtained **(Chabrier, 2010).**

Extracts are obtained by allowing solvents to act on plants, which allows extraction solutes to be prepared. We can find dry, aqueous or hydroalcoholic extracts, depending on the type of solvent used **(Bureau, 2012).**

II.1.2.3. Essential oils (EO)

Essential oils get their name from the word essence, which highlights their connection to the smell, taste and specific properties of plants **(Calsamiglia et al., 2007).** These are natural, volatile plant compounds found in the leaves, flowers and bark of plants **(Thormar, 2011).** Their antiseptic properties make them very useful in various fields such as pharmacy, cosmetics and the food industry **(Kaloustian et al., 2008).**

II.1.3. Medicinal Plants and active ingredients

II.1.3.1. General

Plants have always been used for medicinal purposes across the world. Their use is often associated with treatments that are gentler and perceived as less toxic than pharmaceutical drugs. As a result, pharmaceutical industries are showing increasing interest in the ethnobotanical study of plants **(Didier et al., 2011).** Traditional medicine is also promoted by the World Health Organization, with 70% of populations in many countries using it to treat various ailments **(Jiofack et al, 2010).**

Natural products and their derivatives represent more than 50% of all drugs used clinically worldwide **(Kumar and al., 2012),** Not only as a therapeutic agent, but also as a basic material for manufacturing of medicines **(Gurib-Fakim, 2006).**

Medicinal plants continue to be a source of medical care in developing countries, in the absence of a modern medical system **(Tabuti et al., 2003).** Even in developed countries, such as the United States for example, between 1959 and 1980, 25% of drugs prescribed and purchased in pharmacies contained plant extracts or active ingredients prepared from plants **(Farnsworth et al., 1986).**

II.1.4. Definition of a medicinal plant

Medicinal plants, defined according to the European Pharmacopoeia, are botanical drugs which have medicinal properties at least partially **(Ouedraogo et al., 2001).** Medicinal plant means any plant containing one or more substances that can be used for therapeutic purposes

or as precursors for the synthesis of useful drugs **(Abayomi, 2010)**. Around 35,000 plant species are used for medicinal purposes worldwide **(Benaradj et Boucherit, 2022).**

II.1.5. Definition of active ingredient

The beneficial properties of certain plants have been well known for a long time. However, it is only in recent years that the active compounds responsible for these therapeutic properties have been identified and studied extensively. The term "active ingredient" refers to a molecule present in a medicinal plant or herbal preparation, and which is used in the manufacture of medicines **(Radjah, 2020).**

II.1.5.1. Dosage forms of medicinal plants

The goal of dosage forms is to simplify the administration of all active compounds in medicinal plants **(Mansouri, 2015).**

II.1.6. Natural plant products and their biological activities

The chemical composition of the plant is complex, composed of various substances (figure below).

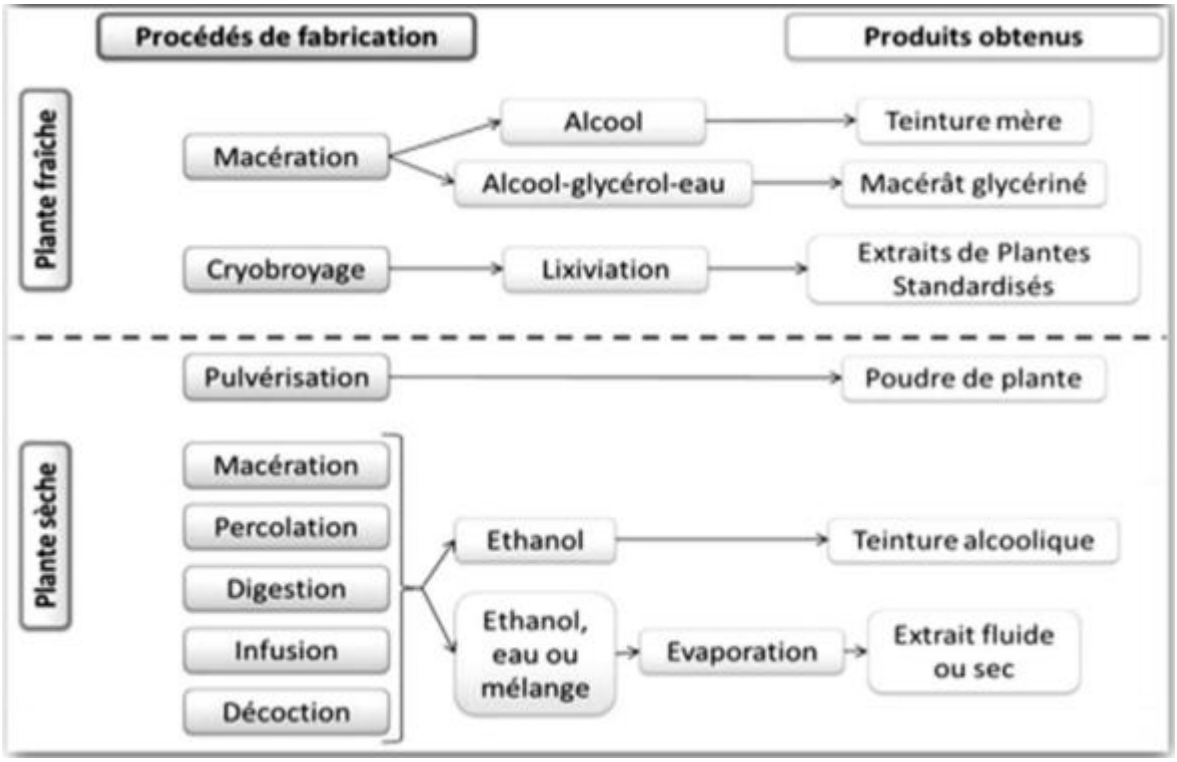


Figure 05: Methods for transforming therapeutic plants **(Mansouri, 2015).**

II.1.6.1. Primary metabolites

Primary metabolites refer to compounds essential for plant function, growth and development. Primary metabolism encompasses all the synthesis pathways of these compounds. Thus, the main primary metabolites include elements such as amino acids and proteins, fatty acids, sugars and polysaccharides, which play key and well-defined roles in all plants **(Royer, 2013).**

II.1.6.2. Secondary metabolites

Secondary metabolites form an extremely diverse set of natural products produced by plants **(Roze et al., 2011).** This group includes a wide variety of compounds, more than 200,000 defined structures. Phenolic compounds, terpenoids, steroids and alkaloids are examples, and they have many pharmaceutical applications **(Hartmann, 2007).**

Generally present in low concentrations in plant tissues, secondary metabolites are characterized by this particularity **(Newman, 2012),** those which are not necessary for the functioning of plant cells, but which provide other important benefits for plants. They are known for their antioxidant action which protects against free radicals generated during photosynthesis **(Yarnell, 2007).** Some of these compounds participate in the defense against pests **(Herms et Mattson, 1992).**

A simple classification of secondary metabolites includes three main groups: terpenes, phenolic compounds (phenolic acids, coumarins, lignans, stilbenes, flavonoids, tannins) and nitrogen-containing compounds such as alkaloids and lignin **(Agostini et al., 2012).**

II.2. Presentation of the plants studied

II.2.1. *Linum usitatissimum*

Flaxseed, also referred to as *Linum usitatissimum,* is considered one of the most essential crops in the world **(Tańska et al., 2016).** It belongs to the genus Lines and the family *Linaceae.* Linnaeus assigned the botanical name *Linum usitatissimum* in his work "Species Plantarum". This family includes around 200 species of flax, among which the most famous, the most cultivated and there the most widespread is *Linum usitatissimum.*

Flaxseeds are among the oldest plants cultivated for their use in oil and fiber production **(Jhala et al., 2010).** They are used in various fields, notably in the textile industry for their fibers, in food for their seeds and their oil, as well as in the chemical industry for their oil **(Beroual et al., 2013).**

II.2.1.1. Historical

As far back as 6000 BC, when flax was first spotted in eastern Turkey. flax cultivation first identified to make fabrics **(Bloedon et al., 2004).** For several centuries, many French workers made a living from growing linen until the industrial revolution of the 18th century **(Tribalat, 2016).**

Linseed, of Mesopotamian origin, was used until the 1990s mainly for the manufacture of fabrics and papers. Today, it is cultivated in more than 2.6 million hectares and the major flax producing countries are India, China, USA and Ethiopia **(Priya et al., 2017).**

II.2.1.2. Classification

Flax, an herbaceous annual plant, belongs to the *Linaceae* family. This family includes more than 200 flax species, among which the most common and widely cultivated is *Linum usitatissimum* **(Bolsheva et al., 2015).**

Order: *Geraniales*

Family: *Linaceae*

Genus: *Linum*

Species: *usitatissimum L*. **(Dill et al., 2009; Bloedon et al., 2004).**

II.2.1.3. Morphology

Flax *(Linum usitatissimum),* is an annual herb growing to about 1.2 m tall. The slender stems bear five-petaled blue flowers, and the fruit capsules are spherical, each containing two seeds in five distinct compartments (Figure 06). Flaxseeds are characterized by their crunchy texture and nutty flavor. They are flat and oval, with pointed ends, measuring 4 to 6 mm in length. There are two main varieties brown and yellow or golden. The color of the seeds is determined by the amount of pigment present in the outer integument **(Nitrayová, 2014; Renouard, 2011; Coşkuner, 2007).**

Figure 06: Flax flowers **(Shekhara et al., 2020; Jroy et al., 2007).**

II.2.1.4. Composition

The composition of flaxseed can be influenced by the genetics of the plant as well as its growing environment. These seeds (Table 05) are known for their high fat, protein and dietary fiber content **(Daun et al., 2003).** Chemical analysis of flaxseed typically reveals an average fat content of 30 to 40%, protein 20 to 25%, and total dietary fiber 20 to 28%, moisture 4 to 8%, and 3 at 4% ash **(Coşkuner et karababa, 2007).**

Table 05: Composition of nutrients and phytochemicals of flaxseed according to the Flax Council of Canada (2007).

Nutrients/bioactive compounds	Quantity/100 g of seed	Nutrients/bioactive compounds	Quantity/100 g of seed
Carbohydrates[a]	29.0 g	Biotin	6 mg
Protein	20.0 g	α-Tocopherol[b]	7 mg
Total fats	41.0 g	δ-Tocopherol[b]	10 mg
Linolenic acid	23.0 g	γ-Tocopherol[b]	552 mg
Dietary fiber	28.0 g	Calcium	236 mg
Lignans	10–2,600 mg	Copper	1 mg
Ascorbic acid	0.50 mg	Magnesium	431 mg
Thiamin	0.53 mg	Manganese	3 mg
Riboflavin	0.23 mg	Phosphorus	622 mg
Niacin	3.21 mg	Potassium	831 mg
Pyridoxin	0.61 mg	Sodium	27 mg
Pantothenic acid	0.57 mg	Zinc	4 mg

- **Proteins**

Proteins' Flaxseeds generally have protein values often exceeding 36% and these differences can be attributed to genetics and environment **(Oomah et al., 1993).** Globulins are the major storage proteins in flaxseed, accounting for approximately 58-66% of the total protein, while albumins constitute approximately 20% **(Venglat et al., 2011).** Flaxseed proteins are rich in arginine, aspartic acid and glutamic acid, but limited in lysine, methionine and cystine. These characteristics make it an interesting source of essential amino acids for human nutrition **(Ganorkar et al., 2013).**

- **Lipids**

Flaxseeds store an appreciable quantity of oil which is relatively rare among oilseed plants (**Gutierrez et al., 2006).** Flaxseed contains approximately 42% oil in its composition. More than 70% of this oil is made up of polyunsaturated fatty acids which are beneficial for health. Flaxseed contains 55 to 57% of essential omega-3 fatty acids, alpha-linolenic acid **(Malcolmson, 2012).** The vast majority of oil is concentrated in the cells of the cotyledons (78%) **(Abidi, 2019).** Linseed oil is mainly used in the industrial sector, which is partly explained by its high content of alpha-linolenic acid (ALA), which is attracting increasing interest for its use in food. Flaxseed oil is used in various food products such as milk, yogurt, ice cream and bread toppings. It is also marketed in the form of soft capsules as a dietary supplement **(Tańska et al., 2016).**

- **Carbohydrates**

Include two types of sugars: starch and dietary fiber Starch, which serves as a reserve in flax seeds, is present in small quantities and is mainly located in the embryos and integuments of flax seeds **(Jhala et al., 2010).**

The dietary fiber component of flax contains both insoluble and soluble fiber. At least some of flax's cardioprotective effects are attributed to the soluble fiber known as mucilage (gum), which makes up about 25% of total dietary fiber or about 7 to 10% of whole flax seeds **(Bloedon et al., 2004).**

The soluble fiber in flax can reduce blood cholesterol levels and help stabilize blood sugar levels, while the insoluble fiber supports intestinal transit by facilitating the movement of stool through the colon, thereby improving bowel function **(Malcolmson, 2012).** Flax fibers used for industrial purposes, are arranged in bundles on the outer surface of the plant stem **(Trochoutsou et al., 2021).**

- **Vitamins**

Flaxseeds contain water-soluble and fat-soluble vitamins. Vitamin E is present in the form of γ-tocopherol, acts as an antioxidant by protecting cellular proteins and fats against oxidation **(Shekhara et al., 2020).**

- **Phenolic compounds**

Flaxseeds contain a variety of phenolic compounds, including polyphenols are distinguished. The latter include phenolic acids, flavonoids, tannins, and a notable concentration of lignans, notably SDG (secoisolariciresinol di-glucoside) **(Nesbitt et al., 1999).** Phenolic acids are found in limited amounts in flaxseed, usually between 8 and 10 mg per gram. Their composition is divided into 72% hydroxycinnamic acids and 28% hydroxybenzoic acids **(Sébastien, 2015).**

Flavonoids, the pigments that color flaxseed, are not simply coloring agents. They are also essential to protect the plant against external aggression **(Oomah et al., 1996).**

Flax seeds (*Linum usitatissimum*) stand out as the most abundant food source of plant lignans **(Tzang et al., 2009).** The lignan Secoisolariciresinol diglucoside (SDG) and other phenolic compounds reveal various bioactivities such as phytoestrogenic, anticarcinogenic and cardioprotective.

Additionally, other phenolic compounds present in flaxseed, such as p-coumaric acid and ferulic acid glucosides, possess antioxidant properties and are of particular interest in dermatology in addition to the antioxidant potential **(Kasote et al., 2011).**

II.2.1.5. Use and therapeutic effect

Flax and its oil find a variety of applications, notably in the food industry where they are used as ingredients, in the pharmaceutical industry, and even in animal feed **(Laiq Khan et al., 2010).**

Flaxseeds have a high content of phytoestrogen lignans and oil containing α-linolenic acid, could have an anti-cancer effect. They can reduce the risk of breast cancer, slow the growth of tumors and even be beneficial in combination with breast cancer treatments **(Mason et al., 2014).**

Flaxseeds contain components that favorably influence the immune system: alpha-linolenic acid (ALA), an omega-3 fatty acid, and lignans, a type of phytoestrogens. These components interact with immune cells as well as mediators of the immune response, such as eicosanoids **(Abdel et al., 2013).**

The effect of n-3 fatty acids on inflammation has attracted much interest. Dietary ALA supplementation significantly decreased inflammatory markers in a study of middle-aged men **(Heli, 2007).**

Studies show that the use of flaxseed oil in household food preparation for 4 weeks inhibits the production of interleukin (30%) and tumor necrosis factor (74%) in healthy volunteers. ALA supplementation for 3 months in 22 patients with rheumatoid arthritis showed no beneficial effects. Improved arterial function in 15 obese individuals is observed by adopting a high-ALA/low-fat diet.

The ingestion of 30 g of flaxseed per day was associated with a reduction in total cholesterol levels as well as LDL cholesterol, and provided a benefit in terms of renal function, inflammatory and atherogenic mechanisms in eight patients suffering from lupus nephritis **(Oomah, 2001).**

II.2.2. Artemisia vulgaris

The Artemisia genus, belonging to the *Asteraceae* family, is one of the largest, encompassing more than 800 different species. *(A. campestris, A. absinthium and A. vulgaris*…) **(Judžentienė et al., 2010),** of the genus Artemisia are often used in the treatment of a range of diseases, including malaria, cancer, inflammations, as well as viral infections **(Tan et al., 1998).**

Artemisia vulgaris L. (Figure 07), also called common mugwort, is a plant widely present in natural environments across the globe, whether in Europe, Asia, North and South America, as well as Africa **(Halina et al., 2020).** *Vulgaris L.*, is a wild-growing perennial herb that is widely used in the Philippines for its antihypertensive actions. It has also been suggested to have other medicinal activities such as anti-inflammatory, antispasmodic, carminative and anthelmintic properties **(Abad et al., 2012).**

Figure 07: *Artemisia vulgaris* **(Weston et al., 2005).**

II.2.2.1. Classification

Among the *Asteraceae*, the genus Artemisia stands out as one of the largest and most widespread. With more than 500 species listed, it represents remarkable diversity. In addition, these plants are of great economic and cultural importance, being used as medicines, foods, ornamental plants or even to stabilize the soil **(Diana et al., 2014).**

The plant is classified as follows:

Kingdom: plantae

Division: *Tracheophyta (Tracheophytes or Vascular Plants)*

Class: *Magnoliopsida*

Order: *Asterales*

Family: *Asteraceae (sunflowers or sunflowers)*

Genus: *A. Vulgaris* (wormwood, mugwort or wormwood). **(Abiri et al., 2018).**

II.2.2.2. Geographic distribution

Mugwort is native to temperate Europe, Asia, and North Africa, but it has been introduced to North America, where it has also become established **(Temraz, 2008).**

Artemisia vulgaris is primarily widespread in regions of Canada and the United States, with particular abundance in Ontario and Quebec. Populations of this species also occur in Newfoundland, Prince Edward Island and Nova Scotia **(Barney et DiTommaso, 2003).**

II.2.2.3. Morphology

The different botanical characters (Table 06) of *Artemisia vulgaris* are gathered in the table below.

Table 06: Morphological description of *Artemisia vulgaris* **(Rambod et al., 2018; Borzabad et al., 2010; Gruenwald et al., 2000; Holm et al., 1997).**

Scientific name	*Artemisia vulgaris*
Plant type	Perennial plant, extremely fragrant, extremely variable, generally herbaceous.
Size	70 to 150 cm.
Spread	Rapidly via a well-developed rhizome system.
Parts used	Dried leaves, roots and branches.
Leaves	Arranged in a spiral, variable shapes, coarsely toothed, green and glabrous above, white woolly below, basal with short petiole, stems sessile.
Flowers	Red-brown or yellowish, almost glabrous, ovoid flower heads 3 to 4 mm long by 2 mm wide, becoming very reflexed stamens with pointed ends, truncated style branches with papillate stigmas.
Fruit	Achene without tuft, widest above the middle, narrowing towards the scar, ends rounded, ending in a small collar, seed generally a little curved, round in cross section, longitudinal, brown to yellow-brown in color.
Stems	Branched, rigid (sometimes drooping if very tall), reddish at the end of the season, suffrutescent, grooved and angular, reproduce mainly by seed but can regenerate from fragments of rhizomatous rootstock.

II.2.2.4. Chemical composition

In *Artemisia vulgaris*, various groups of compounds are present, among which we can mention sesquiterpenoid lactones, flavonoids, coumarins, phenolic acids, sterols, vitamins and glycosides. Terpenoids, in particular, have captivated researchers due to their abundance and variety of chemical structures within this species **(Liu et al., 2023).**

Of particular importance is the essential oil, a significant component of the plant. However, due to the high intraspecific diversity and variations in the chemical composition of the plant, it remains difficult to establish a distinct phytochemical profile for *Artemisia vulgaris* **(Ekiert et al., 2020).**

II.2.2.5. Therapeutic uses

Mugwort is a plant with multiple therapeutic virtues (figure 08) used in traditional herbal medicine as antihelminthics, antiseptics, antispasmodics and tonics for vital organs. Additionally, it is used to treat specific disorders such as hepatosis, stomach ulcers, liver disorders, indigestion and even diabetes in some medicinal traditions **(Rambod et al., 2018; Gilani et al., 2005).**

The essential oil extracted from this plant also exhibits a wide range of beneficial biological activities, including antiseptic, antioxidant, larvicidal, antibacterial, antifungal and antiviral properties. These characteristics make it a useful ingredient in various fields, including the food, flavor and perfume industry **(Anwar et al., 2016).**

A recent study also seems to suggest that the anti-inflammatory effect of *Artemisia vulgaris* may be increased at higher altitudes, which could make it a potential source of drugs for the treatment of chronic inflammation **(Pandey et al., 2021).**

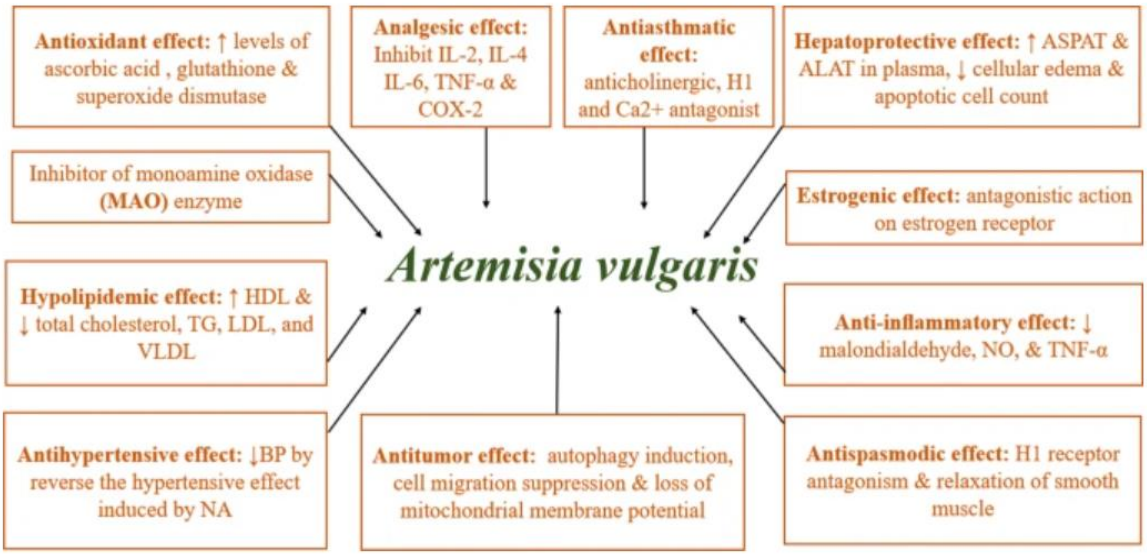


Figure 08: Representation of the pharmacological activities of *Artemisia vulgaris* **(Siwan et al., 2022).**

Part II: Experimental Procedures

Chapter III : Materials and Methods

Our work was carried out in the physicochemical laboratory of the SAIDAL group in Dar El Beida. Our study aims first to extract the phenolic compounds from two medicinal plants, then to evaluate their anti-inflammatory properties (*in vitro* and *in vivo*).

III.1. Materials

The equipment and glassware used in our study are presented in Annexes 01. The chemical reagents used from the host organization SAIDAL are as follows: Methanol, ethanol, distilled water, PBS phosphate buffer, sodium hydroxide, Diclofenac sodium.

III.1. 1. Plant material

The study focuses on flax seeds (*Linum usitatissium*) and roots of Mugwort (*Artemisia vulgaris;* (Figure 09). The flax seeds used in this study were purchased from an herbalist in the city of Algiers.

Artemisia vulgaris was collected in March 2023 in Lakhardia in the Bouira region, dried in the open air and protected from light, then put in an oven at a temperature of 40°C.

Figure 09: Photograph of the plant material used.

The two parts are cleaned to eliminate all traces of dust then crushed using an electric grinder and sieved in order to be able to recover fine and homogeneous powders (Figure 10). They are stored in glass containers for later analysis.

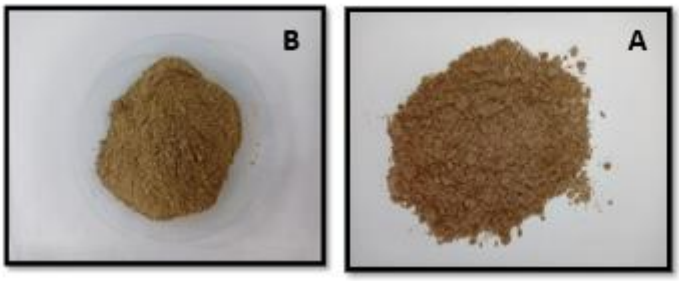


Figure 10: Photograph of the plant material used: *Artemisia vulgaris* (A) and Linum *usitatissium* (B).

III.1. 2. Animal material

Mice (Figure 11) of the male sex of an NMRI species (24 to 27 g) coming from the animal facility of the research and development center of the SAIDAL group, Algiers are used to carry out the anti-inflammatory activity. The animals are randomly placed in cages (50 x 60 x 53cm3; 5 mice per cage) and maintained under constant conditions of temperature (20-24°C) and humidity (50%) with a light/dark cycle from 12 p.m.

Figure 11: Photograph of male mouse of the NMRI specie.

III.2. Methods

III.2.1. Extraction of phenolic compounds

The method for extracting phenolic compounds from our samples is the method described by **Oomah et al. (2010)** with modifications, using ethanol (70%) and pure methanol as extraction solvents (figure 12).

2g of sample are extracted with 80ml of the solvent at room temperature for 2 hours in an ultrasonic bath, then continued stirring for 2 hours. The extracts obtained are filtered with Whatman paper followed by a second vacuum filtration, then dried in an oven (40°C) to constant weight. The dry extracts thus obtained are stored away from light at room temperature in the laboratory for possible use.

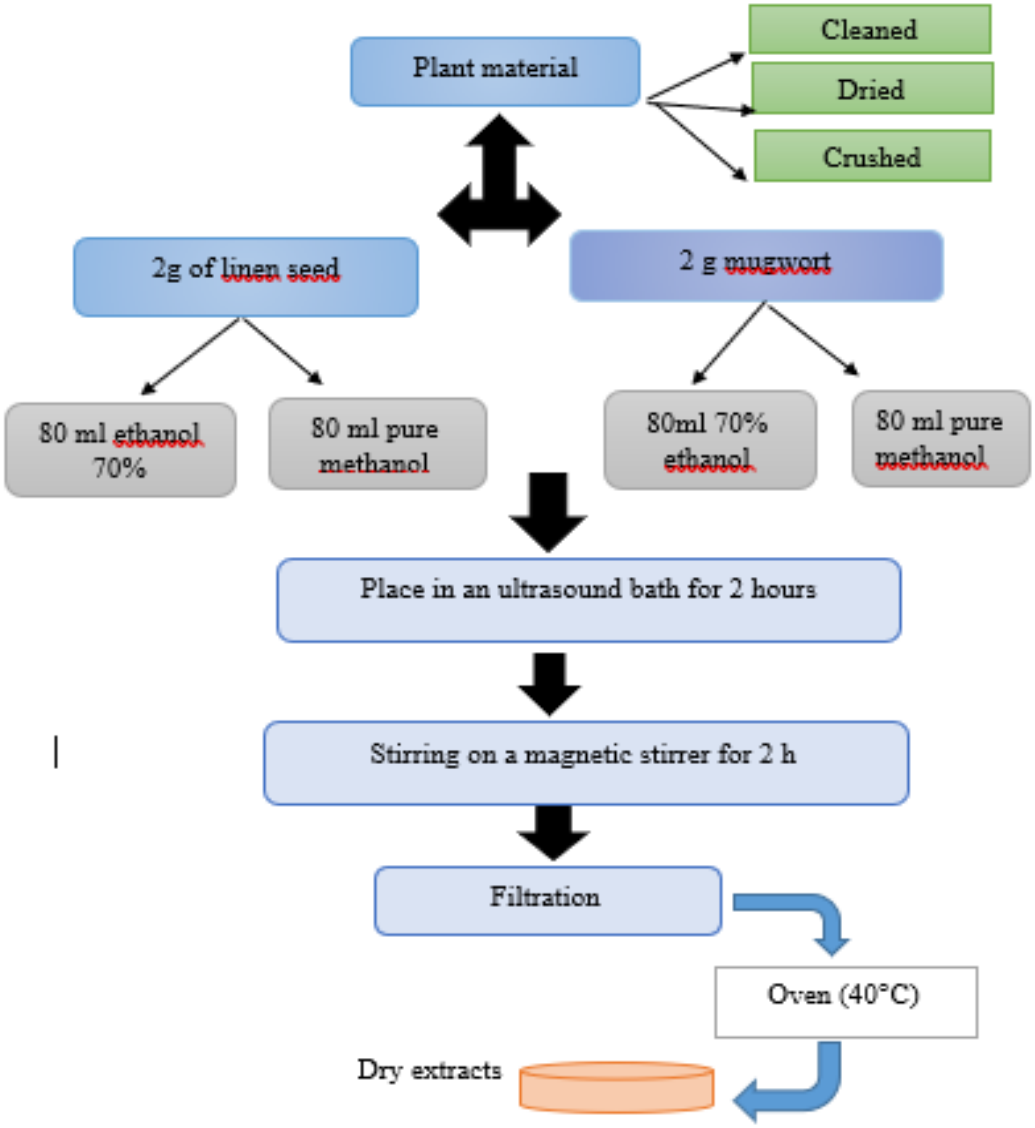


Figure 12: Extraction protocol for phenolic compounds **(Oomah et al., 2010).**

III.2.1.1. Extraction yield

Extract yield is calculated by dividing the weight of the raw extract obtained by the weight of the dry plant matter, then multiplying the result by 100 to obtain the percentage.

Extraction yield (%) = Pe / Ps x 100.

Pe: Weight of the crude extract in grams (g).

Ps: weight of dry plant matter in grams (g).

III.2.2. Determination of phenolic compounds

III.2.2.1. Determination of total soluble polyphenols

The Folin-Ciocalteu method, described by **Wong and colleagues (2006),** is used to determine total polyphenols in our extracts (Figure 13).

Principle

The Folin-Ciocalteu reagent is composed of a mixture of phosphotungstic acid and phosphomolybdic acid ($H_3PMO_{12}O_{40}$). During the oxidation of phenols, this reagent is reduced to form a mixture of blue tungsten and molybdenum oxides. This reaction produces a coloration that can be measured spectrophotometrically, with maximum absorption at 765 nm **(Ainsworth et Gillespie, 2007).**

Operating Mode

In test tubes, 200 µl of each extract is added to 1500 µl of Folin Ciocalteu 10% reagent. The mixture is incubated for 5 minutes in the dark at room temperature. Then 1500 µl of the Na_2CO_3 solution (7.5%) is added in order to stabilize the reaction. The optical density is read at 725 nm by a spectrophotometer after incubation in the dark at room temperature for 90 min.

The calibration curve was performed using gallic acid at different concentrations (0-500 µg/ml), following the same protocols and assay steps. The results are then presented in mg of gallic acid equivalent per g dry weight of the extract (mg EAG/g Ech). All measurements are repeated 3 times.

The stock solutions of the samples to be assayed as well as the standard range are prepared on the same day and under the same operating conditions.

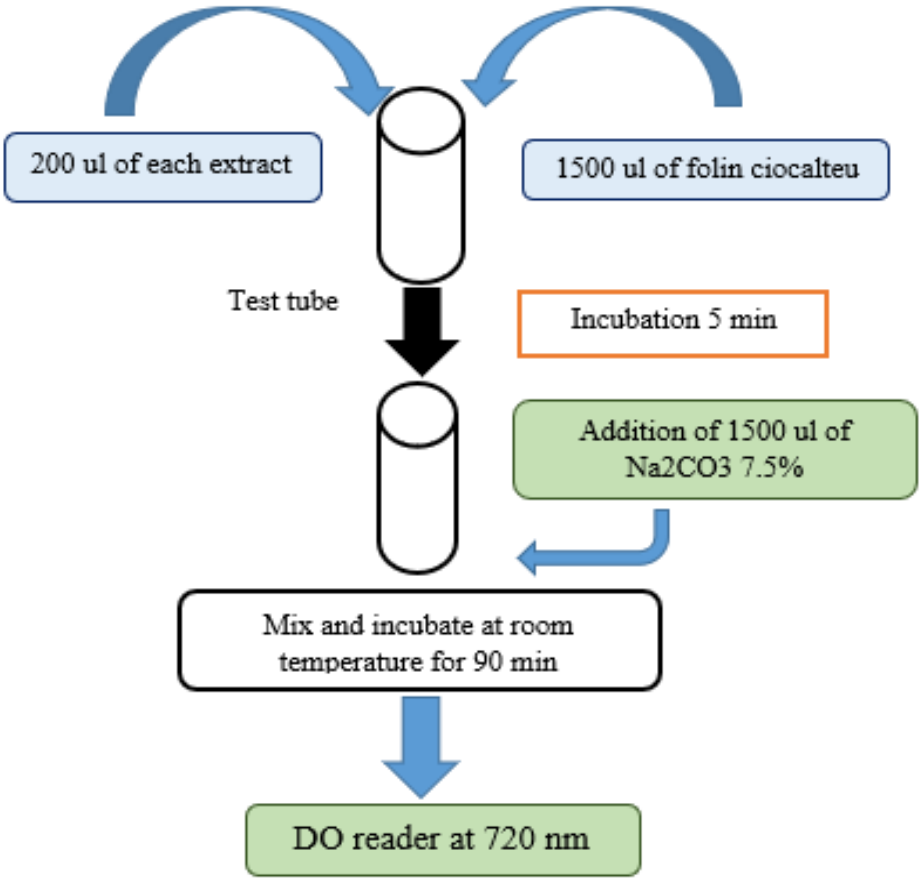


Figure 13: Protocol of total polyphenols' quantification (**Wong et al., 2006**).

III.2.2.2. Determination of flavonoids

The quantification of flavonoids is carried out using the aluminum trichloride $AlCl_3$ method. (Figure 14) cited by **Djeridane et al. (2006)** based on the formation of a flavonoid-aluminum complex, the absorbance maximum of which is at 430 nm.

Operating Mode

In test tubes, 1.5 ml of each extract is added to an equal volume of a solution of $AlCl_3\ {}_6H_2O$ (2% aluminum trichloride, in methanol). The mixture is vigorously shaken and the absorbance is read at 415 nm after 1 hour of incubation.

The calibration curve is established using rutin solutions at different concentrations (from 0 to 0.4 mg/ml), following the same procedures and conditions as those used for the extract samples. The results are then expressed in mg of rutin equivalent per gram of dry weight of the

extract (mg EQ/g E). Each measurement is carried out 3 times to guarantee the accuracy of the data.

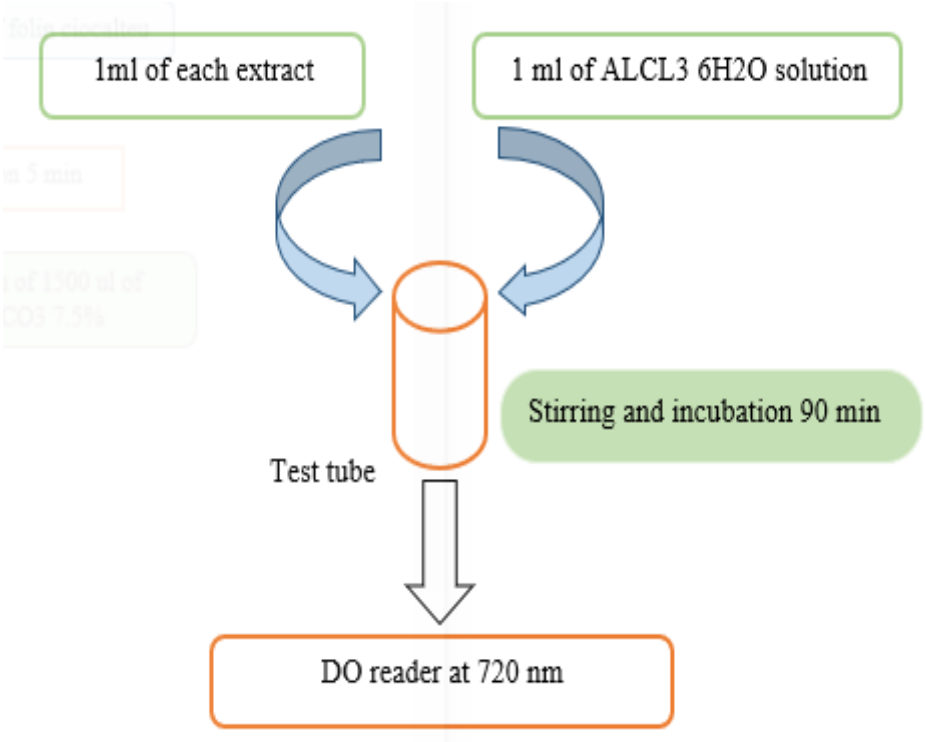


Figure 14: The flavonoid measurement protocol (**Djeridane et al., 2006).**

III.2.3. Evaluation of anti-inflammatory activity *in-vitro*

III.2.3. 1. Test for thermal denaturation of egg white albumin

Inhibition test of denaturation of egg white (Figure 15) was applied caused according the method described by **Aidoo et al. (2021).**

Operating Mode: The reaction mixture (5 ml) consisted of 0.2 ml of freshly prepared egg albumin, 2.8 ml of phosphate buffer solution (PBS; PH 6.4) and 2 ml of extract at different concentrations.

The mixture is incubated at 37 ± 2°C for 15 min then heated to 70°C in a marine bath for 5 min to induce denaturation. After cooling, the absorbances are measured at 660 nm against a control (a double volume of distilled water 4.8 ml and 0.2 ml of egg albumin) and a positive control, Diclofenac sodium at different concentrations (50, 100,250, 500 µl/ml) prepared under the same conditions.

The inhibition percentage is calculated according to the following formula:

% inhibition = (AC- AE / AC) *100

AE: Absorbance of test sample

AC: Absorption of control

The results obtained are the average of three repetitions.

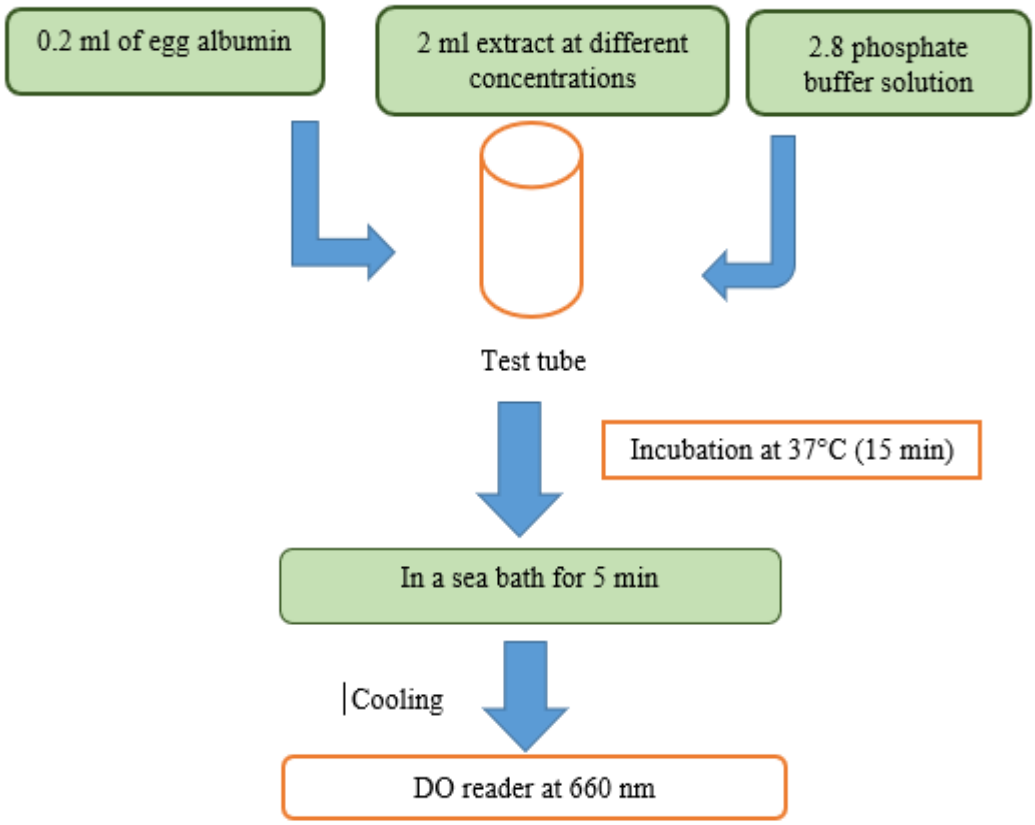


Figure 15: Protocol of the thermal denaturation test of proteins (**Aidoo et al., 2021**).

III.2.4. Evaluation of *in-vivo* anti-inflammatory activity

III.2.4.1. Induction of acute inflammatory edema of the mouse paw by carrageenan

The method of **Levy (1969)** was used to evaluate the anti-inflammatory effect of methanolic extracts of *Artemisia* and *Linum* plants on acute inflammatory edema of the mouse paw caused by carrageenan.

a- Pretreatment with the extract

To carry out this activity we followed the CRD operating mode. Mice of the NMRI strain were selected for this study. They were divided into groups so that each group understood (n=5). Mice were fasted for 16 hours before the start of the experiment.

After a period of 30 minutes before the injection of 1% carrageenan, a group of 20 mice weighing 24±2 g is divided into 4 groups (Figure 16). Mice were identified at the tail using an indelible filter. Each group receives the following experimental solutions by gastric gavage:

-Control group (n=5): The mice in this batch receive the vehicle solution (0.5ml of physiological water).

-Standard group (n=5): The mice from this batch were treated with the anti-inflammatory diclofenac (75 mg/Kg).

-Test group (n=5): The methanolic extracts of *Artemisia* and *Linum* to be tested were administered (0.5 ml/mouse) at a dose of 500 mg/Kg.

b- Induction of inflammation

1% carrageenan is administered inside the footpad of the left paw of the mouse at a dose of 0.025 ml (Figure 16). After 4 hours, the mice were anesthetized with ketamine intraperitoneally (IP), then proceed to cervical dislocation (killing).

The left and right paws of each mouse were cut at the joint and weighed individually.

c- Calculation of the percentage increase in paw volume (%AUG)

The following formula allows you to calculate the percentage increase (% AUG) in edema for each group of mice:

$$\%AUG = (Mpg - Mpdt) / Mpdt \times 100$$

Mpg: The average weight of the left paw after the carrageenan injection.

Mpdt: The average weight of the right paw without carrageenan injection.

d- Calculation of Edema Inhibition Percentage (%INH)

For each group of treated mice, the percentage of inhibition (% INH) of edema is evaluated compared to the control group using the following formula:

%INH= (%AUG control - %AUG test) / %AUG control X 100

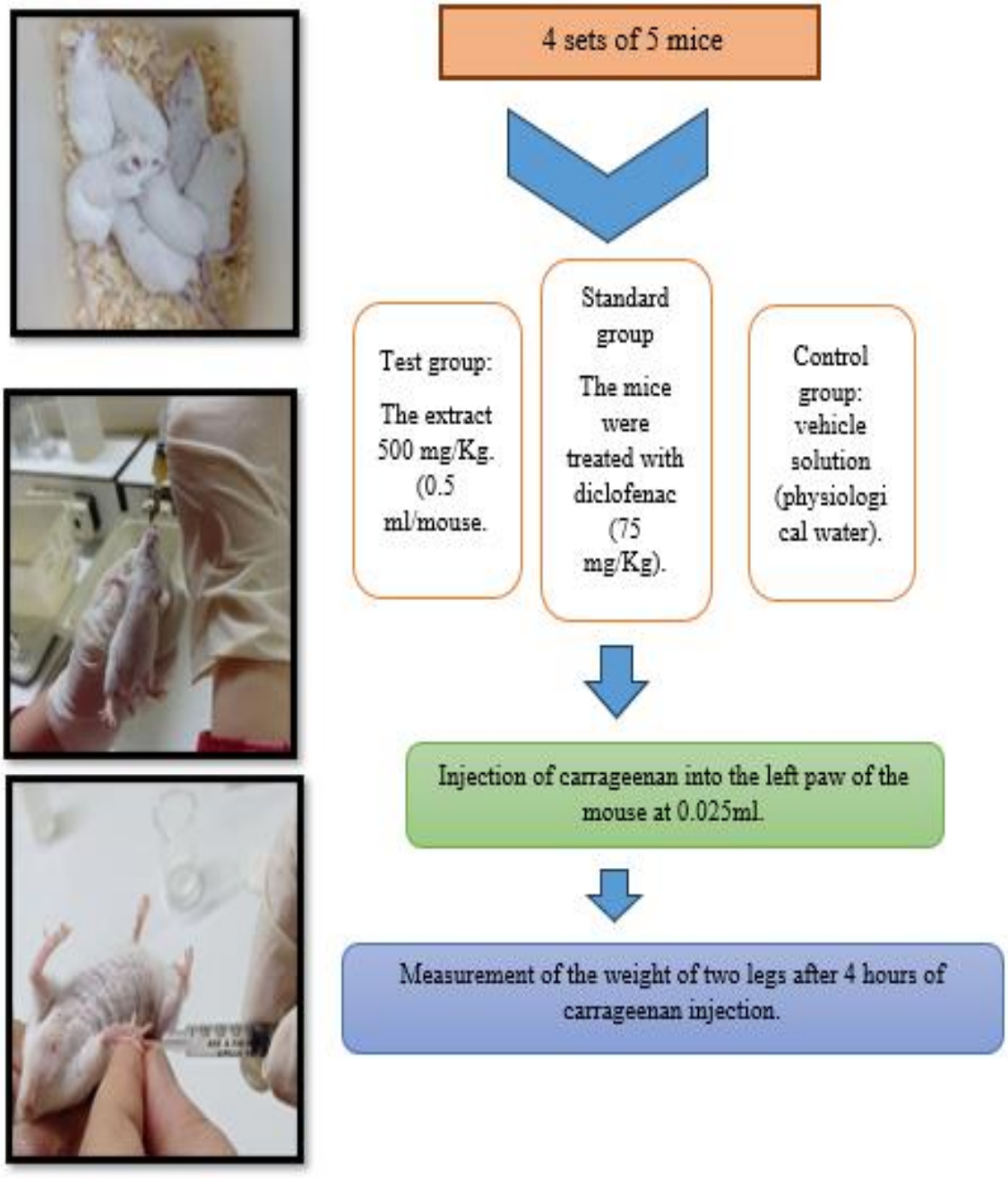


Figure 16: Diagram of the stages of anti-infla0mmatory activity *in vivo* (**Levy, 1969).**

Chapter IV: Results and discussions

I. IV.1. Extract yield

The Table below shows the extraction yields of the two plants studied.

Table 07: Extraction yields of the plants studied.

The extract	**Solvents used**	**Yield%**
Artemisia	Ethanol 70%	8.68%
	Methanol	11.91%
Linum usitatissimum	Ethanol 70%	9.52%
	Methanol	19.94%

According to the data in the table, the highest yields are obtained using methanol as extraction solvent: 11.91 and 19.94% for *Artemisia vulgaris* and *Linum usitatissimum*, respectively. Powder particle sizes after grinding and sieving, more uniform and smaller particles, promote more effective surface contact with extraction solvents. **Azwanida (2015)** highlights the importance of this method which ensures efficient extraction.

The extraction of mugwort using ethanol gives a yield of 8.68% which remains lower than that found by **Ferhat et Mehyach (2017),** who used the same extraction protocol with the leaves of *Artemisia campestris* L. (with a yield of 24.25%). The extraction rate by methanol, on the other hand (11.91%), is close to that found by **Boudjouref (2019)** using the aerial parts of *Artemisia campestris.*

This difference in yields may reflect the different chemical composition of the different extracts. Several factors influence the extraction process such as: the matrix properties of the part of the plant, the solvent used, the temperature, pressure and contact time **(Azmir et al., 2013).**

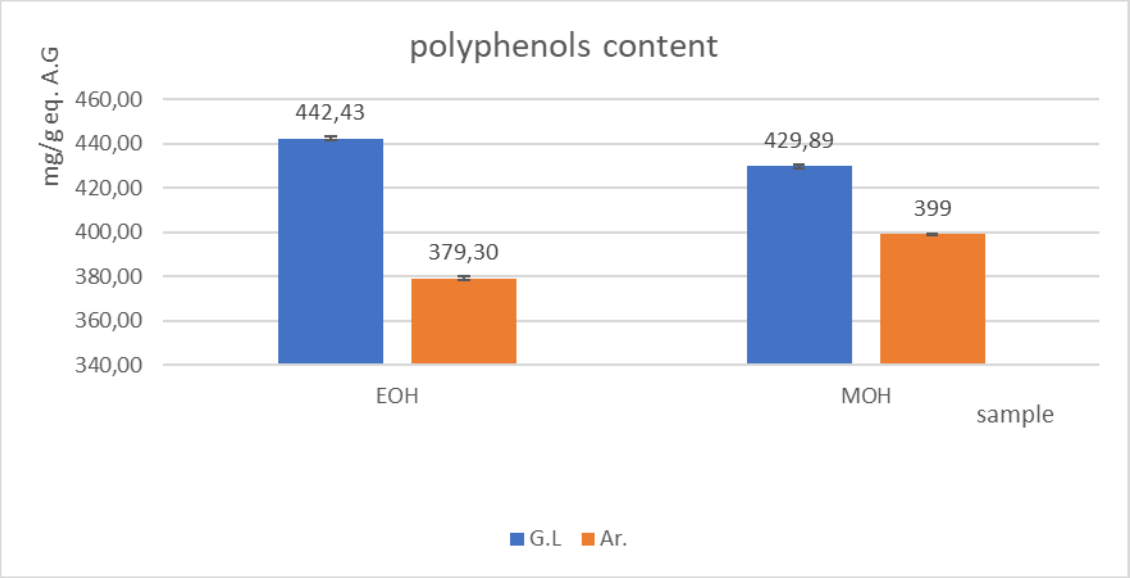
IV.2. Phenolic compound content of extracts

IV.2.1. Content of total polyphenols (PTS)

An evaluation of total polyphenols was carried out by spectrophotometry, using the colorimetric method with the Folin-Ciocalteu reagent **(Ali-Rachedi et al., 2018).**

The quantity of polyphenols present in plant extracts is directly linked to the coloring produced, with a maximum absorption between 725 and 750 nm **(Boizot et Charpentier 2020).**

The content of total soluble phenols determined by referring to a standard range (annexes 02), varies depending on the solvent used and the plant substrate to which it is applied (Figure 17).



GL: grain de lin Ar : armoise

Figure 17: Content of extracts in total soluble polyphenols.

According to the results obtained and illustrated, we note that *L. usitatissimum* has the highest contents of total polyphenols in comparison with *A. vulgaris* and this for both extracts.

It appears that the methanolic extract of flax grain has a lower content of total phenols (429.89mg EAG/g) by contribution to the hydroethanolic extract with an average value of 442.43mg EA G/g. These contents are higher compared to those found by **Boukeria (2020)** (0.065 mg EAG/g) in the methanolic extract of flax seeds.

The methanolic extract of *Artemisia vulgaris* showed a higher content of total phenolic compounds (399 mg EAG/g) compared to the hydroethanolic extract which recorded a lower content (379.30 mg EAG/g). **Boudjouref and colleagues (2018),** observed total polyphenol levels ranging from 82.61 to 88.61 mg EAC/g in the methanolic extract of *Artemisia campestris*.

Our extract also displays the highest amount of phenolic compounds than reported by **Tawaha et al. (2007),** who found contents of 34.60 mg EAG/g of DM in the methanolic extract of *A. herba alba.*

A content of total polyphenols lower than that which we recorded (20.38 mg EAG/g DM) was obtained in the 70% ethanolic extract of *A. campestris* and (13.06 ± 0.40 mg EAG/g DM) for *Artemisia herba halba* **(Djeridane et al., 2006).**

The polyphenolic content varies from one plant to another depending on several factors such as climate and environment, harvest period, plant development stage and genetic background **(Bentabet et al., 2014).**

According to **Khoddami et al. (2013)** and **Amaral et al. (2010**), different factors can influence the yield of phenolic compounds, such as extraction protocol and time, temperature, type of solvent and type of plant and its active compounds.

IV.2.2. Content of flavonoids

The objective of the quantitative study of the extracts using spectrophotometric assays, using the aluminum trichloride method, was to determine the total amount of flavonoids. Using a standard range (Annexe 02), total flavonoid concentrations was measured using the milligram of rutin equivalent per gram of extract (mg EQUE/g of extract).

Our analytical data show that there is an apparent variability in flavonoid contents depending on the plant and the solvent used (Figure 18).

The methanolic extract is richer in flavonoids compared to the ethanolic extract of the same plant. Indeed, the total flavonoids of this extract represent a significant content with 11,292 mg EG/g for *L. usitatissimum* compared to 9,141 mg EG/g for the ethanolic extract. Our results are far superior to those found by **Oomah et al. (1996)** varying from 0.302 to 0.835 mg/g, and those of **Anwar et Przybylski (2012),** who found contents in the crude methanolic extract of flax between 1.9 and 4.8 mg EC/g using catechin as standard.

The same result was displayed for the extracts of *A vulgaris* which show a higher content for the methanol extraction solvent (8.577 mg EQ/g against 7.251 mg EQ/g for the hydroethanolic solvent. Our results are lower than those obtained by **Boudjouref et al. (2018)** who reported a value of 12.91 to 13.72 mg EQ/g in the methanolic extract of *Artemisia campestris.*

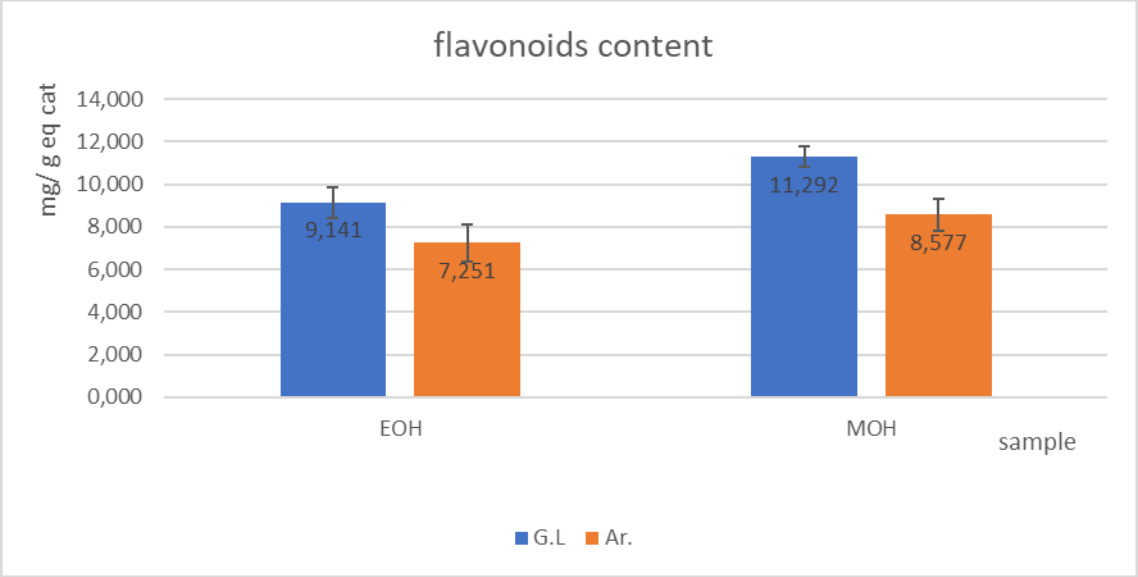


Figure 18: Flavonoid content of extracts.

Flavonoid contents are similar to those we recorded in the extracts of *A. campestris* using ethanol at 70% and 80% (v/v) with values of 7.46 and 5 mg EQ/g DM, respectively (**Djeridane et al., 2006; 2007).**

Different research has demonstrated that external elements such as geographical location, climate, genetic factors and the stage of maturation of the plant can have a significant influence on the quantity of flavonoids present in extracts **(Aganga et Mosase, 2001).**

IV.3. Anti-inflammatory effect of extracts *in vitro*

IV.3.1. Thermal denaturation of proteins

The graph below illustrates a fluctuation in the rate of protection against thermal denaturation of albumin depending on the various concentrations of extracts. These results are compared to those obtained for diclofenac (reference molecule).

From the results obtained, we note that the percentage of inhibition of protein denaturation increases with decreasing extract concentration.

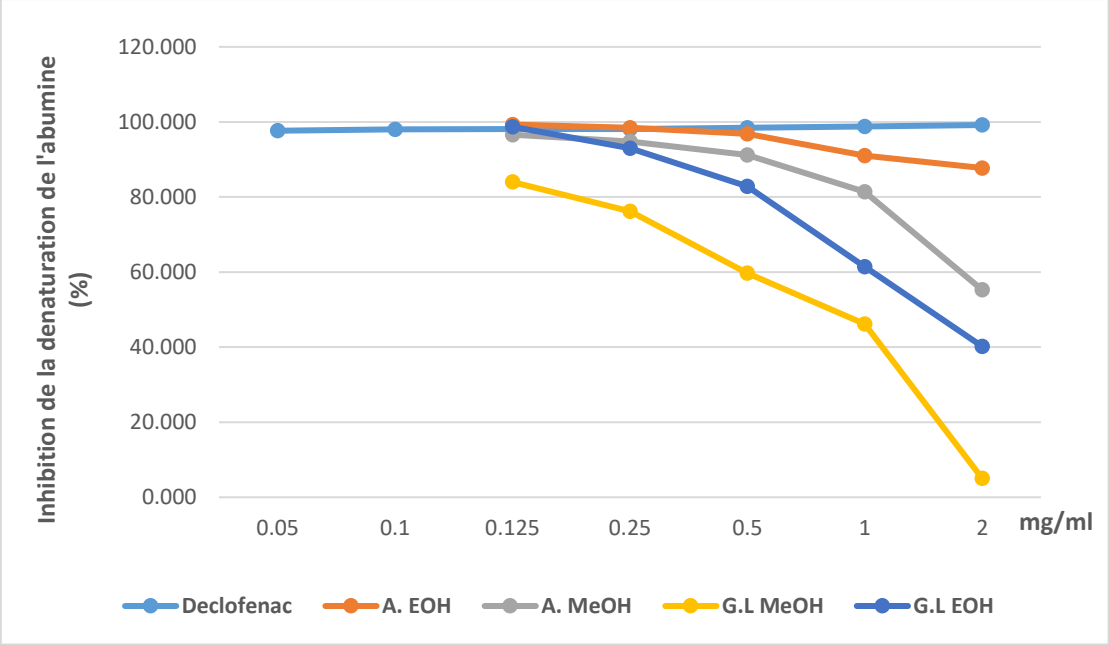


Figure 19: Analysis of inhibition rates of egg albumin denaturation.

Our results show that the percentage inhibition of albumin denaturation for the extracts was lower than that of diclofenac for all concentrations used, except for the 0.125mg/ml concentration. At the latter, the hydroalcoholic extracts of the two plants display percentages of inhibition of denaturation similar to that of the standard used (99.30% for the extract of Artemisia vulgaris and 98.71% for the extract of *L. usitatissimum).*

The other extracts have a significant capacity to inhibit protein denaturation (84% and 96.61% for the methanolic extracts of linum and Artemisia, respectively) at the same concentration.

For a concentration of 2 mg/ml, diclofenac recorded a percentage of maximum inhibition of denaturation of 99.18%.

When their tertiary and secondary structure is altered by an external stress or compound (strong acid or base, high concentration of an organic solvent, or heat), proteins become denatured. Protein denaturation is frequently responsible for inflammation **(Govindappa et al., 2011).** A well-known cause of inflammation is protein denaturation, which has been employed in the study of mechanisms of anti-inflammatory activity *in vitro* **(Fetni et Bertella, 2020).**

According to recent research, many flavonoids and polyphenols have been shown to play important roles in the antioxidant and anti-inflammatory properties of several plants. Bioactive

compounds present in our extracts may contribute to their anti-inflammatory activity **(Marliyah et Ananthi, 2015).**

IV.4. Anti-inflammatory effect of extracts (*in vivo*)

IV.4.1. Increased edema

The use of foot edema is commonly employed to analyze the inflammatory process of the skin and identify anti-inflammatory agents that could be useful in the search for anti-inflammatory extracts and compounds that act at various levels **(Okombe et al., 2019).**

The injection of carrageenan causes a notable increase in the volume of the left paws compared to the right paws in control mice, in the standard group as well as in those in the group treated with the extracts.

In this study, we examined the anti-inflammatory effect of *Artemisia vulgaris* and *Linum usitatissimum* extracts by examining paw edema caused by carrageenan.

Anti-inflammatory test results (table 08) indicate that the extracts significantly decrease edema caused by carrageenan compared to diclofenac.

Table 08: Anti-inflammatory activity.

Lots	**% edema**
Witness	53.84%
Diclofenac	21.42%
Linum usitatissimum	23.07%
Artemisia vulgaris	38.46%

IV.4.2. Inhibition of edema

According to our results (Figure 20), we note that the extracts of the plants studied present an anti-inflammatory effect linked to the significant reduction in edema with a percentage of inhibition reaching 58.34 in the group treated with flax. and reaching 38.91% in the group treated with mugwort.

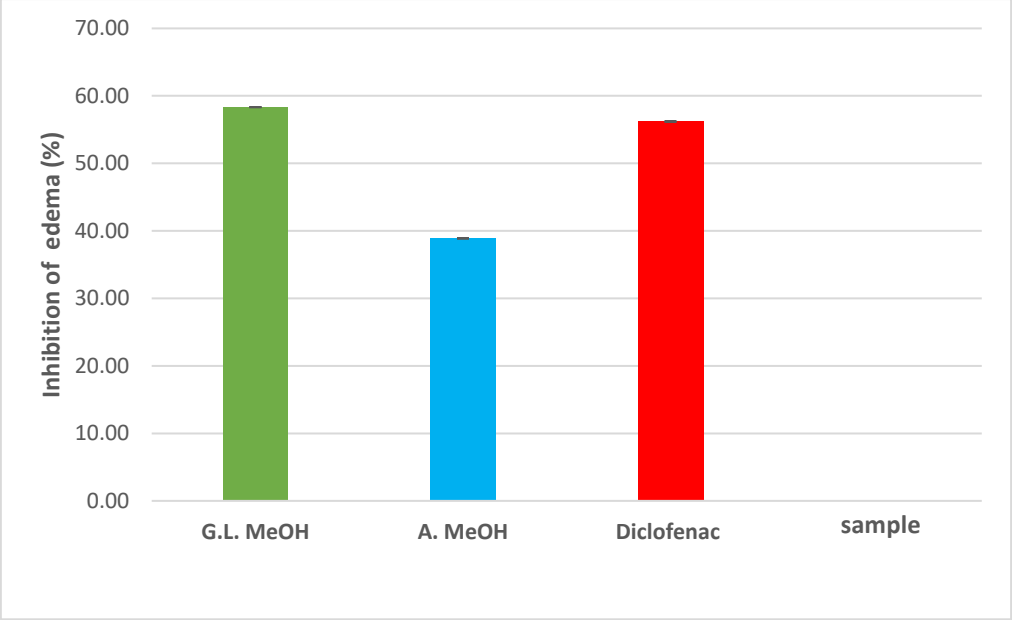


Figure 20: Effect of different extracts and diclofenac on edema induced by carrageenan (Percentage of edema inhibition).

Within four hours of treatment, we observed that Linum methanolic extract at a dose of 500 mg/kg resulted in a reduction of 58.34%.

This rate is higher than that obtained after treatment with diclofenac, which caused a reduction in edema of 56.24%. This confirms that Linum extract has anti-inflammatory activity. Furthermore, **Rafieian-kopaei and colleagues (2017)** demonstrated that the ethanolic extract of *L. usitatissimum* has significant anti-inflammatory activity in the ear of mice affected by xylene.

In mice treated with *Artemisia vulgaris* extracts, after injection of 1% carrageenan, the inhibition of edema was less effective than that obtained with diclofenac (38.91 versus 56.24%). These results are lower than those found by **(Mansouri, 2015)** who worked with the aqueous extract of *Artemisia herba alba* and *Artemesia absinthium* (96.3% and 89.98%, respectively).

The presence of bioactive compounds such as phenolics and saponins could explain this result, which gives both plants an anti-inflammatory mechanism of action similar to that of nonsteroidal anti-inflammatory drugs **(Santengelo, 2007).**

According to **(Saleh et al., 1985; 1987),** it is possible that flavonoids are responsible for the anti-inflammatory effect.

The presence of flavonoids in our extracts of *Artemisia vulgaris* and *Linum usitatissimum* explains the anti-inflammatory effect observed.

Conclusion

The diversity of medicinal and aromatic plants presents in the Algerian flora, each offering secondary metabolites with unique therapeutic properties. This plant wealth motivates researchers to conduct in-depth studies to explore the benefits and medicinal applications of these plants. The species *L. usitatissimum* and *A. vulgaris* present interesting nutritional and functional properties. These plants provide a large reserve of biologically active compounds that serve as the basis for many effective drugs.

We aimed to examine the anti-inflammatory efficacy of ethanolic and methanolic extracts of *Linum usitatissimum* and *Artemia vulgaris*, both *in vivo* and *in vitro*.

In the initial phase of our research, the quantitative analysis of total polyphenols using the Folin-Ciocalteu method highlighted the presence of significant quantities of polyphenols in the extracts of the two plants studied. Likewise, a richness in flavonoids measured by the AlCl3 method.

In the second phase of this study, we evaluated the anti-inflammatory activity *in vitro* using the protein denaturation test. We have shown that both plants have good anti-inflammatory activity.

The *in vivo* anti-inflammatory activity, at the dose (500 mg/kg) of the methanolic extract of *Linum usitatissimum* has an appreciable anti-inflammatory power on mice, in which inflammation induced by carrageenan, the percentage reduction in oedema was particularly high, reaching 58.34%.

The exploration of active compounds and therapeutic applications of plants opens new avenues of research. It is essential as a perspective to continue research in order to:

- ✓ Identify the compounds responsible for these activities and to deepen our knowledge of these species;
- ✓ Expand *in vitro*, Cell-Based Anti-Inflammatory Activity Testing;
- ✓ Continue and deepen analyses of anti-inflammatory activity, *in vivo*, of linseed;
- ✓ Study other biological activities of these two plants in order to highlight possible activities: antioxidant and antimicrobial

Bibliographic references

-A-

Abad, M. J., Bedoya, L. M., Apaza, L. & Bermejo, P. (2012). The Artemisia L. Genus: A Review of Bioactive Essential Oils. *Molecules*, 17(3), 2542–2566.

Abayomi, S. (2010). Plantes médicinales et médecine traditionnelle d'Afrique. KARTHALA Editions. P25.

Abiri, R., Silva, A. L. M., de Mesquita, L. S. S., de Mesquita, J. W. C., Atabaki, N., de Almeida, E. B., … Malik, S. (2018). Towards a better understanding of Artemisia vulgaris: Botany, phytochemistry, pharmacological and biotechnological potential. *Food Research International.*

Abbal, M., Alric, L., Cantagrel, A., Delisle, B. (2013). Réaction inflammatoire : Aspects Biologique et clinique. Conduite à tenir. Module 8 – Item 112 :1-25.

Abdel-Nabey, A. A., Abu–Tor, E. S. M. & Abou-Gharbia, H. A. (2013). Chemical and Technological Studies on Flaxseed (Linum usitatissimum) and Its Application in Some Functional Foods. Journal of Food and Dairy Sciences, 4(5), 193-216.

Abdulkhaleq, L. A., Assi, M. A., Abdullah, R., Zamri-Saad, M., Taufiq-Yap, Y. H., & Hezmee, M. N. M. (2018). The crucial roles of inflammatory mediators in inflammation: A review. *Veterinary world*, 11(5), 627.

Abeer Temraz & Walid H El-Tantawy. (2008). Caractérisation de l'activité antioxydante de l'extrait d'Artemisia vulgaris.

Abidi, A., Bahri, S., Ben Khamsa J. (2019). Caractéristiques phytochimiques et thérapeutiques du lin ou LINUM USITATISSIMUM : revue de la littérature.

Aganga, A. A., & Mosase, K. W. (2001). Tannin content, nutritive value and dry matter digestibility of Lonchocarpus capassa, Zizyphus mucronata, Sclerocarya birrea, Kirkia acuminata and Rhus lancea seeds. *Animal Feed Science and Technology*, 91(1-2), 107-113.

Aggarwal, B. B. & Sung, B. (2009). Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends in pharmacological sciences*, 30(2), 85-94.

Agostini, C. T. S., Vieira, R. F., Bizzo, H. R., Silveira, D. & Gimenes, M. A. (2012). Secondary metabolites in chromatography and its applications. Sasikumar Dhanarasu.131-164.

Ahmed, A. U. (2011). An overview of inflammation: mechanism and consequences. *Frontiers in Biology*, 6(4), 274-281.

Aidoo, D. B., Konja, D., Henneh, I. T. & Ekor, M. (2021). Protective effect of bergapten against human erythrocyte hemolysis and protein denaturation in vitro. International Journal of Inflammation, 2021(1), p7.

Ainsworth, E. A. & Gillespie, K. M. (2007). Estimation of total phenolic content and other oxidation substrates in plant tissues using Folin–Ciocalteu reagent. *Nature Protocols*, 2(4), 875–877.

Alessi, M. C. (2002). Le système fibrinolytique: activation et inhibition. Ses modifications en cas de CIVD. *Réanimation,* 11(8), 591-598.

Ali-Rachedi, F., Meraghni, S., Touaibia, N. & Mesbah, S. (2018). Analyse quantitative des composés phénoliques d'une endémique algérienne Scabiosa Atropurpurea sub. Maritima L. *Bulletin de la société royale des sciences de liège.*

Amaral, J. S., Valentão, P., Andrade, P. B., Martins, R. C., & Seabra, R. M. (2010). Phenolic composition of hazelnut leaves: Influence of cultivar, geographical origin and ripening stage. *Scientia horticulturae,* 126(2), 306-313.

Andrianne, P. (2008). La gemmothérapie : passé, présent et avenir. *Phytothérapie*, 6(1), 29–32.

Anwar F. & Przybylski R. (2012). Effect of solvents extraction on total phenolics and antioxidant activity of extracts from flaxseed (Linum usitatissimum L.). ACTAS cientiarum Polonorum Technologia Alimentaria 11(3), 293-302.

Anwar, F., Ahmad, N. & Alkharfy, K. M. (2016). Mugwort (Artemisia vulgaris) oils. *In Essential oils in food preservation, flavor and safety*. 573-579.

Azmir, J., Zaidul, I. S. M., Rahman, M. M., Sharif, K. M., Mohamed, A., Sahena, F., ... & Omar, A. K. M. (2013). Techniques for extraction of bioactive compounds from plant materials: A review. *Journal of food engineering,* 117(4), 426-436.

Azwanida, N. N. (2015). A review on the extraction methods uses in medicinal plants, principle, strength and limitation. *Med. Arom. Plants,* 4(3), 3-8.

-B-

Bacchi, S., Palumbo, P., Sponta, A. & Coppolino, M. F. (2012). Clinical Pharmacology of Non-Steroidal Anti-Inflammatory Drugs: A Review. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, 11(1), 52–64.

Bamoniri, A., Mirjalili, B. B. F., Mazoochi, A. & Batooli, H. (2010). Chemical composition of Artemisia Vulgaris L. from Kashan area isolated by nano scale injection. *Iranian Journal of Organic Chemistry*, 2(4), 533-536.

Barnes, P. J. (1998). Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clinical science*, 94(6), 557-572.

Barney, J. N., & DiTommaso, A. (2003). The biology of Canadian weeds. 118. Artemisia vulgaris L. *Canadian journal of plant science*, 83(1), 205-215.

Bascands, J. L. & Girolami, J. P. (1996). La bradykinine. *Médecine/sciences*. 582-92.

Benaradj, A. & Boucherit, H. (2022). Ethnobotanical study of the plant of medicinal interest Coss. & Durieu (Lamiaceae) in the region of Naâma (Algeria). *Biodiversity Research and Conservation*, 68(1), 27-34.

Benloukil M. (2015). Etude de l'activité anti-inflammatoire, anti-histaminique et anti-sérotoninique des extraits éthanoliques de Fraxinus angustifolia et de Pistacia lentiscus.

Bentabet, N., Boucherit-Otmani, Z. & Boucherit, K. (2014). Composition chimique et activité antioxydante d'extraits organiques des racines de Fredolia aretioides de la région de Béchar en Algérie. *Phytothérapie*, 12(6), 364–371.

Beroual, K., Maameri, Z., Halmi, S., Benleksira, B., Agabou, A. & Hamdi-Pacha,Y. (2013). Effects of Linum usitatissimum L. ingestion and oil topical application on hair growth in rabbit. Int. J. Med. Arom. Plants, 3(4), 459-463.

Bezeaud, A. & Guillin, M. C. (2001). Physiologie de la coagulation. *EMC-hématologie*, 11(1), 1-7.

Bidaut-Russell, M. & Gabriel, S. E. (2001). Adverse gastrointestinal effects of NSAIDs: consequences and costs. *Best Practice & Research Clinical Gastroenterology*, 15(5), 739–753.

Boizot, N. & Charpentier, J. P. (2006). Méthode rapide d'évaluation du contenu en composés phénoliques des organes d'un arbre forestier. *Le Cahier des Techniques de l'INRA,* 79-82.

Blain, H., Jouzeau, J. Y., Netter, P. & Jeandel, C. (2000). Les anti-inflammatoires non stéroïdiens inhibiteurs sélectifs de la cyclooxygénase 2. Intérêt et perspectives. *La revue de médecine interne*, 21(11), 978-988.

Blank, U. & Vitte, J. (2015). Les médiateurs du mastocyte. *Revue Française d'Allergologie*, 55(1), 31–38.

Bloedon L.T, Szapary P.O. (2004). Flaxseed and cardiovascular risk. *Nutrition Review*, 62(1),18-27

Bolsheva, N. L., Zelenin, A. V., Nosova, I. V., Amosova, A. V., Samatadze, T. E., Yurkevich, O. Y., ... & Muravenko, O. V. (2015). The diversity of karyotypes and genomes within section Syllinum of the genus Linum (Linaceae) revealed by molecular cytogenetic markers and RAPD analysis.

Borzabad, R. K., Sudarshana, M. S. & Niranjan, M. H. (2010). In vitro plant regeneration from leaf explants of Artemisia vulgaris L.-a medicinal herb. *Modern Applied Science*, 4(9), 130–134.

Boudjouref M, Belhattab R, Bouteghrine S. (2018). Antioxidant Activity and Phenolic Content of Artemisia Campestris from Two Regions of Algeria, *World Journal of Environmental Biosciences*, Vol 7, Issue 2: 61-66.

Boudjouref M. (2019). Activités antioxydante et anti-inflammatoire des extraits d'Artemisia campestris. Thèse de doctorat. Université Ferhat Abbas Sétif 1.p41.

Bouhassira, D. & Calvino, B. (2009). Douleurs : physiologie, physiopathologie et pharmacologie.

Barnes, P. J. (1998). Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clinical science*, 94(6), 557-572.

Buckley, C., Filer, A., Haworth, O., Parsonage, G., Raza, K. & Salmon, M. (2005). Defining a role for fibroblasts in the persistence of chronic inflammatory joint disease. *Arthritis Research & Therapy*. 92–95.

Bureau, L. (2012). La phytothérapie pertinente. Altal Editions. P 23

Buxeraud J. (2008). Les anti-inflammatoires non stéroïdiens.

-C-

Calsamiglia, S., Busquet, M., Cardozo, P. W., Castillejos, L. & Ferret, A. (2007). Invited Review: Essential Oils as Modifiers of Rumen Microbial Fermentation. *Journal of Dairy Science*, 90(6), 2580–2595.

Campbell, D. J. (2001). The Kallikrein-Kinin System in Humans. *Clinical and Experimental Pharmacology and Physiology*, 28(12), 1060–1065.

Golias, C., Charalabopoulos, A., Stagikas, D., Charalabopoulos, K. & Batistatou, A. (2007). The kinin system-bradykinin: biological effects and clinical implications. Multiple roles of the kinin system-bradykinin. *Hippokratia*, 11(3), 124-128.

Chabrier, J. Y. (2010). Plantes médicinales et formes d'utilisation en phy d'utilisation en phytothérapie tothérapie.

Charpentier, E. (2020). Médiateurs lipidiques de l'inflammation et populations lymphocytaires au cours des infections à Pneumocystis: études cliniques et modèle murin (Doctoral dissertation, Université Paul Sabatier-Toulouse III).

Château, M. T., Rabesandratana, H. & Caravano, R. (1996). Differentiated U937 cells and human monocytes exhibit a differential production of extracellular oxygen species: O2·− excretion versus H2O2 diffusion. FEMS *Immunology & Medical Microbiology*, 13(1), 19-28.

Chevallier, A. (2001). Encyclopedia des plantes médicinales. Paris : Edit. La Rousse., p 293, 295.

Cooper, M. D. (1987). B Lymphocytes. *New England Journal of Medicine*, 317(23), 1452–1456.

Coşkuner, Y. & Karababa, E. (2007). Some physical properties of flaxseed (Linum usitatissimum L.). *Journal of food Engineering*, 78(3), 1067-1073

Couic-Marinier, F. & Lobstein, A. (2013). Les huiles essentielles gagnent du terrain à l'officine. *Actualités Pharmaceutiques*, 52(525), 18–21.

-D-

Danowski, R, (1991). Inflammation en rhumatologie. *In Annales de Kinésithérapie* Vol 18, 237-238.

Daun, J. K., Barthet, V. J., Chornick, T. L. & Duguid, S. (2003). Structure, composition, and variety development of flaxseed. Flaxseed in human nutrition, (Ed. 2), 1-40.

Davide M., Jonathan R., Davide B Roth., Ivan R., Pierre l. Masson. (2007) Immunologie.7éme édition. P29.

Davide M. (2004). Immunologie aide-mémoire illustré. 4éme édition p2.

Davide M. (2015). Immunologie aide-mémoire illustré. 4ém édition. P2.

Degos V., Chhor V., Gressens P., Mantz J. (2009). Neuro-inflammation aiguë et stratégies neuroprotectrices. *Réanimation*, 18(7), 556-565.

Dejean, C. & Richard, D. (2013). Mécanismes d'action des glucocorticoïdes. *La Revue de Médecine Interne,* 34(5), 264–268.

Diana O., Roméo T., Ivo Schmerold., Rémigius Chizzola., Klaus Stolze., Ileana Nichita. &Viorica Chiurciu. (2014). Caractérisation chimique par GC-MS et activité in vitro contre Candida albicans de fractions volatiles préparées à partir d'Artemisia dracunculus, Artemisia abrotanum, Artemisia absinthium et Artemisia vulgaris. Vol 8, article numéro 6.

Didier, D. S., Emmanuel, M. M., Alfred, N., France, K. M. & Lagarde, B. J. (2011). Ethnobotanique et phytomédecine des plantes médicinales de Douala, Cameroun. *Journal of Applied Biosciences*, 37(9), 2496-2507.

Djeridane A., Yousfi M., Nadjemi B., Boutassouna D., Stocker P. et Vidal N., (2006). Antioxidant activity of some Algerian medicinal plants extracts containing phenolic compounds. *Food Chemistry*. 97(4): 654–660.

Djeridane A., Yousfi M., Najemi B., Vidal N., Lesgards J.F. et Stocker P., (2007). Screening of some Algerian medicinal plants for the phenolic Compouds and their antioxidantactivity. *European Food Research and Techenology*. 224(6): 801-809.

Dyckaets C., Fouret P., Hauw J.J. (2003). Anatomie pathologie. Université Marie curie.

-E-

Ekiert, H., Pajor, J., Klin, P., Rzepiela, A., Ślesak, H., & Szopa, A. (2020). Significance of Artemisia vulgaris L. (Common Mugwort) in the history of medicine and its possible contemporary applications substantiated by phytochemical and pharmacological studies. *Molecules*, 25(19), 4415.

Eléna Charpentierle. (2020). Médiateurs lipidiques de l'inflammation et populations lymphocytaires au cours des infections à Pneumocystis : Etudes cliniques et modèle murin.

Erdemoglu, N., Küpeli, E. & Yeşilada, E. (2003). Anti-inflammatory and antinociceptive activity assessment of plants used as remedy in Turkish folk medicine. *Journal of ethnopharmacology*, 89(1), 123-129.

-F-

Fahima Ali-Rachedi, Souad Meraghni, Nourhène Touaibia & Sabrina Mesbah. (2018). Analyse quantitative des composés phénoliques d'une endémique algérienne Scabiosa Atropurpurea sub. Maritima L.Vol 87.

Farnsworth N. R., Akerele O., Bingel A. S., Soejarto D. D. et Guo Z. (1986). Places des plantes médicinales dans la thérapeutique. *Bulletin de l'organisation mondiale de la santé*., 64(2) : 159-164.

Ferhat I., mehyach R. (2017). Etude de l'activité anti-inflammatoire et antioxydant d'Artemisia campestris L et S pitzelia coronopifolia Désf dans la région d'El-oued. Memoire de fin d'étude. Université echahid hamma lakhdar -el oued. P40.

Fougère, B. J. & Wynn, S. G. (2007). Herb Manufacture, Pharmacy, and Dosing. *Veterinary Herbal Medicine*, 221–236.

-G-

Ganorkar, P. M. & Jain, R. K. (2013). Flaxseed – a nutritional punch. *International Food Research Journal*, 20(2). 519-525.

Ghorbani, A. & Esmaeilizadeh, M. (2017). Pharmacological properties of Salvia officinalis and its components. *Journal of Traditional and Complementary Medicine*, 7(4), 433-440.

Gilani, A. H., Yaeesh, S., Jamal, Q. & Ghayur, M. N. (2005). Hepatoprotective activity of aqueous–methanol extract of Artemisia vulgaris. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, 19(2), 170–172.

Goetz, P. (2004). Plaidoyer pour la tisane médicinale. *Phytothérapie*, 2(1), 8–15.

Govindappa, M., Naga Sravya, S., Poojashri, M. N., Sadananda, T. S., Chandrappa, C. P., Santoyo, G., ... & Anil Kumar, N. V. (2011). Antimicrobial, antioxidant and in vitro anti-inflammatory activity and phytochemical screening of water extract of Wedelia trilobata (L.) Hitchc. *Journal of medicinal plants research*, Vol. 3(3), p. 43-51.

Gruenwald J., PhD Thomas B., BAChristof Jaenicke, MD. (2000). PDR for Herbal Medicine Medical Economics Company.p530.

Guilpain, P. & Le Jeunne, C. (2012). Effets anti-inflammatoires et immunosuppresseurs des glucocorticoïdes. *La Presse Médicale*, 41(4), 378-383.

Guislaine C. (2018). *Immunologie fondamentale et immunopathologie.* Enseignement thématique et intégré tissu lymphoïdes sanguin immunologie et immuno--intervention. 2eme édition.

Gurib-Fakim, A. (2006). Medicinal plants: Traditions of yesterday and drugs of tomorrow. *Molecular Aspects of Medicine*, 27(1), 1–93.

Gutierrez, L., Conejero, G., Castelain, M., Guénin, S., Verdeil, J. L., Thomasset, B., & Van Wuytswinkel, O. (2006). Identification of new gene expression regulators specifically expressed during plant seed maturation. *Journal of experimental botany*, 57(9), 1919-1932.

-H-

Hartmann, T. (2007). From waste products to ecochemicals: Fifty years research of plant secondary metabolism. *Phytochemistry*, 68(22-24), 2831–2846.

Heli Jroy R. LUNDY, S. & ERIKSEN, C. (2007). Healthier lives through education in nutrition and preventive medicine. Flaxseed a review of health benefits. *Pennington Nutrition Series*, (5), 1-4.

Henzen C, (2003). Traitement aux glucocorticoïdes : risques et effets secondaires. *Forum médical suisse*,19, 442,446

Herms, D. A. & Mattson, W. J. (1992). The Dilemma of Plants: To Grow or Defend. *The Quarterly Review of Biology*, 67(3), 283–335.

Heymonet, C. (2013). Les plantes à visée anti-inflammatoire utilisées en phytothérapie. Thèse de doctorat en pharmacie. Université de Lorraine. France. 36-37.

Holm, L., Doll, J., Holm, E., Pancho, J. & Herberger, J. (1997). *World weeds: Natural histories and distribution*. John Wiley and Sons.

-I-

Iwalewa E O, McGaw L J, Naidoo V, Eloff J N. (2007). Inflammation: the foundation of diseases and disorders. A review of phytomedicines of South African origin used totreat pain and inflammatory conditions. *African Journal of Biotechnology*, 6, 2868-2885.

-J-

Januario, A. H., Santos, S. L., Marcussi, S., Mazzi, M. V., Pietro, R.C.L. R., Sato D. N., Ellena, J., Sampaio, S.V., Franca, S.C., Soares, A. M. (2004). Neoclerodane diterpenoid, a new metalloprotease snake venom inhibitor from Baccharis trimera (Asteraceae): antiproteolytic and anti-hemorrhagic properties. *ChemicoBiological Interactions*, 150, 243-251.

Jaradat, N. A., Al-Masri, M., Hussen, F., Zaid, A. N., Ali, I., Tammam, A., ... et Rajabi, A. (2017). Preliminary Phytochemical and Biological Screening of Cyclamen coum a Member of Palestinian Flora. *Pharmaceutical Sciences*, 23(3): 231-237.

Jhala, A. J., Hall, L. M. (2010). Flax (Linum usitatissimum L.): current uses and future applications. *Aust. J. Basic Appl. Sci*, 4(9), 4304-4312

Jiofack, T., Fokunang, C., Guedje, N., Kemeuze, V., Fongnzossie, E., Nkongmeneck, BA., Mapongmetsem, PM. & Tsabang, N. (2010). Ethnobotanical uses of medicinals plants of two

ethnoecological regions of Cameroon. *International Journal of Medicine and Medical Sciences* 2 (3): 60-79.

Judžentienė, A. & Buzelytė, J. (2006). Chemical composition of essential oils of Artemisia vulgaris L.(mugwort) from North Lithuania. Chemija, 17(1).

-K-

Kaloustian, J., Chevalier, J., Mikail, C., Martino, M., Abou, L. & Vergnes, M.-F. (2008). Étude de six huiles essentielles : composition chimique et activité antibactérienne. *Phytothérapie*, 6(3), 160–164.

Kantari, C., Pederzoli-Ribeil, M. & Witko-Sarsat, V. (2008). The Role of Neutrophils and Monocytes in Innate Immunity. *Trends in Innate Immunity*, 118–146.

Kasote, D. M., Hegde, M. V. & Deshmukh, K. K. (2011). Antioxidant activity of Phenolic components from n-butanol fraction (PC-BF) of defatted flaxseed meal. *American Journal of Food Technology,* 6(7), 604-612.

Khandzian, M., Hacard, F., Braire-Bourrel, M., Jaulent, C., Bérard, F., Nicolas, J.-F., & Nosbaum, A. (2019). Urticaire aux AINS : une prise en charge similaire à celle de l'urticaire aiguë. *La Revue de Médecine Interne,* 40(3), 166-172.

Khoddami, A., Wilkes, M. & Roberts, T. (2013). Techniques for Analysis of Plant Phenolic Compounds. *Molecules*, 18(2), 2328–2375.

Kumar S., Saini M., Kumar V., Prakash O., Arya R., Rana M. & Kumar D. (2012). Traditional medicinal plants curing diabetes: A promise for today and tomorrow. *Asian Journal of Traditional Medicines* 7: 178-188.

-L-

Laiq Khan, M., Sharif M, Sarwar Sameea M, Ameen M., (2010). Chemical composition of different varieties of linseed. *Pakistan Veterinary Journal*, 30(2), p 79-82.

Lehmann, H. (2013). Le médicament à base de plantes en Europe: statut, enregistrement, contrôles (Doctoral dissertation, Université de Strasbourg. P35.

Létard, J.-C., Costil, V. & Dalbiès, P. (2015). Phytothérapie - principes généraux. *HEGEL* - HEpato-GastroEntérologie Libérale, (1).29-35.

Levy, L. (1969). Carrageenan paw edema in the mouse. *Life Sciences*, 8(11), 601–606.

Limonier Anne-Sophie, (2018). En vue d'obtenir le Diplôme D'état de Docteur en Pharmacie, La Phytothérapie de demain : les plantes médicinales au cœur de la pharmacie, Faculté de Pharmacie, Université de MARSEILLE, p20.

Liu T., Minghui D., Hai Z., Yanling H., Jiming C., Menghe Li, Yuying G., Chen H., Caiwenjie L., Zui W., Zhe R., Cuifang Y., Xinglong Z., Yifei W. (2023). Isolement guidé par l'activité et identification des terpénoïdes actifs antiherpèsvirus et antineuroinflammatoires d'Artemisia vulgaris L. sur la base du réseau moléculaire LC-MS/MS.

-M-

Male, D. (2019). *Immunologie* : Aide-mémoire illustré. De Boeck Supérieur.

Malcolmson, L. **(2012).** La graine de lin-un grain ancien, riche en bienfaits pour la santé et en avantages culinaires.

Mansouri Sadia, (2015). Pour l'obtention du diplôme de Doctorat en Science, Evaluation de l'effet antiinflammatoire de trois plantes médicinales : Artemisia absinthium L, Artemisia herba alba Asso et Hypericum scarboides - Etude in vivo-, Université des Sciences et de la Technologie d'Oran Mohamed BOUDIAF, p20.

Marfaing-Koka, A., (1998). Les chimiokines. *Revue francaise des laboratoires*, (308) 37-44.

Marliyah M. and Ananthi T. (2015). In vitro anti-inflammatory activity of seed extract of

Marsolais, D., & Frenette, J. (2005). Inflammation et réparation tendineuse. *Médecine/sciences*, 21(2), 181-186.

Mason, J. K., & Thompson, L. U. (2014). Flaxseed and its lignan and oil components: can they play a role in reducing the risk of and improving the treatment of breast cancer? *Applied Physiology, Nutrition, and Metabolism*, 39(6), 663–678.

McDill, J., Repplinger, M., Simpson, B. B., Kadereit, J. W. (2009). The Phylogeny of Linum and Linaceae Subfamily Linoideae, with Implications for Their Systematics, Biogeography, and Evolution of Heterostyly. *Systematic Botany*. 34(2), 386–405

Medzhitov R. (2008). Origin and physiological roles of inflammation. *Nature* 454 :428–35.

Medzhitov, R (2010). inflammation 2010: New adventure of an olf flame. *Cell*, 140 (6), 771-776.

Millet, A. (2014). Rôle pro-inflammatoire et immuno-modulateur de la proteinase 3 membranaire exprimée au cours de l'apoptose ; Implications dans la granulomatose avec polyangéite. Thèse de doctorat de Biologie et Biotechnologie. Université Paris Descartes, France. P : 14-16.

Mitul P, Murugananthan, Schivalinga GK. (2012). In vivo animal models in preclinical evaluation of anti-inflammatory activity. *International Journal of Pharmaceutical Research and Allied Sciences,* 1 (2) :2277-3657.

Moldoveanu, A.I., Shephard, R.J., Shek, P.N. (2001). The cytokine response to physical activity and training. *Sports Medicine*. 31:115-44.

Murdoch, C. & Finn, A. (2000). Chemokine receptors and their role in inflammation and infectious diseases. Blood, *The Journal of the American Society of Hematology*, 95(10), 3032-3043.

Muster, D, (2005). Médicaments de l'inflammation. *EMC-Stomatologie*, 21.

-N-

Nadji, S. & Wabont, G. (2019). *Immunologie*. De Boeck Superieur.

Naguib, Y. W. & Cui, Z. (2014). Nanomedicine: The Promise and Challenges in Cancer Chemotherapy. *Nanomaterial*, 207–233.

Nathan, C. (2002). Points of control in inflammation. *Nature*, 420(6917), 846-852.

Nemudzivhadi, V. & Masoko, P. (2014). In vitro assessment of cytotoxicity, antioxidant, and anti-inflammatory activities of Ricinus communis (Euphorbiaceae) leaf extracts. *Evidence-Based Complementary and Alternative Medicine*, 2014(1),1-8.

Nesbitt, P. D., Lam, Y. & Thompson, L. U. (1999). Human metabolism of mammalian lignan precursors in raw and processed flaxseed. *The American Journal of Clinical Nutrition*, 69(3).

Newman, D. J. & Cragg, G. M. (2012). Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010. *Journal of Natural Products,* 75(3), 311–33

Nitrayová, S., Brestenský, M., Heger, J., Patráš, P., Rafay, J., & Sirotkin, A. (2014). Amino acids and fatty acids profile of chia (Salvia hispanica L.) and flax (Linum usitatissimum L.) seed. *Slovak Journal of Food Sciences*, 8(1). 72-76.

Noack, M., & Kolopp-Sarda, M.-N. (2018). Cytokines et inflammation : physiologie, physiopathologie et utilisation thérapeutique. *Revue Francophone Des Laboratoires*, 2018(499), 28–37.

Nunes, C. D. R., Barreto Arantes, M., Menezes de Faria Pereira, S., Leandro da Cruz, L., de Souza Passos, M., Pereira de Moraes, L., ... & Barros de Oliveira, D. (2020). Plants as sources of anti-inflammatory agents. *Molecules*, 25(16).

O' Connor, C. & Nichol, A. (2015). Inflammation, immunity and allergy. *Anaesthesia & Intensive Care Medicine*, 16(7), 328–333.

-O-

Okombe, E. V., Nzuzi, M. N. G. (2019). Evaluation de l'activité antipyrétique, analgésique et anti-inflammatoire de l'extrait méthanolique de Vitex congolensis De Wild. & T. Duran. *Int. J.Biol. Chem. Sci* ,13 :7, 3066-3078.

Oomah, B. D. (2001). Flaxseed as a functional food source. *Journal of the Science of Food and Agriculture*, 81(9), 889–894.

Oomah, B. D. & Mazza, G. (1993). Flaxseed proteins.A review. *Food Chemistry*, 48(2), 109-114.

Oomah, B.D., Mazza, G. & Kenaschuk, E. O. (1996). Flavonoid content of flaxseed. Influence of cultivar and environment. *Euphytica*, 90(2), 163-167.

Orhan a, E. K¨upeli a, M. Aslan a, M. Kartal b, E. Yesilada. (2006). Bioassayguided evaluation of anti-inflammatory and antinociceptive activities of pistachio, Pistacia vera L., *Journal of Ethnopharmacology* .105 :235–240.

Orliaguet, G., Gall, O. & Benabess-Lambert, F. (2013). Nouveautés concernant les anti-inflammatoires stéroïdiens et non stéroïdiens. *Le Praticien en Anesthésie Réanimation*, 17(5), 228-237.

Ouedraogo, S., Yoda, J., Traore, T. K., Nitiema, M., Sombie, B. C., Diawara, H. Z., ... & Semde, R. (2021). Production de matières premières et fabrication des médicaments à base de plantes médicinales. *International Journal of Biological and Chemical Sciences*, 15(2), 750-772.

-P-

Pahwa R, A Goyal, I Jialal. (2018) - Chronic inflammation europepmc.org.

Palta, S., Saroa, R. & Palta, A. (2014). Overview of the coagulation system. *Indian Journal of Anaesthesia*, 58(5), 515.

Pandey, J., Bhusal, S., Nepali, L., Khatri, M., Ramdam, R., Barakoti, H., ... & Bhandari, R. (2021). Anti-Inflammatory Activity of Artemisia vulgaris Leaves, Originating from Three Different Altitudes of Nepal. *The Scientific World Journal.*

Pasquier, C. (1995). Stress oxydatif et inflammation. *Revue française des laboratoires*, (276), 87-92.

Payne, D. N. R. & Adcock, I. M. (2001). Molecular mechanisms of corticosteroid actions. *Paediatric respiratory reviews*, 2(2), 145-150.

Pohl, P., Dzimitrowicz, A., Jedryczko, D., Szymczenia-Madeja, A., Welna, M. & Jamroz, P. (2016). The determination of elements in herbal teas and medicinal plant formulations and their tisanes. *Journal of Pharmaceutical and Biomedical Analysis,* 130, 326–335.

-R-

Rabesandratana, H. (1996). Exploration des cellules phagocytaires sanguines en cytométrie en flux. *Revue Française Des Laboratoires,* (287), 107–110.

RADJAH Abir (2020). Thèse de doctorat, Valorisation et identification phytochimique des principes actifs de quelques plantes médicinales de la région de Biskra. Université Mohamed Kheider – Biskra. P9.

Rafieian-kopaei, M., Shakiba, A., Sedighi, M. & Bahmani, M. (2017). The Analgesic and Anti-Inflammatory Activity of Linum usitatissimum in Balb/c Mice. *Journal of Evidence-Based Complementary & Alternative Medicine,* 22(4),1-5.

Rajju Priya Soni, Mittu Katoch, Ashish Kumar & Pramod Verm. (2017). Flaxseed – composition and its health benefits.

Rankin, J. A. (2004). Biological mediators of acute inflammation. *AACN Advanced Critical Care,* 15(1), 3-17.

Rambod Abiri, R. A., Silva, A. L. M., Mesquita, L. D., Mesquita, J. D., Atabaki, N., Almeida Júnior, E. D., ... & Malik, S. (2018). Towards a better understanding of Artemisia vulgaris: botany, phytochemistry, pharmacological and biotechnological potential. *Food Research International*, 109, 403–415.

Ravat, F., Payre, J., Peslages, P., Fontaine, M. & Sens, N. (2011). La brûlure: une pathologie inflammatoire. *Pathologie Biologie*, 59(3), 63-72.

Renouard S. (2011). Régulation transcriptionnelle de la biosynthèse des liganes du lin (linum usitatissimum et linum flavum) et amélioration de l'extraction de Lignanes.Science du vivant, Thèse de doctorat (Université d'Orléans), p231.

Revillard, J.-P. (2001). Immunolgie, Immunologie. Bruxelles.4éme édition. P140.

Rousselet, M. C., Vignaud, J. M., Hofman, P. & Chatelet, F. P. (2005). Inflammation et pathologie inflammatoire. *Association française des enseignants et chercheurs en anatomie pathologie,* 1-57.

Ripoche, J., Demares, M. J., Julen, N., Lemercier, C., Dauchel, H., Davrinche, C., ... & Fontaine, M. (1989). Les protéines régulatrices du système du complément. M/s n° 4 vol. 5,234-243.

Royer M. (2013). Thèse pour obtenir le grade de Docteur de L'université de Lorraine, Etude des relations entre croissance, concentrations en métabolites primaires et secondaires et disponibilité en ressources chez la tomate avec ou sans bioagresseurs. Université de Lorraine – INRA.p11.

Roze, L. V., Chanda, A. & Linz, J. E. (2011). Compartmentalization and molecular traffic in secondary metabolism: A new understanding of established cellular processes. *Fungal Genetics and Biology*, 48(1), 35–48.

ROY, H., LUNDY, S. & ERIKSEN, C. (2007). Healthier lives through education in nutrition and preventive medicine. Flaxseed a review of health benefits. *Pennington Nutrition Series*, (5), 1-4.

-S-

Saleh, N. A., El-Negoumy, S. I., Abd-Alla, M. F., Abou-Zaid, M. M., Dellamonica, G., & Chopin, J. (1985). Flavonoid glycosides of Artemisia monosperma and A. herba-alba. *Phytochemistry*, 24(1), 201-203.

Saleh NAM, El-Negoumy SI, Abou-Zaid MM., (1987). Flavonoids of Artemisia judaica, A. monosperma and Artemisia herba-alba. *Phytochemistry*, 26: 3059 - 3064.

Samira FETNI1, Nabil BERTELLA. (2020). Etude in vitro des propriétés anti-inflammatoires de l'extrait méthanolique des fruits de Rosa canina L. (Rosacées). *Nutr et Santé.* Vol. 09.117-125.

Santangelo, C., Varì, R., Scazzocchio, B., Di Benedetto, R., Filesi, C., et Masella, R. (2007). Polyphenols, intracellular signalling and inflammation. *Annali-Istituto Superiore Di Sanita,* 43:4,394.

Sawadogo, W. R., Lompo, M., Guissou, I. P., et Nacoulma, O. G. (2008). Dosage des triterpènes et stéroïdes de Dicliptera verticillata et évaluation de leur activité anti-inflammatoire topique. *Médecine d'Afrique Noire*, 55(12) : 223-229.

Sébastien A., (2015). Implication du métabolisme carbone pour une production différentielle d'huile chez les plantes oléagineuses – lin : modélisation des systèmes. Thése doctorat. Université de Technologie de Compiègne, France.

Sekhar, S., Karmakar, R., Ramachandra, K., Siddapura, R.N. and Harischandra, S. P. Potential anti-inflammatory bioactives from medicinal plants of Western Ghats, India. *Pharmacognosy Communications*. Vol 2.

Setty, A. R. & Sigal, L. H. (2005). Herbal medications commonly used in the practice of rheumatology: mechanisms of action, efficacy, and side effects. *In Seminars in arthritis and rheumatism*, Vol. 34, 773-784.

Shekhara, N. R., Anurag, A. P., Prakruthi, M. & Mahesh, M. S. (2020). Flax Seeds (Linum usitatissimmum): Nutritional composition and health benefits. IP J. *Nutr. Metab. Health Sci*, 3, 35-40.

Siwan, D., Nandave, D. & Nandave, M. (2022). Artemisia vulgaris Linn: an updated review on its multiple biological activities. Futur J Pharm Sci 8, 47.

Shapouri-Moghaddam, A., Mohammadian, S., Vazini, H., Taghadosi, M., Esmaeili, S. A., Mardani, F., ... & Sahebkar, A. (2018). Macrophage plasticity, polarization, and function in health and disease. *Journal of cellular physiology*, 233(9), 6425-6440.

Serhan, C. N., Ward, P. A. & Gilroy, D. W. (2010). *Fundamentals of inflammation.* Cambridge University Press. 2-3.

Soares-Bezerra, R., Calheiros, A., da Silva Ferreira, N., da Silva Frutuoso, V. & Alves, L. (2013). Natural Products as a Source for New Anti-Inflammatory and Analgesic Compounds through the Inhibition of Purinergic P2X Receptors. Pharmaceuticals, 6(5), 650–658.

Soni, R. P., Katoch, M., Kumar, A. & Verma, P. (2016). Flaxseed-Composition and its health benefits. Res. Environ. *Life Sci*, 9, 310-316.

Spronk, H. M. H., Govers-Riemslag, J. W. P. & ten Cate, H. (2003). The blood coagulation system as a molecular machine. *BioEssays*, 25(12), 1220–1228.

-T-

Tabuti, J. R.., Lye, K. & Dhillion, S. (2003). Traditional herbal drugs of Bulamogi, Uganda: plants, use and administration. *Journal of Ethnopharmacology*, 88(1), 19–44.

Tan, R., Zheng, W. & Tang, H. (1998). Biologically Active Substances from the Genus Artemisia. *Planta Medica*, 64(04), 295–302.

Tańska, M., Roszkowska, B., Skrajda, M. & Dąbrowski, G. (2016). Commercial Cold Pressed Flaxseed Oils Quality and Oxidative Stability at the Beginning and the End of Their Shelf Life. *Journal of Oleo Science*, 65(2), 111–121.

Tariket, S., Guerrero, J., Garraud, O., Ghevaert, C. & Cognasse, F. (2019). Le contenu des granules alpha des plaquettes module la réponse inflammatoire, après injection systémique de lipopolysaccharides dans un modèle murin. *Transfusion Clinique et Biologique*, 26(3), S89.

Tawaha K., Alali F.Q., Gharaibeh M., Mohammad M. & El-Elimat T. (2007). Antioxidant activity and total phenolic content of selected Jordanian plant species. *Food Chemistry*.104(4): 1372-1378.

Tribalat, M. A. (2016). Etude métabolomique de lin (Linum usitatissimum) mutant pour la voie de biosynthèse des lignanes (Doctoral dissertation, Université de Picardie). p12-13.

Thormar, H. (2011). Lipids and Essential Oils as Antimicrobial Agents. Faculty of Life and Environmental Sciences, University of Iceland, Reykjavik, Iceland, John Wiley & Sons,Ltd, Pp : 211-219.

Trochoutsou, N., Di Benedetti, M., Pilakoutas, K. & Guadagnini, M. (2021). Mechanical Characterisation of Flax and Jute Textile-Reinforced Mortars. *Construction and Building Materials*, 544-545.

Tzang, B. S., Yang, S. F., Fu, S. G., Yang, H. C., Sun, H. L. & Chen, Y. C. (2009). Effects of dietary flaxseed oil on cholesterol metabolism of hamsters. *Food chemistry*, 114(4), 1450-1455.

-V-

Venglat, P., Xiang, D., Qiu, S., Stone, S. L., Tibiche, C., Cram, D. & Bekkaoui, F. (2011). Gene expression analysis of flax seed development. *BMC plant biology*, 11(1), 1-15.

Vernex-Lozet C, (2011). Les possibilités de la phytothérapie en Gériatrie canine. Thèse de doctorat Université de Lyon.p37.

Viatte. S, G. Waeber, P. Vollenweider (2007). Effets secondaires méconnus des glucocorticoïdes : prévention et traitement spécifiques requis. *Revue Médicale Suisse*.2472-2477.

Vidya Sarma. J, Peter A. Ward. (2011). The complement system. *Cell Tissue Res*. Vol 343, 227–235.

Vonkeman, H. E. & van de Laar, M. A. (2010). Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. *In Seminars in arthritis and rheumatism*.Vol. 39, 294-312.

Weill B, Batteux F. & Dhainaut J, (2003). Immunopathologie et réactions inflammatoires. Eds, De Boeck Université (Paris), p : 12-23.

-W-

Weill, B. & Batteux, F. (2003). Immunopathologie et réactions inflammatoires. De Boeck.

Weston, L. A., Barney, J. N. & DiTommaso, A. (2005). A review of the biology and ecology of three invasive perennials in New York State : Japanese knotweed (Polygonum cuspidatum), mugwort (Artemisia vulgaris) and pale swallow-wort (Vincetoxicum rossicum). *Plant and soil*, 277, 53-69.

Wong, C. C., Li, H. B., Cheng, K. W. & Chen, F. (2006). A systematic survey of antioxidant activity of 30 Chinese medicinal plants using the ferric reducing antioxidant power assay. *Food Chemistry*, 97:4,705-711.

Wongrakpanich, S., Wongrakpanich, A., Melhado, K. & Rangaswami, J. (2018). A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. *Aging and Disease*, 9(1), 143.

-Y-

Yarnell, E. (2007). Plant Chemistry in Veterinary Medicine: Medicinal Constituents and Their Mechanisms of Action. *Veterinary Herbal Medicine,* 159–182.

Yves L, Gies JP. (2014). Pharmacologie des cibles à la thérapeutique, (3e édition). Pharmarcie-medecine-Sciences de la vie. Dunod-Sciences Sup, Paris, 544 P.

-Z-

Zea Mays (L.), J. Journal of Global Biosciences. Vol. 4, n°5. 2168-2173.

Zeghal K M. & Sahnooun Z. (2013). La réaction inflammatoire et le stress oxydant. In : Abrégé de physiologie à l'usage des acupuncteurs et des réflexothérapeutes. Springer Paris: 47-53.

Ziltener. J.-L., S. Leal, P.-E. Fournier. (2010). Non-steroidal anti-inflammatory drugs for athletes: An update. *Annals of Physical and Rehabilitation Medicin*e 53 278–288.

Annexes

Appendix 01: Equipment used.

Glassware	Beakers, Flasks Test tubes, Test tubes Erlenmeyer Funnel Whatman paper Adjustable micropipette Magnetic bars, spatula, wash bottle, racks Dissection bowl Micropipette 1000 µl
Equipment	Magnetic agitator Precision scale PH meter Water bath Visible UV spectrophotometer Vortex Universal oven from 5 to 220°C Autoclave

Solutions' preparation.

Sodium Carbonate (7.5%)	7.5g of Na2CO3 in 50 ml of distilled water.
Folin solution (10%)	10ml of Folin in 90ml of distilled water.

Albumin preparation: 0.2ml (0.2%) of egg albumin in 100ml of distilled water.

Preparation of PBS phosphate buffer (PH 6.4): 2.5g of disodium phosphate, 2.5 of monosodium phosphate, 8.2 of sodium chloride in 950ml of distilled water.

The pH is subsequently adjusted to 6.4 with sodium hydroxide and the volume is made up to 1000ml with distilled water.

Appendix 02: Calibration curves.

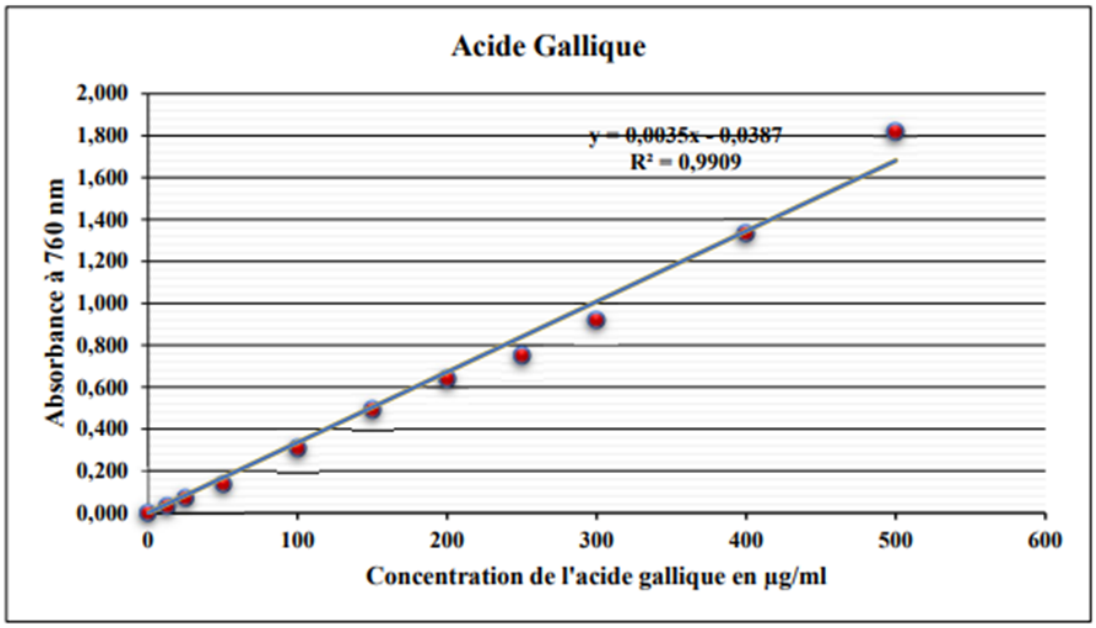


Figure: Gallic acid calibration curve

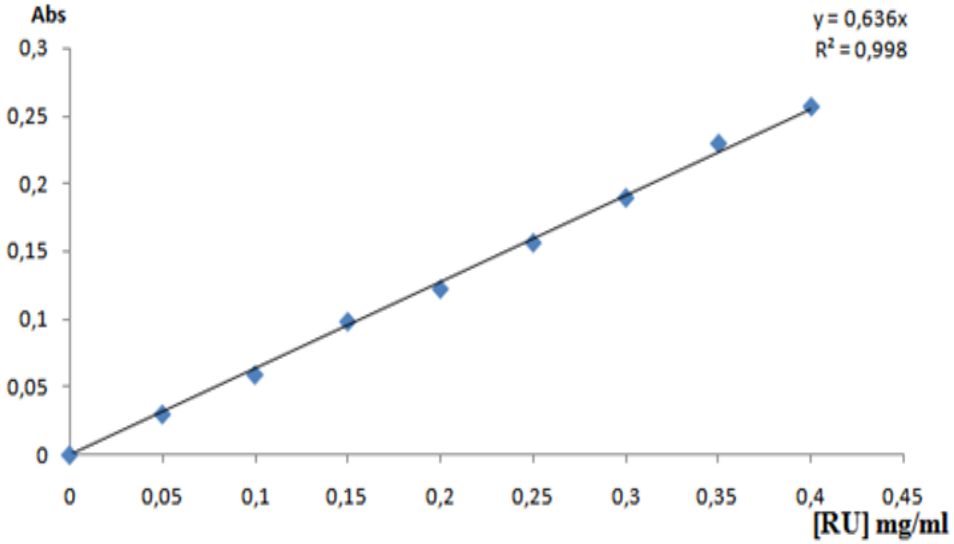


Figure: Quercetin calibration curve for the determination of total flavonoids.

Résumé

L'objectif de cette étude est d'évaluer les activités antiinflammatoires, Les extraits sont obtenus par macération (extrait méthanolique, éthanolique). Un dosage des polyphénols, des flavonoïdes a été effectué.

Notre étude a montré que l'extrait de Linum usitatissimum est plus riche en polyphénols (442.43 et 429.89 mg EAG/g EXT) et en flavonoïdes (9.141 ET 8.57 mg EQUE/g EXT) que l'extrait d'Artémia vulgaris (379.30ET 399 mg EAT/g EXT)

L'administration de l'extrait méthanolique aux doses de 500 mg/kg a prévenu l'œdème plantaire en comparaison avec le groupe ayant reçu du l'eau physiologique, a montré un pourcentage d'inhibition de l'inflammation très important comparable à Diclofénac anti-inflammatoire de référence.

Les résultats de cette étude soutiennent l'utilisation traditionnelle de ces deux plantes dans le traitement de diverses maladies. Cependant, des recherches supplémentaires sont essentielles pour identifier les molécules biologiquement actives et comprendre précisément les mécanismes moléculaires responsables de ces effets.
Mots cles : Activités antiinflammatoire, polyphénols, flavonoïdes, *Linum usitatissimum, Artémsia vulgaris.*

Abstract

The aim of this study was to evaluate, the anti-inflammatory activities of the extracts obtained by maceration (methanolic and ethanolic extracts). Polyphenols and flavonoids were assayed.

Our study showed that Linum usitatissimum extract is richer in polyphenols (442.43 and 429.89 mg EAG/g EXT) and flavonoids (9.141 AND 8.57 mg EQUE/g EXT) than Artemisia vulgaris extract (379.30 AND 399 mg EAT/g EXT).

Administration of the methanolic extract in doses of 500 mg/kg prevented plantar oedema compared with the saline group, showed a very significant percentage inhibition of inflammation comparable to the reference anti-inflammatory Diclofenac.

The results of this study support the traditional use of these two plants in the treatment of various diseases. However, further research is essential to identify the biologically active molecules and precisely understand the molecular mechanisms responsible for these effects.

Keywords : Anti-inflammatory activities, polyphenols, flavonoids, *Linum usitatissimum, Artemsia vulgaris.*

الملخص

كان الهدف من هذه الدراسة هو تقييم الأنشطة المضادة للالتهابات في المستخلصات التي تم الحصول عليها عن طريق النقع (المستخلصات الميثانولية والإيثانولية). تم قياس البوليفينول والفلافونويدات .

أظهرت دراستنا أن بذور الكتان كان أغنى بالبوليفينول (442.43 و429.89 ملجم إيكوي/غ إكس) والفلافونويدات (9.141 و8.57 ملجم إيكوي/غ إكس) من مستخلص الأرتيميا فولغاريس (379.30و399 ملجم إيكوي/غ إكس)

إعطاء المستخلص الميثانولي بجرعة 500 مجم/كلغ منع حدوث الوذمة مقارنة بالمجموعة المعالجالة بالماء أظهر تثبيطاً كبيراً جداً للالتهاب بنسبة مئوية كبيرة جداً مقارنةً بمضاد الالتهاب المرجعي ديكلوفيناك

تدعم نتائج هذه الدراسة الاستخدام التقليدي لهذين النباتين في علاج الأمراض المختلفة. ومع ذلك، من الضروري إجراء المزيد من الأبحاث لتحديد الجزيئات النشطة بيولوجيًا وفهم الآليات الجزيئية المسؤولة عن هذه التأثيرات بدقة

الكلمات المفتاحية: أنشطة مضادة للالتهابات، بذور الكتان، الشيح. البوليفينول، الفلافونويدات.