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Evaluation of anti-oxidant and anti-inflammatory activity of *Hammada scoparia* (*in vitro & in vivo*)

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Dedication

I dedicate this humble work

To my parents.

To my husband ABDELMALEK who gave me strength to go on to Until to the end.

To my sons, Mossaab, Anfal, Ekhansaa, El moatassim Billah .

To my sisters ... especially Nawel

To my brothers.... especially Nasr Eddine.

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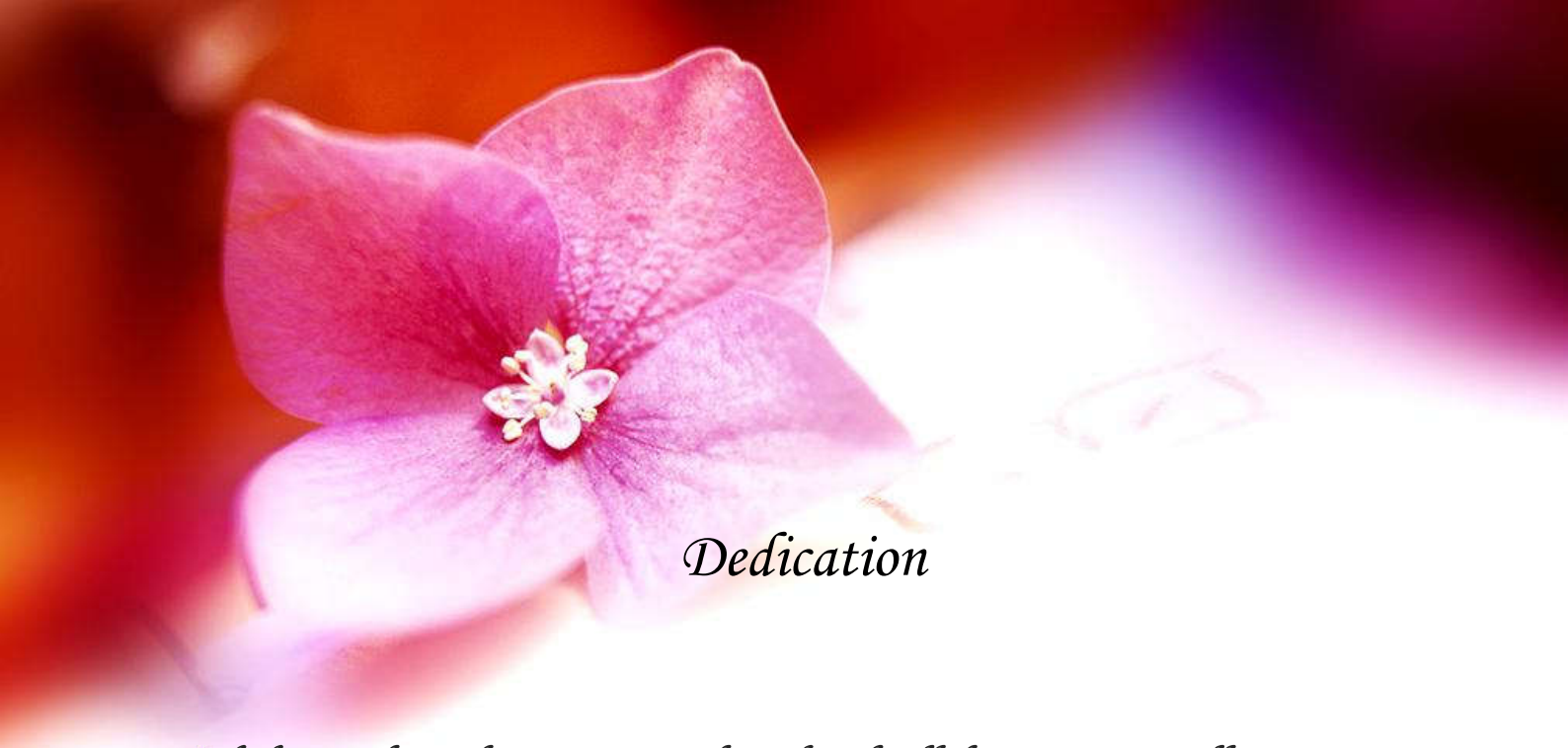

Dedication

I dedicate this achievement to the sake of Allah, my strong pillar.

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الملخص

عادة ما تكون الإستجابة الإلتهابية مفيدة، لكنها قد تكون في بعض الأحيان مؤذية كذلك. ترتبط الأدوية المضادة للإلتهاب بآثار جانبية خطيرة. نتيجةً لذلك تزايدَ الإهتمام بالنباتات الطبية الطبيعية ذات الخصائص المضادة للإلتهاب. يعتبر الرمث (HS) من أشهر النباتات المستوطنة (شجيرات رعوية صحراوية) ومعروف جيدًا بنشاطه المضاد للإلتهابات. لذا كان الغرض من هذه الدراسة هو تقييم النشاط المضاد للإلتهاب لمنقوع الجزء الهوائي من نبات الرمث في الجسم الحي. لتحقيق هذا الهدف، قمنا أولاً بإجراء فحص كيميائي للمستخلص المائي الخام لـهذا النبات قبل إجراء فحوصات لونية للمركبات الفينولية (البوليفينول، الفلافونويد والعفص المكثف). بعد ذلك قمنا بتقييم القوة المضادة للأكسدة لهذا المستخلص عن طريق إختبار ال DPPH . تم تقييم التأثير المضاد للإلتهاب لنبات الرمث بحقن الكاراجينان (1%) في مخلب الجرذان ويستار (Wistar Rats) وتتبعها لمدة 6 ساعات تَمّ خلالها قياس الوذمة. في نهاية التجربة تم تشريح الفئران وتقديم عينات الدم للتحاليل الكيميائية الحيوية الخاصة بأمراض الدم والبلازما.

كشفت الإختبارات الكيميائية النباتية عن تنوع المُستَقلَبَات الثانوية (بوليفينول، تربنويدات، الأكلويدات.. الخ) في النبات المدروس. أظهرت فحوصات مستويات المركبات الفينولية أن الرمث يحتوي على نسبة كبيرة من البوليفينول تقدر ب **3.95ملغ/غ**. أشار إختبار **DPPH** إلى أن للمستخلص المائي للنبات المدروس نشاط فعال ضد الأكسدة حيث قدر تركيز المادة الموافق للتثبيط النصفي (IC_{50}) بـ **0.0135 مغ/ملل**، كما أنه يتفاعل بسرعة مثل حمض الغاليك. أكدت نتائج الدراسة على النماذج الحيوانية المخبرية النشاط المضاد للإلتهاب لنبات الرمث حيث سجلنا في الفئران المعالَجة بالمستخلصات االمائية بجرعة**2000 ملغ/كغ** و **1000ملغ/كغ** تثبيطاً واضحاً لحجم الوذمة مقارنة بالحيوانات غيرالمعالجة, بنسب تصل إلى **66.04%**و **69.81%** على التوالي في الساعة السادسة. ومن هذا نستنتج أن الخاصية المضادة للإلتهابات لنبات الرمث ترتبط بالقوة المضادة للأكسدة للمُستَقلَبَات الثانوية وخاصة البوليفينول. إضافة إلى أن هذه النتائج تدعم بشكل واضح الإستخدام التقليدي لهذا النبات كمركبات بديلة خاصة في معالجة الأمراض الإلتهابية.

الكلمات المفتاحية: الرمث, منقوع, كاراجينان, مثبط الاكسدة , الكيمياء النباتية, جرذان ويستار, الإلتهاب.

Abstract

The inflammatory response is generally beneficial process but can lead to a harmful overeaction. The anti-inflammatory drugs are associated with numerous side effects. Therefore, there is an increasing interest in medicinal plants with anti-inflammatory proprieties.*Hammada scoparia* (HS) is an endemic plant (shrubs and subshrubs) which is well known for its anti-inflammatory activity. Hence, The objective of this work was to evaluate *in vivo* the anti-inflammatory activity of the infusion from HS aerial part. To achieve this goal, phytochemical screening was carried out before the colorimetric assays of the phenolic compounds (polyphenols, flavonoids, and condensed tannins). Then, we evaluated the antioxidant activity of (HS) crude extract by the DPPH scavenging test. The anti-inflammatory activity of (HS) was assessed by injection of 1% carrageenan in the hind paw of Wistar Albino rats and evaluated for 6 hours during which the edema was mesured (*in vivo*). At the end of the experimentation, the rats were sacrificed and the drawed blood was served to the hematological and biochemical analysis. The phytochemical screening revealed the diversity of secondary metabolites (polyphenols, terpenoids, alkaloids…etc) present in the studied plant. Polyphenols assessement indicates that the extract is rich in polyphenols (up to **3.95 mg/g GAE**). We found that the (HSI) has a potent antioxidant activity with an $\mathbf{IC_{50}}$ value of **0.0135µg/mL** and reacts as fast as gallic acid. The *in vivo* study confirms the anti-inflammatory activity of *Hammada scoparia*. Moreover, we noted that rats treated with **2000 mg/kg** and **1000 mg/kg** of HSI exhibited a very significant inhibition of the edematous paws increase compared to the untreated rats, where it reached **66.04%** and **69.81%** respectively at the 6 hour. We can conclude that the anti-inflammatory property of HSI would be linked to the antioxidant power of its secondary metabolites, particularly polyphenols. Therefore, these results clearly support the traditional use of this plant as alternative compounds in the control of inflammatory diseases.

Keywords: *Hammada scoparia,* infusion, phytochemistry, anti-oxidant, Wistar Rats, carrageenan, inflammation.

Résumé

La réponse inflammatoire est un processus habituellement bénéfique, mais Parfois elle peut être néfaste. Les anti-inflammatoires sont associés à des effets secondaires graves. Par conséquence, on s'intéresse aujourd'hui de plus en plus aux plantes avec des propriétés anti-inflammatoires. *Hammada scoparia* (HS) est une plante endémique (arbuste), bien connue pour son activité anti-inflammatoire. L'objectif de ce travail était d'évaluer *in vivo* l'activité anti-inflammatoire de l'infusion de la partie aérienne de *Hammada scoparia*. Pour atteindre cet objectif, tout d'abord, nous avons procédé un criblage phytochimique de l'extrait aqueux de HS avant de faire des dosages colorimétriques des composés phénoliques (polyphénols, flavonoïdes, et tanins condensés). Ensuite, nous avons évalué le pouvoir antioxydant de l'extrait brut de HS par le test au **DPPH**. L'effet anti-inflammatoire de (HSI) a été évalué en utilisant la méthode de l'œdème plantaire provoquée par la carragénine chez les rats Wistar à 1%. L'expérimentation *in vivo* s'est déroulée pendant 6 h durant laquelle l'œdème a été surveillé. A la fin de l'expérimentation animale, les rats sont sacrifiés et les paramètres hématologique et biochimiques plasmatiques ont été dosés. Les tests phytochimiques ont révélé la diversité des métabolites secondaires (polyphénols, terpenoids, alcaloïdes...etc) dans la plante étudiée. Les dosages des composés phénoliques ont montré que *Hammada scopaaria* contient une teneur considérable en polyphénols estimée à **3,95 mg EAG /g MS**. Le test au **DPPH** a indiqué que l'extrait aqueux de HS a un pouvoir antioxydant puissant avec un $\mathbf{IC_{50}}$ estimé à **0,0135 mg/ml** et réagit rapidement comme l'acide gallique. L'étude *in vivo* a confirmé l'activité anti-inflammatoire du *Hammada scoparia*. D'ailleurs, nous avons enregistré chez les rats traités avec les extraits aqueux de HS au dose **2000 mg/kg** et **1000 mg/kg** une inhibition très importante des volumes des pattes œdémateux par rapport aux rats non traités atteignent jusqu'au **66.04%** et **69.81%** respectivement au 6 ème heur. Nous pouvons conclure que la propriété anti-inflammatoire du HSI serait liée au pouvoir antioxydant de ses métabolites secondaires, particulièrement les polyphénols. Par conséquent, ces résultats soutiennent clairement l'utilisation traditionnelle de cette plante comme composés alternatifs particulièrement dans le contrôle des maladies inflammatoires.

Mots clés: *Hammada scoparia,* infusion, anti- oxidant, phytochimique, Wistar Rats, carragénine, inflammation.

5-HT: 5-Hydroxytryptamine

5-LOX :5-lipoxygenase

AA: Arachidonic acid

Abs: absorbance

AP-1: activating protein-1

AUG %: percentage of augmentation

Cg: Carrageennan

COX-1 and COX-2: Cyclooxygenase

CVD: cardiovascular desease

CRP: C- Reactive Protein

DAMPs: Damage-associated molecular

DCs: Dendritic cells

DINC: Description, Identification, Nomenclature, and classification patterns

DNA: Deoxyribonucleic acid

FMet-Leu-Phe: N-formyl-methionyl-leucyl-phenylalanine

GM-CSF: granulocyte–macrophage colony-stimulating factor

HETE: Hydroxyeicosatetraenoic acid.

HPETE: Hydroperoxyeicosatetraenoic acid.

HSI: *hammada scoparia* infusion

ICAM-1: Intercellular adhesion molecule-1;

IFN-γ: Interferon Gamma

IKK: IκB kinase.

IL-1β: Interleukin-1β

IL-6: Interleukin-6

IL-8: Interleukin 8

IM: intramuscular injection

INH %: Percentage of inhibition

IP: intraperitoneal injection

IV: Intravascular injection

IκB: Inhibitor of nuclear factor kappa B kinase proteins

IκB: Inhibitors of NF-κB

JAK: Janus kinase signal transducer

LOX: Lipoxygenase

LPS: lipo-polysaccharides

LTA4: leukotriene A4

LTA4: leukotriene A4

LTB4: leukotriene B4

LTB4: leukotriene B4

LXA4: Lipoxin A4

LXB4 :Lipoxin B4

MAPK: Mitogen-activated protein kinase

MCP: Monocyte chemoattractant proteins

MIP: Macrophage inflammatory protein

MAPK: Mitogen-activated protein kinase

MCP: Monocyte chemoattractant proteins

MIP: Macrophage inflammatory protein

MCP-1: monocyte chemotactic protein-

Mres: Resolving Macrophages

NADPH: Nicotinamide

NO: Nitric oxide

NOSi : Nitrite oxyde synthétaseinductible

NF-κB: Nuclear factor kappa-B

NK: Natural killer

NSAIDs: Non-steroidal anti-inflammatory drugs

NSAID: Non-steroidal anti-inflammatory drug

PAMPs: Pathogen-associated molecular patterns

PGE2 :Prostaglandin E2

PGI2: Prostacyclin

PLA2: Phospholipase A2

PLC: Phospholipase C

PGE2:prostaglandinE2

PGH2: Prostaglandin H2

PLA2: Phospholipase A2

PGH2: Prostaglandin H2

PLA2: Phospholipase A2

PMNs: Polymorphonuclear neutrophils

PRRs: Pattern recognition receptors

PMNs: Polymorphonuclear neutrophils

PRRs: Pattern recognition receptors

PRR: Patern Recognition Receptor

RANTES: Regulated upon activation, Normal T Cell Expressed and presumably Secreted

ROS: Reactive oxygen species

SAID: Steroidal anti-inflammatory drug

SC, LQ: Subcutaneous injection

E-selectin: Endothelial selecti

TLR: Toll-like receptor

TNF-α: Tumor necrosis factor-α

TXA: Thromboxane

TLR4: Toll-like receptor 4

TNF-α: Tumor necrosis factor-α

TXA2: Thromboxane A2

VCAM-1: Vascular cell adhesion molecule-1.

W/V: weight per volume

W/W: weight per weigh

WHO: World Health Organization

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INTRODUCTION

INTRODUCTION

Reports have shown that inflammation is usually triggered by living tissues damage caused by infections, physical agents, and defective immune response. The fundamental aim of inflammatory response is to localize and eliminate the harmful agents; secondarily, to remove damaged tissue components to culminate in healing of the affected tissues, organs, or system (**Barnes, 2009; Ahmed, 2011**). An inflammatory response involves macrophages and neutrophils known to secrete different mediators that are responsible for the initiation, progression, persistence, regulation, and eventual resolution of the acute state of inflammation. A failure in inflammatory acute response is the onset of a chronic phase of inflammation (**Oluwafemi, 2018**).

The treatment of chronic inflammatory diseases is still problematic, since, anti-inflammatory used drugs have numerous side effects (**Li *et al.*, 2003**). Recently, there is an increasing interest in medicinal plants with anti-inflammatory proprieties and low or no side effects.In additionto its safety, green medicine is believed to be of a low cost as compared to synthetic drugs (**Rajkumar and Malathi, 2015; Canli *et al.*, 2015**).

To assess the efficacy of bioactive molecules extracted from medicinal plant ,researches use laboratory animals for this purpose. Rat is considered as an animal model widely used in fundamental research conducted on diseases etiology and complications, but also to check the safety and the efficacy of newtherapeutic agents. The laboratory rat has become a standardized physiological and toxicological model due to their similar physiology , to some extent, with humans and they share the most common pathways in normal and pathological conditions.Thus results from animal experimentation,such as the effect of environmental agents including toxins,stress, diet and vaccination on health ,can be extrapolated to humans (**APG IV, 2016**).

Algeria,a broad country for its country known for its natural resources, has a singularly rich and varied flora estimated at around 3000 plant species, and 15% of which are endemic and belonging to several botanical families (**Dif *et al.,* 2015**). Out of these families, the Amaranthaceae family contains 183 genus and 2500 (**Singh,2019**). *Hamada scoparia* is a species belonging to Amaranthaceae family.Isis known as “Remth” in Algeria, Tunisia and Morocco. *Hammada scoparia* isfrequently used in Algerian folk medicine for the treatment of inflammatory conditions such as pain, wounds, swelling, rheumatism, severecolds, infections and snakebite (**Taïr *et al.*,2016 ; Maire,1962 ; Lamchouri,2022**).

Previous pharmacological study showed that HSI has anti microbial, antifungal, anti oxidant activity (**Allaoui *et al.*, 2016;Fatehi *et al.*, 2017**). However, to the best to our knowledge,no attempt has been made to investigate anti-inflammatory effect of this plant on animal model. Therefore, this research was conducted, first,to determine some phytochemicals in the *H. scoparia* namely polyphenols,flavnoids,and condensed tannins, and then to test the antioxidant activity of *H. scoparia* crude extract .secondly to investigate the anti-inflammatory proprirties of infusion from *H. scoparia* on carrageenan-induced acute inflammation in Wistar Rats.

LITERATURE REVIEW

I. An overview of inflammation

1.1. The process of inflammation

Inflammation is a biological response of vascularized tissues to infections and damaged tissues, involving a complex network of cell-cell, cell-mediator & tissue interactions (**Sporn *et al.*, 1986; Vinay *et al.*, 2014**). This process is generally beneficial, leads to the elimination of possible pathogens and the return to homeostasis of the injured tissue (**Wollinger *et al.*, 2016**). However, inflammation itself can damage otherwise healthy cells which could then further stimulate inflammation (**Rukmini *et al.*, 2018**).

1.2. Halmark signs of inflammation

The inflammatory symptoms are the results of plasma extravasations and increased leukocytes infiltration to the site of inflammation (**Tracey, 2002; Lawrence *et al.*, 2002**). They are the main basis for describing any type of inflammation even today.

Table 01: Halmark signs of inflammation (**Donna, 2017**).

Signs	Cause
Heat (warmth)	Vasodilation Bradykinin
Redness	Vasodilation and increased blood flow
Swelling (edema)	Leakage of fluid from vessel
Pain	Bradykinin and prostaglandins (E series): Stimulation of nerve endings

1.3. Factors of inflammation

Inflammation can be initiated by various factors that can be infectious or non-infectious (Table1) (**Chen *et al.*, 2018**) .

Table 02: Factors of inflammation (**Chen *et al.*, 2018**).

Non-infectious factors	Infectious factors
Physical: burn, frostbite, physical injury, foreign bodies, trauma, lionizing radiation	Bacteria
Chemical: glucose, fatty acids, toxins, alcohol, chemical irritants (including fluoride, nickel and other trace elements)	Viruses
Biological: damaged cells	
Psychological: excitement	Other micro-organisms

1.4. Inflammatory cells

1.4.1. Neutrophils

Because of their nuclear morphology, neutrophils are also called polymorphonuclear leucocytes (PMNs) (**Abul *et al*, 2017**). They capture and destroy invading microorganisms, through phagocytosis and intracellular degradation, release of granules, and formation of neutrophil extracellular traps after detecting pathogens. Neutrophil granules contain more than 20 enzymes, of these: elastase, collagenase and gelatinase, have the greatest potential for inducing tissue damage (**Reeves *et al.*, 2002; Lazaar *et al.*, 2011**).

1.4.2. Monocytes

During both homeostasis and inflammation, circulating monocytes leave the bloodstream and migrate into tissues where, following conditioning by local growth factors, pro-inflammatory cytokines and microbial products, they differentiate into macrophage or dendritic cell populations (**Auffray *et al.*, 2009**).

1.4.3. Macrophages

They have a major role as the first defence mechanism in phagocytosis of cellular debris, microbes and any other foreign substances. They initiate inflammation by secreting pro-inflammatory mediators and cytokines like IL-6 and TNF-α (**Murray and Weynn, 2011**). Classically activated macrophages produce NO and ROS and upregulate lysosomal enzymes, all of which enhance their ability to kill ingested organisms (**Vinay *et al.*, 2014**).

1.5. Inflammatory mediators

1.5.1. Vasoactive amines and peptides

1.5.1.1. Histamine

The richest sources of histamine are the mast cells, that are normally present in the connective tissue adjacent to blood vessels (**Aderiano and Deborah, 2008**). It is also found in blood basophils and platelets (**Vinay, 2014**). Histamine causes dilation of arterioles and increases the permeability of venules.

1.5.1.2. Serotonin (5-hydroxytryptamine)

A well-known neurotransmitter, produced by various cells types such as mast cells, and platelets. Serotonin regulates numerous biological processes such as platelets aggregation and cardiac function (**Berger *et al.*, 2009**). It activates human monocytes, prevents their apoptosis and modulates cytokine and chemokine production in lipopolysaccharide (LPS)-primed monocytes (**Durk *et al.*, 2005; Soga *et al.*, 2007**).

1.5.1.3. Bradykinin

It is a nanopeptide derived from plasma kinin (**Baumann *et al.*, 2011**). Similar to histamine and serotonin, bradykinin can increase the synthesis of prostaglandins and produces pain locally (**Hsieh, 2014**).

1.5.2. Cytokines

Cytokine expression is regulated by NF-κB and activating protein-1 (AP-1) and may be triggered by LPS, ROS and microbial species, among others (**Han *et al.*,1998**). Pro-inflammatory cytokines such as IL-1, IL-6 and tumor necrosis factors α, (TNF-α) travel trough the blood and stimulate hepathocytes in the liver to secrete acute phase proteins including C-reactive protein (CRP), fibrinogen… etc (**Richard and Geoffrey, 2015**).

Out of cytokines, chemokines are small molecules produced by many types of cells that influence the movement of leukocytes. For example, MCP 1-5, Eotaxins 1-3, MCP 4-5 and MIP-1 α and β, MIP-2 attract monocytes, eosinophils ,basophils, lymphocytes and neutrophils respectively to the sites of inflammation (**Sell, 2001**).

1.5.3. Eicosanoids

Biosynthesized from arachidonic acid by the initial activities of either cyclooxygenases (isoforms COX1 or COX2) or lipoxygenases and downstream enzymatic reactions. There are several main classes of eicosanoids: prostaglandins, prostacyclins, thromboxanes, leukotrienes, and lipoxins .They are critical for generating, maintaining, and mediating inflammatory responses (**Charles *et al.*, 2010**).

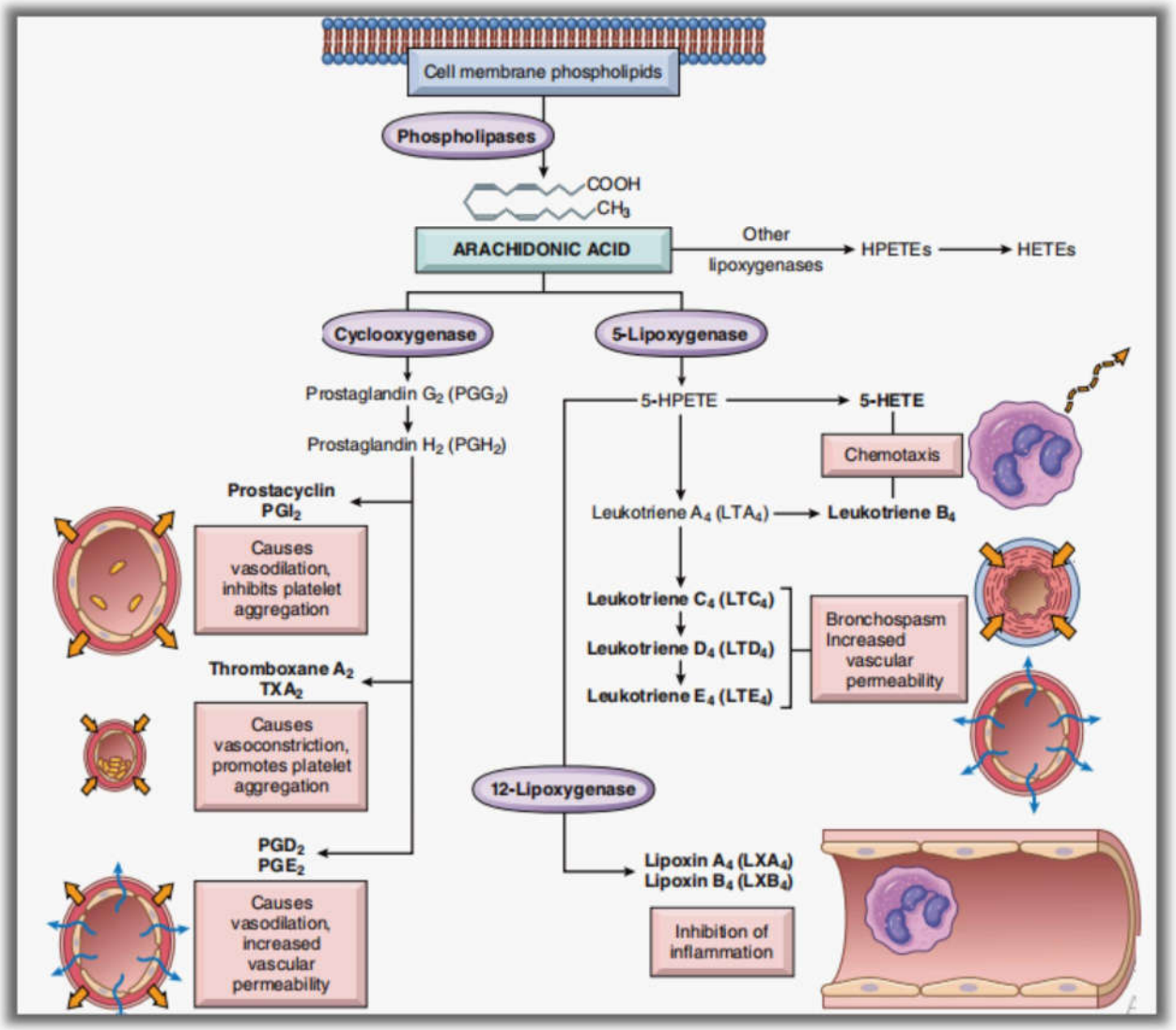

Figure 01: Production of arachidonic acid metabolites and their roles in inflammation (**Vinay *et al.*, 2014**).

1.6. Types of inflammation

There are generally two types of inflammation: acute and chronic inflammation (**Fritsch *et al.*, 2019; Michels *et al.*, 2019; Zhang *et al.*, 2019**).

1.6.1. Acute Inflammation

Acute inflammation is of relatively short duration, lasting from minutes to days, depending on the extent of injury. Its main characteristics are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes (predominantly neutrophils) (**Gownolla *et al.*, 2015**). Major outcomes of acute inflammation are healing and resolution of injury, where abscess formation and progression to chronic inflammation depending on the type of inflammatory agent, severity of tissue damage and the ability of inflammatory cells to divide and replicate within the damaged tissue (**Giresha, 2021**). It can be divided into 2 phases: initiation and resolution.

1.6.1.1. Initiation

a. Vascular responses

Tissue injury (sterile or following infection) leads to recognition of molecular pattern (DAMPs or PAMPs) by PRR of immune cells (including the Toll-like receptors (TLRs)), which rapidly stimulate the production of several pro-inflammatory mediators, such as TNF-α, IL-1β, IL-6, IL-12 IFN-γ, and IL-8(**Dinarello, 2000; Umukoro and Ashorobi, 2006; Keyel, 2014**). In addition histamine, bradykinin, prostaglandins, and leukotrienes are also produced. In this productive phase of inflammation, mediators act by promoting vasodilatation and consequent increase of local blood flow, and modifying endothelial wall permeability. These events are accompanied by hyperemia and exudation of plasma proteins and fluid (edema) (**Ana *et al.*, 2013**).

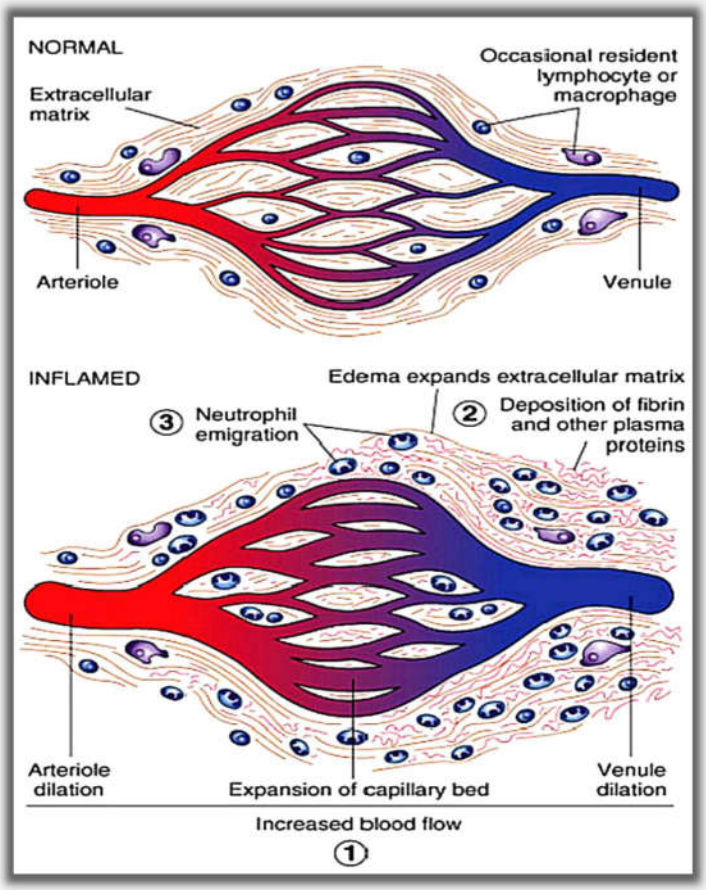

Figure 02: Vascular events of acute inflammation (Inflammatory edema) (**Giresha, 2021**).

b. Cellular responses

Among the leukocytes, neutrophils are the first inflammatory cells that are recruited at the acute inflammation site cells (**Stramer *et al.*, 2007; Robb *et al.*, 2016**). They infltrate within a few hours into the tissue area where the inflammatory response is occurring. Their migration from the blood to the tissue site is controlled by the expression of adhesion molecules by vascular endothelial cells (e.g., E- and P-selectin, ICAM), which, in turn, bind to selectin ligands

expressed on the surface of neutrophils (mechanism regulated by mediators of acute inflammation including IL-1 and TNF-α). The neutrophils attach securely to the endothelial cells and undergo a process of end-over-end rolling. Chemokines also activate the neutrophil causing a conformational change in their membrane integrin molecules. This change increases the affnity of neutrophils for the adhesion molecules on the endothelium (ICAM-1). Finally, the neutrophil undergoes transendothelial migration, resulting in their extravasation and subsequently engulf and degrade pathogens within phagolysosomes (**Granger *et al.*, 2010; Richard and Geoffrey, 2015; Gimbrone and Garcia, 2016**).

All leukocytes use the same basic steps as the neutrophil, although different combinations of adhesion molecules are involved (**Richard and Geoffrey, 2015**).

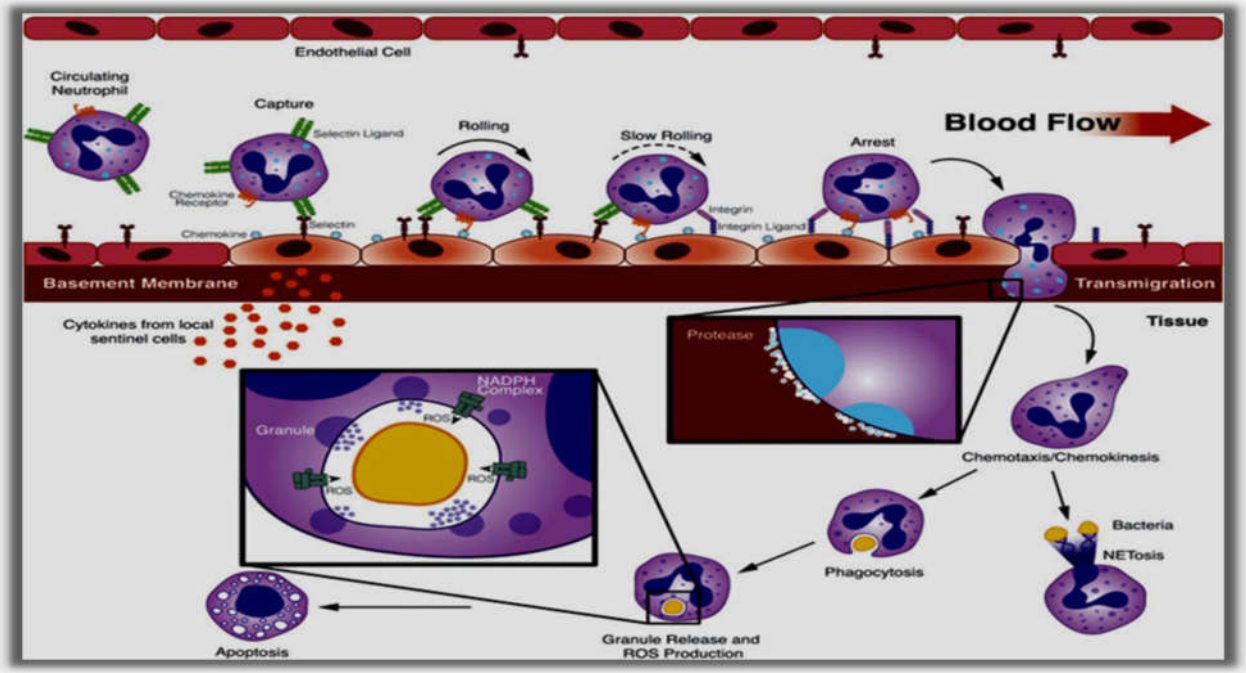

Figure 03: The sequential steps of classic neutrophil recruitment (**Dawn *et al.*, 2018**).

1.6.1.2. Resolution

Once recruited to the inflammatory site, leukocytes directly recognize, phagocytose, and destroy foreign pathogens. The resolution phase is already being enacted at this early point as the influx of PMN is halted at a level appropriate for the insult and is accompanied by their timely apoptosis (**Buckley *et al.*, 2014**). It's involves granule fusion, toxic oxygen radical production, activation of latent proteolytic enzymes, and the activity of antibacterial proteins (**Charles *et al.*, 2010**), followed by uptake of this apoptotic cells by macrophages (efferocytosis). Resolution macrophage (Mres) and lymphocyte repopulations increased production of pro-resolving mediators, anti-inflammatory, anti-oxydant and anti-fibrotic agents. Finally lymph node drainage

or apoptosis of macrophage close the inflammatory process and restore tissue homeostasis (**Ana *et al.*, 2013**).

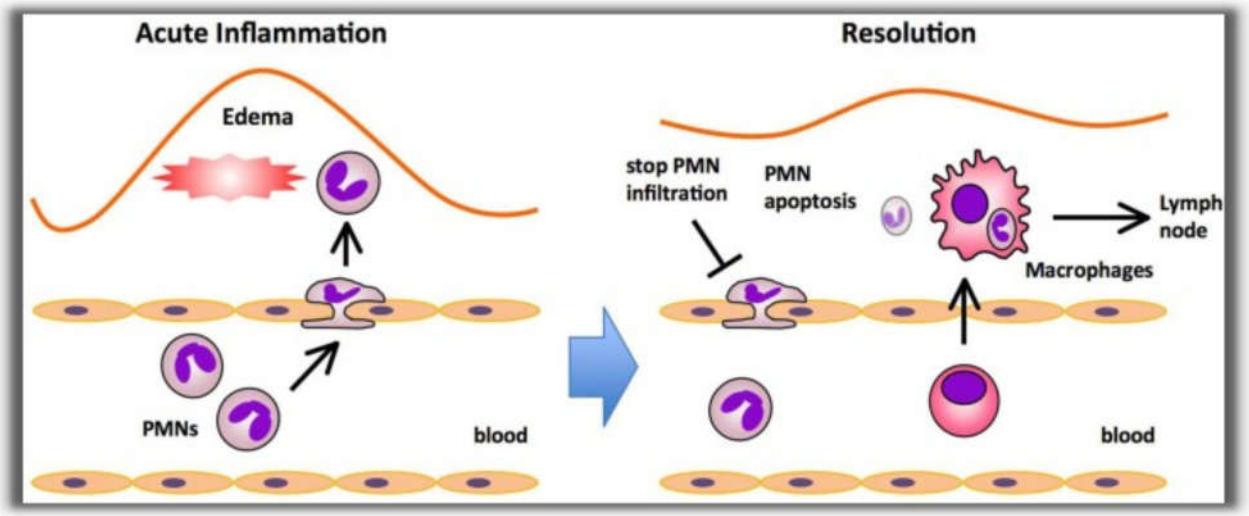

Figure 04: Major process in acute inflammation and resolution (**Yosuke *et al.*, 2012**).

1.6.2. Chronic Inflammation

Persistence of the inflammatory agents for a longer period of time leads to chronic inflammatory condition or non-resolving inflammation, which ultimately results in loss of tissue or organ function (**Giresha, 2021**). The hallmarks of chronic inflammation are the infiltration of the primary inflammatory cells and plasma cells in the tissue site, producing inflammatory cytokines, growth factors, and enzymes, contributing to the progression of tissue damage (**Kevin and Adam, 2020**).

1.7. Synthetic anti-inflammatory drugs

Substances with anti-inflammatory activity are intended to control excess specific reaction of the tissues and to avoid the transformation of the acute phase inflammation in the chronic phase (**Muster, 2005**).

There are two major classes of drugs with anti-inflammatory effects: nonsteroidal and glucocorticoids, where both appear to inhibit production of pro-inflammatory prostaglandins (PGs) in a variety of biological systems (**Van, 1971; Folman and Zor, 1976**).

1.7.1. Steroidal anti-inflammatory drugs

Glucocorticoids are able to inhibit all phases of the inflammatory reaction whether acute or chronic. They bind to intracellular receptors, the complex formed acting at DNA level and modifying the transcription of many genes. In inflammation, glucocorticoids inhibit the

transcription of COX2 genes (they have no effect on COX1), phospholipase A2 and therefore inhibit both the synthesis of prostaglandins and leukotrienes (**Jacqz-aigrain and Guillonneau, 1998; Mallem and Gogny, 2014**).

1.7.2. Non steroidal anti-inflammatory drugs(NSAIDs)

The widely accepted mechanism of action of NSAIDs is the inhibition of the conversion of arachidonic acid to endoperoxides cyclic by the enzyme cyclooxygenase (**Blain, 2001**). Most of the NSAIDs are nonselective and inhibit both COX-1 and COX-2. COX-1 is constitutive and makes PGs that protect the stomach and kidney from damage and COX-2 is induced by inflammatory stimuli, such as cytokines, and produces PGs that contribute to the pain and swelling of inflammation. wherefore, Drugs that have the highest potency on COX-2 and a better COX-2/COX-1 activity ratio will have potent anti-inflammatory activity, with few side effects on the stomach and kidney comparable to the strongest inhibitors of COX-1 (**Vane and Botting, 1998; Chaiamnuay *et al.*, 2006**).

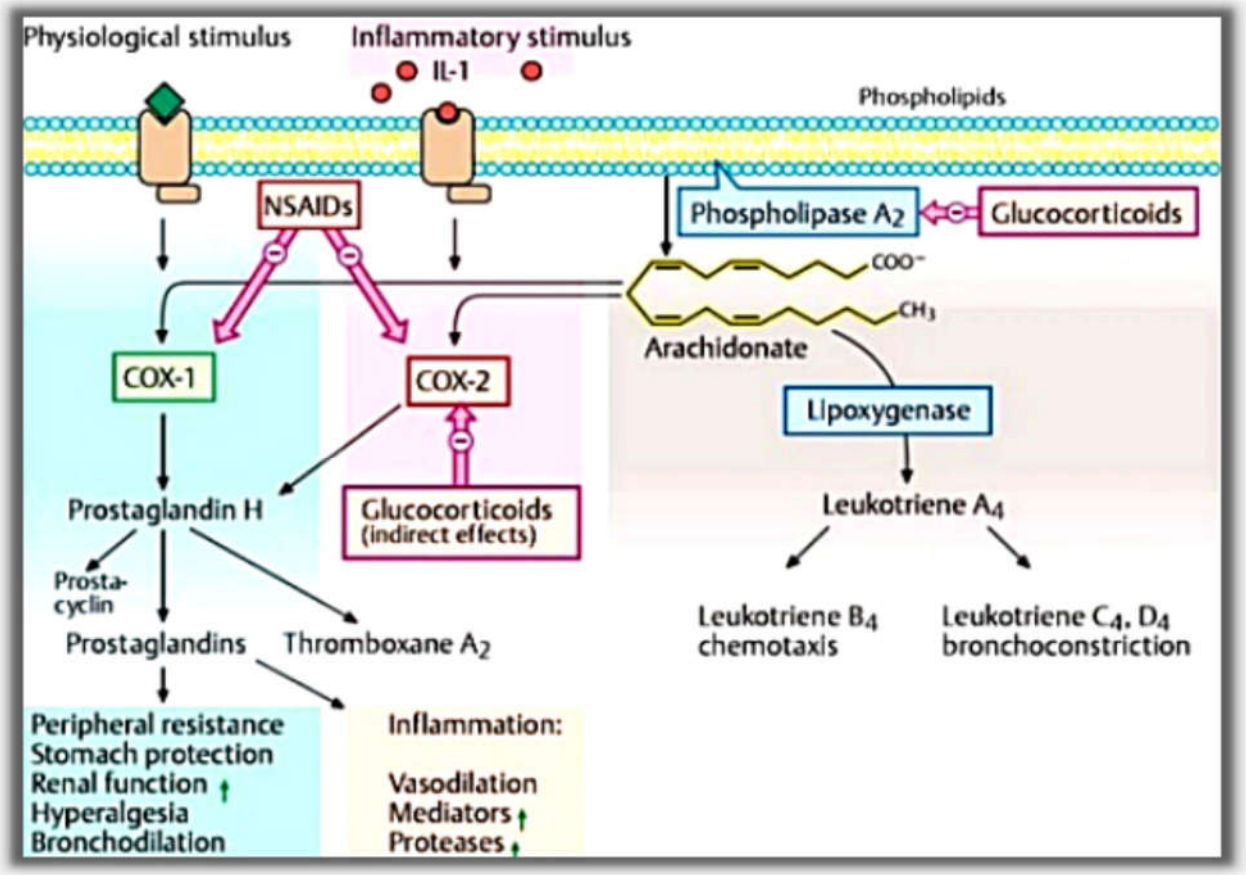

Figure 05: Mechanism of anti-inflammatory drugs action (**Jacqz-aigrain and Guillonneau, 1998**).

II. An overview of polyphenols

II.1. plant secondary metabolites

Secondary metabolites are complex organic molecules synthesized by autotrophic plants (**Boudjourff, 2011**). Secondary metabolites bio synthesized from primary metabolites and plays a major role in the interactions of the plant with its environment (**Peeking *et al.*, 1987**).

Three large molecule families are generally considered: Phenolics, Terpenes and Steroids, and Alkaloids, Flavanoids (**Bourgaud, 2001**).

II.2. Definition of polyphenols

To date, thousands of different types of secondary metabolites have been identified in plants chemically, these compounds are either nitrogen-containing (alkaloids) or nitrogen-deficient (terpenoids and phenolics) (**Patra *et al.*, 2013; Deepak *et al.*, 2015**).

It has commonly been assumed that the antioxidant capacity of phenolics will increase with the number of free hydroxyls and conjugation of side chains to the aromatic rings Flavonoids and phenylopropanoids are also oxidized by peroxidase, and act as H_2O_2 scavengers (**Lee *et al.*, 2017**).

II.3. Classification of polyphenols

Plant phenolics are mainly classified into five major groups, phenolic acids, flavonoids, lignans, stilbenes and tannins (**Myburgh, 2014**).Phenolic compounds generally possess one or more aromatic rings with one or more hydroxyl groups (**Tanase *et al.*, 2019**).

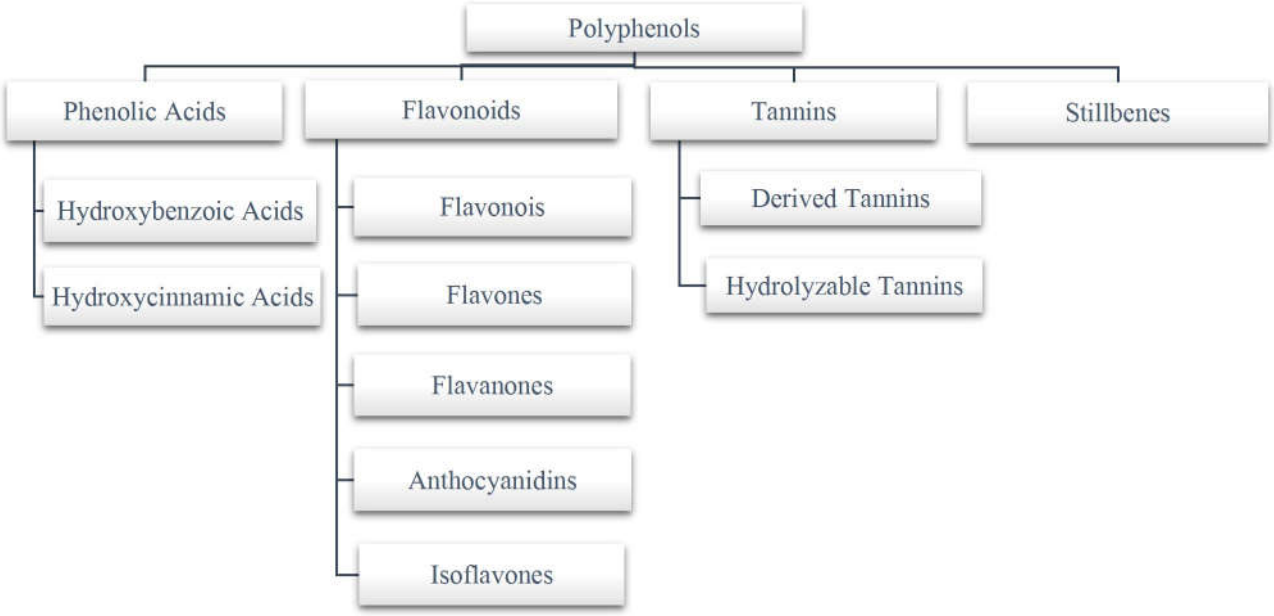

Figure 06 : Classification of phenolic compounds (**Boros *et al.,* 2010**).

II.4. Sources of polyphenols

Phenolics found in food material can be divided into three major groups: simple phenol and phenolic acids, hydroxycinnamic acid derivatives and flavonoids. Phenolic acids, flavonoids and tannins are considered as the main dietary phenolics (**Ștefănescu *et al.,* 2019**). Flavonoids constitute the largest group of low-molecular-weight plant phenolics and have been studied most extensively Tannins are the third important group of polyphenolics which can further be divided into two subcategories: condensed and hydrolysable tannins (**Bhuyan and Basu., 2017**).These are high-molecular-weight polymers. Fruits, grains and legumes consist of condensed tannins which are mainly polymers of catechins or epicatechins, whereas hydrolysable tannins are polymers of Gallic or ellagic acid and found in berries and nuts (**Smeriglio *et al.* 2017**).

II.5. potential health benefits of plant polyphenolics

Numerous studies have reported the potential health benefits of plant polyphenolics in particular. Due to their potent antioxidant properties, plant phenolics have scientifically proven to prevent various oxidative stress-related as well as chronic diseases, such as cancer, cardiovascular and neurodegenerative diseases (**Koch, 2019**). Therefore, phenolics with antioxidant properties have been found to be beneficial in preventing or treating the oxidative damage that can induce cancer (**Liu *et al.*, 2018**). Polyphenols may affect the molecular events in the initiation, promotion and progression stages of carcinogenesis and isoflavones and lignans

may affect the estrogen-related activities related to tumour formation (**Hsu *et al.*, 2015; Moein, 2015**). As polyphenols are known for their antioxidant activities, increased intake of dietary antioxidants may protect against the development of CVD. In addition, recent evidence suggests that polyphenols have immunomodulatory and vasodilatory properties which may also contribute in reducing the risk of CVD (**Mahmoud *et al.*, 2019**).

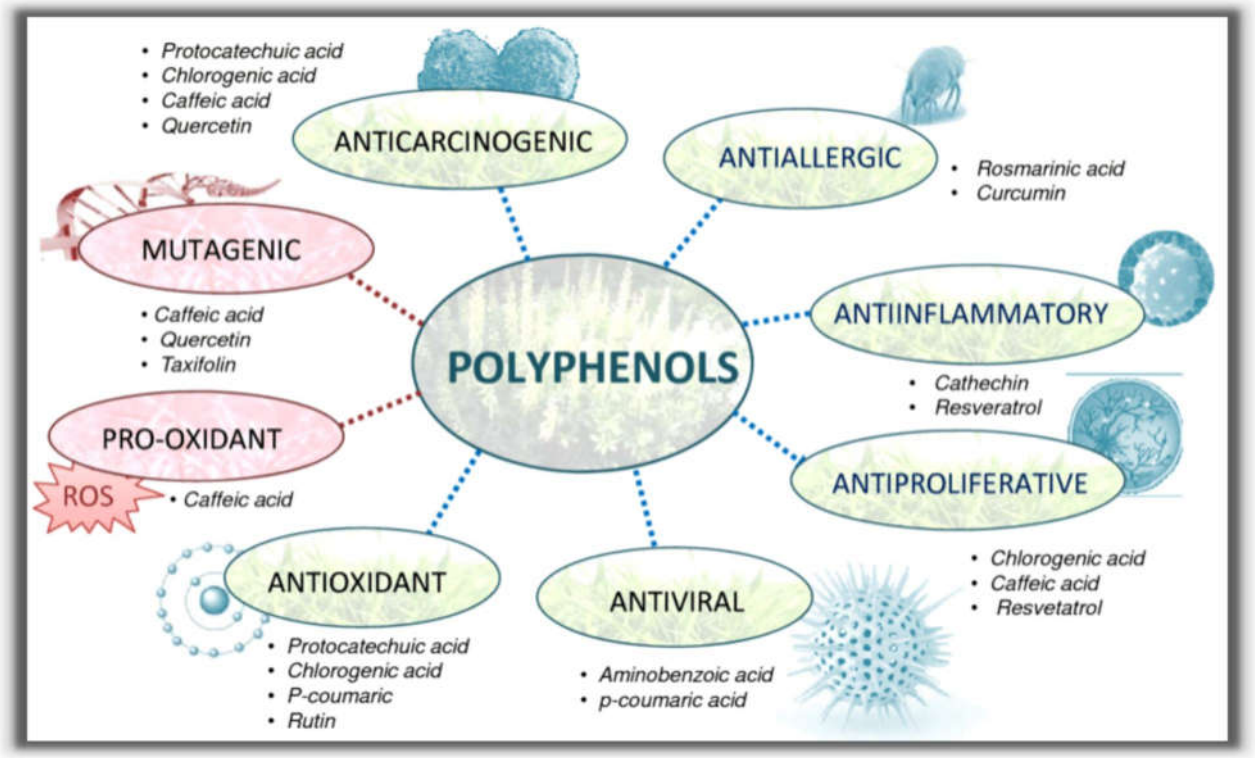

Figure 07 :Biological activities of polyphenols (**Martin and Andriantsitohaina, 2002**).

II.6. Biological effects of flavonoids

Flavonols are the major dietary flavonoid particularly abundant in fruits and vegetables (**McCarty, 2001**). Flavonoids have been reported to modulate key enzymes and receptors involved in signal transduction pathways of cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis, metastasis and reversal of multidrug resistance (**Baião *et al.*, 2017**). Several epidemiologic studies and intervention trials suggest that polyphenols present in fruits and vegetables are associated with decreased risk of cardiovascular diseases **(Rangel-Huerta *et al.*, 2015)**. It has been reported that flavonoids possess a number of biological effects such as antiallergic, anti-inflammatory, antiviral, anti-proliferative and anti carcinogenic activities (**Scalbert and Williamson, 2000; Parr and Bolwell, 2000**). Quercetin can suppress lipopolysaccharide-induced prostaglandin E2 production *in vitro*, but not *in vivo* (**Shen *et al.*, 2002)**. Anti-inflammatory effect of quercetin has been shown in several cell culture studies

(**Pelzer *et al.*, 1998; Ocete *et al.*, 1998; Sato *et al.*, 1997; Shen *et al.*, 2002**). but its mechanism of action has not been clear. (**Sedwick and Lees, 1986**).

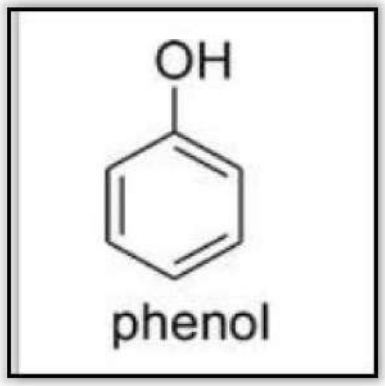

Figure 08: The structure of phenol.

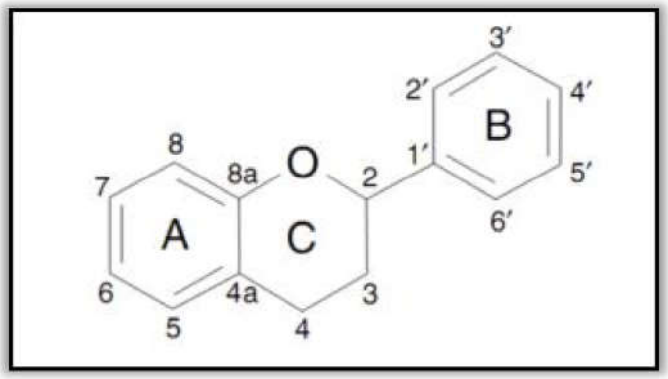

Figure 09: General structure of Flavonoids (**Irfan *et al.*, 2006**).

III. An overview of *Hammada scoparia*

III.1. Taxonomy of *Hammada scoparia*

Taxonomy is a major part of systematics that includes four components: **D**escription, **I**dentification, **N**omenclature, and **C**lassification (DINC) (**Simpson, 2019**).

III.1.1. Description

Hammada scoparia belongs to the **Amaranthaceae** family, which is composed of 2500 species spread over 183 genera (**Singh, 2019**). The **Amaranthaceae** consist of annual or perennial, hermaphroditic, dioecious, monoecious, or polygamous, herbs, vines, shrubs, or rarely trees. The leaves are simple, spiral or opposite, usually entire. The inflorescence is of solitary flowers, cymes, or thyrses, with bracts and bracteoles often bristle-like and pigmented. The flowers are bisexual or unisexual, hypogynous. The perianth is uniseriate, 3–5 [0–2], apotepalous, rarely basally syntepalous. The stamens are 3–5 [0–2], generally the same number as perianth parts, antitepalous, basally connate, forming a tube. Anthers are dithecal or monothecal (**Simpson, 2019**).

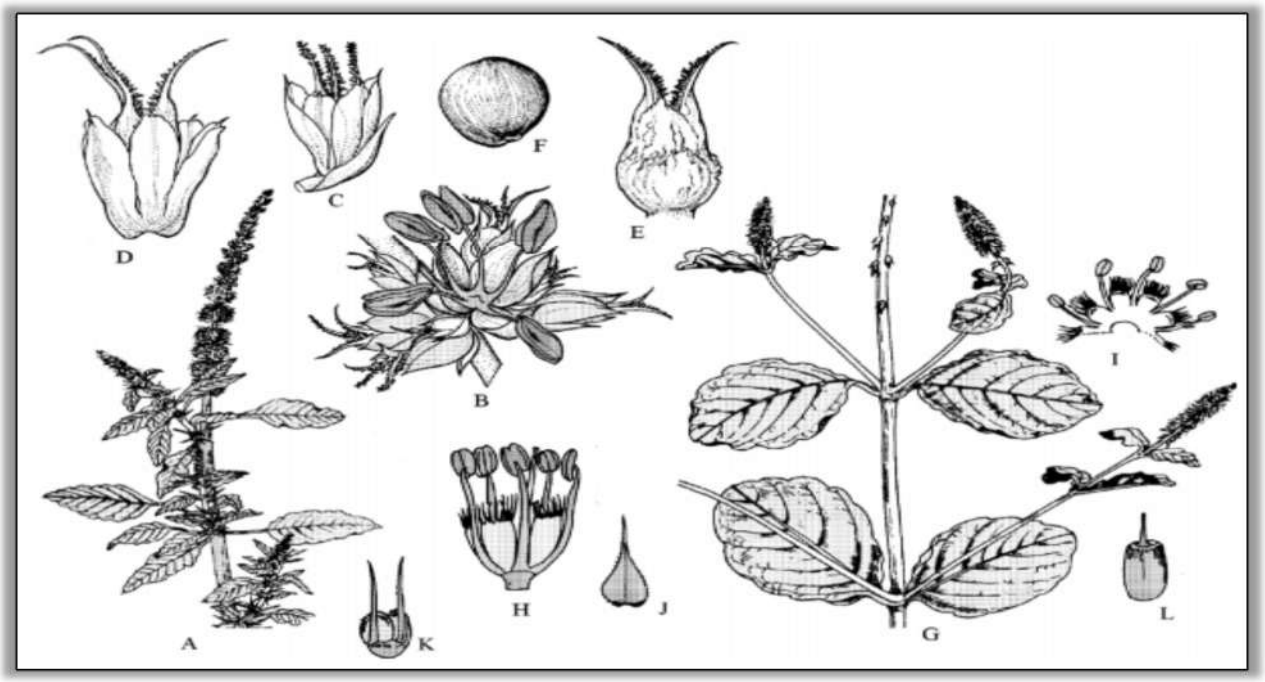

Figure 10: Amaranthaceae. Amaranthus spinosus. **A:** Part of plant in flower; **B:** Cymose cluster with one male and several female flowers; **C:** Female flower with 3 carpels; **D:** Mature fruit of same with enlarged persistent perianth; **E:** Mature utricle developed from flower with 2 carpels, perianth removed; **F:** Seed (**Peeking *et al.*, 1987**). Achyranthes aspera. **G:** Part of plant in flower; **H:** Flower with bract and perianth removed; **I:** Androecium showing stamens and staminodes; **J:** Bract; **K:** Bracteoles; **L:** Utricle with persistent style (**Singh, 2019**).

III.1.2. Identification

The plants are herbs, shrubs, sub shrubs and rarely small trees **(Mabberley, 1997).** Annual branches terete or obtusely 4-angled, jointed, slightly fleshy. Leaves opposite, sessile, linear, semiterete or clavate, fleshy, rarely subulate or scale-like, base slightly expanded, apex obtuse or with a short, acicular awn; leaf axil usually cottony. Perianth subglobose; five segments, orbicular to broadly elliptic, herbaceous, abaxially somewhat thickened, bearing a transverse, winglike process a little below apex in fruit, adaxially convex, margin membranous, apex usually recurved (**Miguel *et al.*, 2014**).Its flowers are discrete but at the end of the autumn, when humidity is sufficient, the end of its branches covers fruits surrounded by a crown of brilliant membranous and highly colored of pink or red. In Algeria, it is commonly known as «*Remth*» (**Taïr *et al.*, 2016**). It is a shrub with very numerous slender stems, which turn black when drying, with short flower spikes, fruits with brightly colored wings, often pink or red. It is a plant that is found in the arid and semi-arid regions of Algeria, and other regions of the Mediterranean, and also in the Near East. (**Ozenda, 1991 ; Quezel and Santa, 1963; EL Shazly *et al.*, 2003**).

Figure 11: Morphological appearance of HS ,(A): Stem; (B,C): Flowers; (D): Leaves; (E,F): aerial part (**Boucherit *et al.* 2018**).

III.1.3. Nomenclature

III.1.3.1. Scientific names: the species of *Hammada scoparia* has other names: *Hammada scoparia* (Pomel) Iljin, *Arthrophytum scoparium (Pomel) Iljin*, *Salsola articulata (Cav)*, *Haloxylon articulatum*.

III.1.3.2. Common (vernacular) names: Saligne à balai (in French), *Remth* (in Algerian Arabic).

III.1.4. Classification

According to the primary taxonomic ranks accepted by the International Code of Nomenclature for algae, fungi, and plants, *H. scoparia* is classified as below:

Table 03: The taxonomic of *H. scoparia* (**Mohammedi, 2013**).

Major Taxonomic Ranks	Taxa
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiosperm
Class	Magnoliopsid
Order	Caryophyllales
Family	Amaranthaceae
Genus	Hammada
Species	*Hammada scoparia pomel (Iljin)*

III.2. Geographical distribution

Subtropical Africa (Sahara, Egypte), Asia temperate and subtropical (Arabic, Jordanie, Iraq). Desert, steppe. (Algeria, Egypt, Iraq, Lebanon-Syria, Libya, Mauritania, Morocco, Palestine, Sinai, Tunisia, Western Sahara).(**Boulos, 1999**).

Figure 12 : Geographical distribution HS (Pomel) Iljin (**Boulos, 1999**).

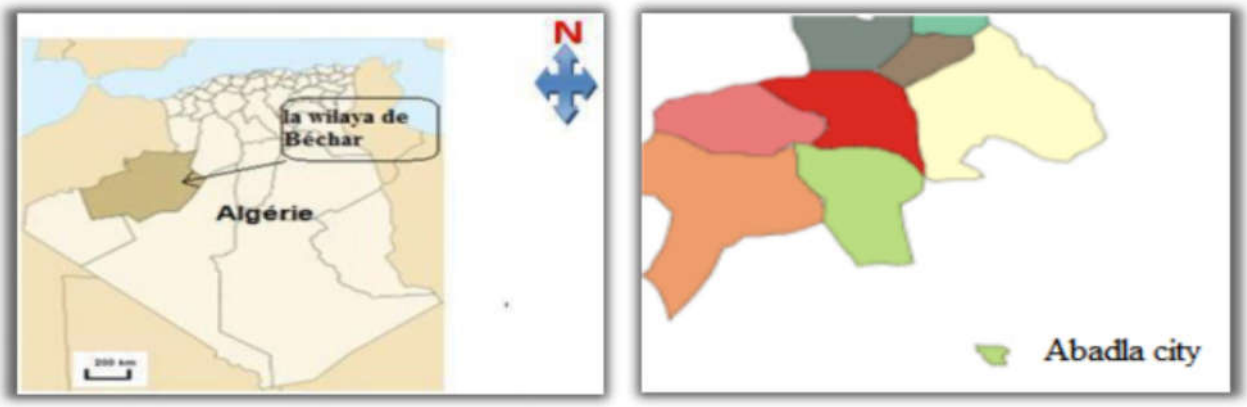

Figure 13: Location of HS in Abadla (Bechar southwest of Algeria) (**atlas-sahara.org**).

III.3. Chemical composition

Hammada species contain sterols, flavonoid glycosides, and pyranones and volatile oils (**Li *et al.*, 2010**). HS contains polyphenols, saponosides and more particularly alkaloids (**Mohammedi, 2013**). Extensive study of this plant material has now led to the isolation of eight minor alkaloids and one flavonoid. Several alkaloids, including four isoquinolines (isosalsoline, salsolidine, dehydrosalsolidine, and isosalsolidine), an isoquinolone (N-methylcorydaldine), tryptamine, N-omega-methyltryptamine, and a betacarboline (tetrahydroharman) have been extracted for this plant. Additionally, some flavonoids have been identified as isorhamnetin-3-O-beta-D-robinobioside (**Kharchofa *et al.*, 2020**). Another analysis of flavonoid-enriched HS extract indicated the presence of isorhamnetin–xylose–galactose, quercetin–xylose–rhamnose–galactose, and quercetin–glucose–rhamnose (rutin) **(Bourogaa *et al.*, 2011; Lamchouri *et al.*, 2012**). HS has been described as a plant rich in alkaloids (**Carling and Sandberg, 1970**). The bibliographic research carried out on the species HS of the family of Amaranthaceae, showed the richness of the latter in alkaloids (**Benkrief *et al.*, 1990**), in saponosides (**Aynehchi *et al.*, 1981**), and flavonoids (**Benkrief *et al.*, 1990; Farnsworth *et al.*, 1966; Paris *et al.*, 1968**). In figures (14) and (15) , we report as an example some compounds isolated from this species:

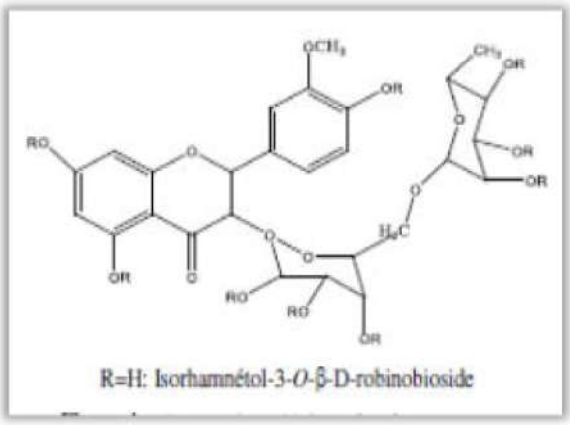

Figure 14 : Flavonoid isolated from HS.

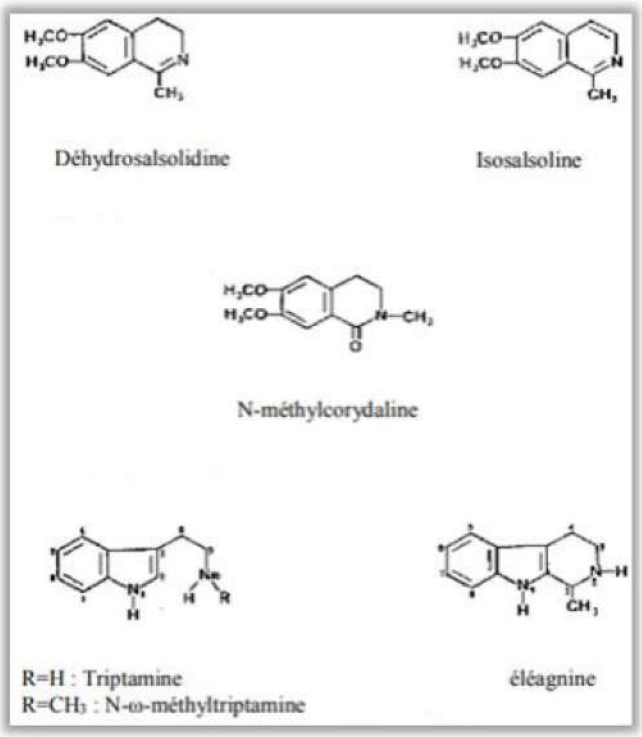

Figure 15 : Example of alkaloids isolated from HS (**Belhadj *et al.*, 2015**).

III.4. Traditional and medicinal uses

Hammada scoparia is a common herb amongst practitioners, herbalists, and users. This popular plant is widely used as a decoction, infusion, or cataplasm to treat various ailments. It has frequently used in the treatment of hypertension,cutaneous neoplasms, dermatitis, diabetes, food poisoning, rheumatoid arthritis, osteoarthritis, scabies, injury healing, indigestion, stomachache, gastroenteritis, and cold (**Fakchich, 2014; Abouri *et al.*, 2012; Eddouks *et al.*, 2002**). Moreover, the plant is also used as an antidote of scorpion stings and snakebites (**Abouri *et al.*, 2012**). The leaves, infused or decocted, are used as a mouthwash to treat mouth diseases and toothache (**Ghourri *et al.*, 2012**). Pharmacological studies have shown that the plant has antimicrobial, antioxidant activities, larvicidal activity, cytotoxic and antimalarial activities, molluscicidal activity, anticancer properties, reno-protective, and hepatoprotective effects. Furthermore, a recent study suggested that HS extract could possibly restore the altered neurological capacities and antioxidant power in rats (**Taïr *et al.*, 2016**). It is used to treat numerous human diseases especially infectious (skin infections, urinary and genital infections), Rheumatism, diabetes, cancer, infertility, hair problems and stomach disorder (**Allaoui *et al.*, 2016; Fatehi *et al.*, 2017**). It is a plant used in traditional medicine as a remedy for the treatment of eye and vision disorders, skin diseases, diabetes mellitus (**Bellakhdar, 1997; Allali *et al.*, 2008**). *H. scoparia* leaves were used in traditional medicine as antiseptic to hasten wound

healing, and bark powder reduces scars (**El-Shanawani, 1996**), anti-cancer and anti-plasmodial activities (**Sathiyamoorthy *et al.*, 1999**), and anti-leukemic agent (**Bourogaa *et al.*, 2011**). And anticoagulant in laboratory animals (**Awaad *et al.*, 2001**). The aqueous extract of HS showed antiplasmodium (**Sathiyamoorthy *et al.*, 1999**). In addition, the volatile oil of *Haloxylon schmittiana* has also been studied, and shown to exhibited antimicrobial activities against Bacillus subtilis and Staphylococcus aureus (**Lamchouri.F *et al.*, 2012**). In Oman the stems of this species are used as a mordant for dyeing wool in traditional weaving (**Lamchouri *et al.*, 2012**). Hepato-protective and antioxidant activities have been linked to the presence of phenolic compounds in the plant (**Bourogàa *et al.*, 2014**) Another study, it was demonstrated that *Hammada scoparia* is able to trigger a pro-apoptotic process against leukemic cells with a chemo-resistant character, and the molecules responsible are the flavonols triglycosides "Rutin" (**Bourogaa *et al.*, 2011**). Recently an ethanolic extract of HS, showed *in vitro* melanogenesis inhibition activity, this activity was attributed to catechol and tetrahydroisoquinolinic derivatives (**Chao *et al.*, 2013**).

IV. The laboratory rat

The use of Wistar rats in biomedicine dates back to 1828 and the first breeding experiments were performed in 1870. In the year 1906, the Wistar Institute developed the Wistar rat model. These animals are easily available. They are simple to rear and breed. They are characterized by long ears, long body, wide head, and short tail. They find an important role in the study of CNS drugs, anticancer, antidiabetic, anti-inflammatory drugs, and immunomodulators (**Festing, 2016**).

IV.1. Rat models

Rattus norvegicus (brown rat, 2n = 42) was commonly found in Europe in the 1700s. Today's laboratory rats are the domesticated descendants of wild brown rats. Albino animals were held and used for rat shows, and frequent handling is thought to have tamed these animals (**Sharp and Villano, 2012**).

Rats are genetically classified as outbred stocks, inbred strains, or genetically engineered. Outbred stocks are valuable in modeling natural populations that inherently possess genetic diversity. Three of the most common outbred stocks of rats used in research are the Sprague-Dawley, Wistar, and Long-Evans. Sprague-Dawley and Wistar rats are albinos, in contrast to the Long-Evans which is hooded (color on the head and shoulders with a pigmented dorsal stripe) (**Colby *et al.*, 2019**).

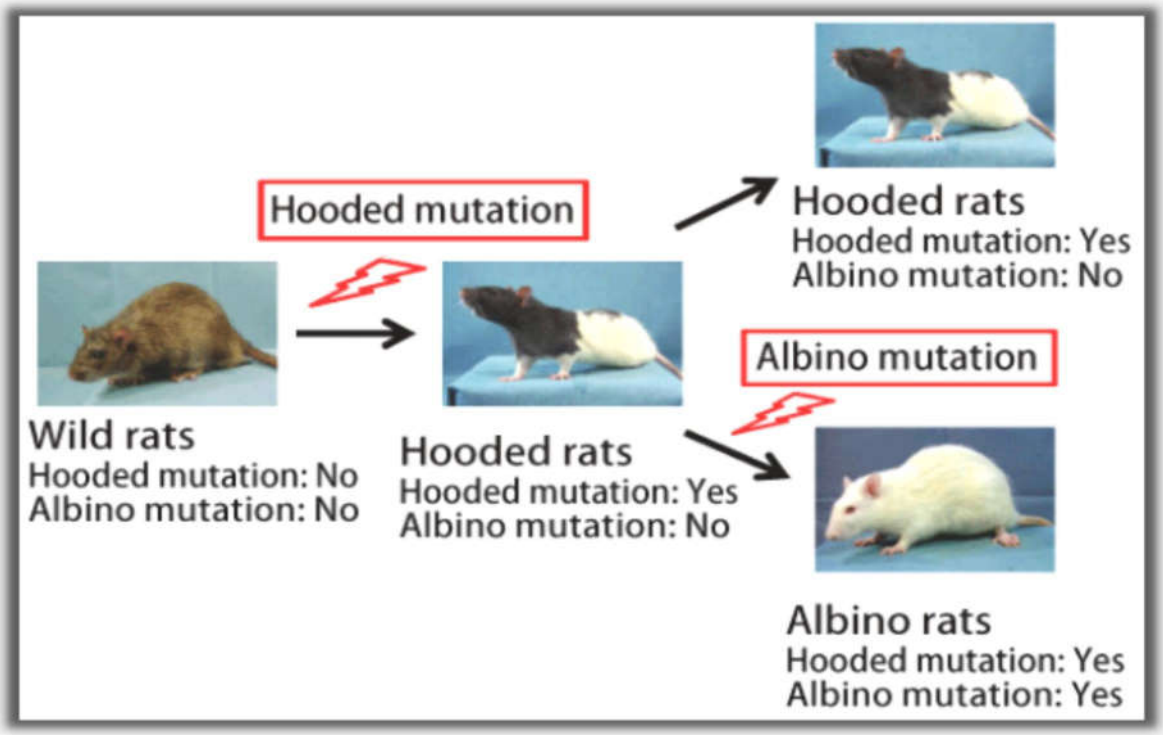

Figure 16 : Relationship between the albino and hooded rats **(Takashi, 2012)**

IV.2. Taxonomy

The order Rodentia is the largest order of living Mammalia with 2277 species placed in 28 families or approximately 42% of worldwide mammalian biodiversity (**Carleton and Musser, 2005**). Within the order of Rodentia, Wistar rat is one of many species named collectively the laboratory rat.

Table 04 Taxonomy of the laboratory rat **(Sharp and Villano, 2012).**

Major Taxonomic Ranks	Taxa
Kingdom	Animal
Phylum	Chordata
Class	Mammalia
Order	Rodentia
Family	Muridae
Genus	*Rattus*
Species	*norvegicus*

IV.3. General Characteristics

The laboratory rat generally has short hairs and a long, hairless, scaly tail. The ears are round and erect. The mouth has a pointed snout with a long whisker (vibrissae). Front and hind feet have five digits each with sharp claws (Figure 17). They have moderately long legs and can stand upright on their two rear legs. The soles of hind feet have fleshy footpads. Self-grooming is an innate behavior and a most frequently performed activities in rodents (**Kalueff *et al.*, 2015**).

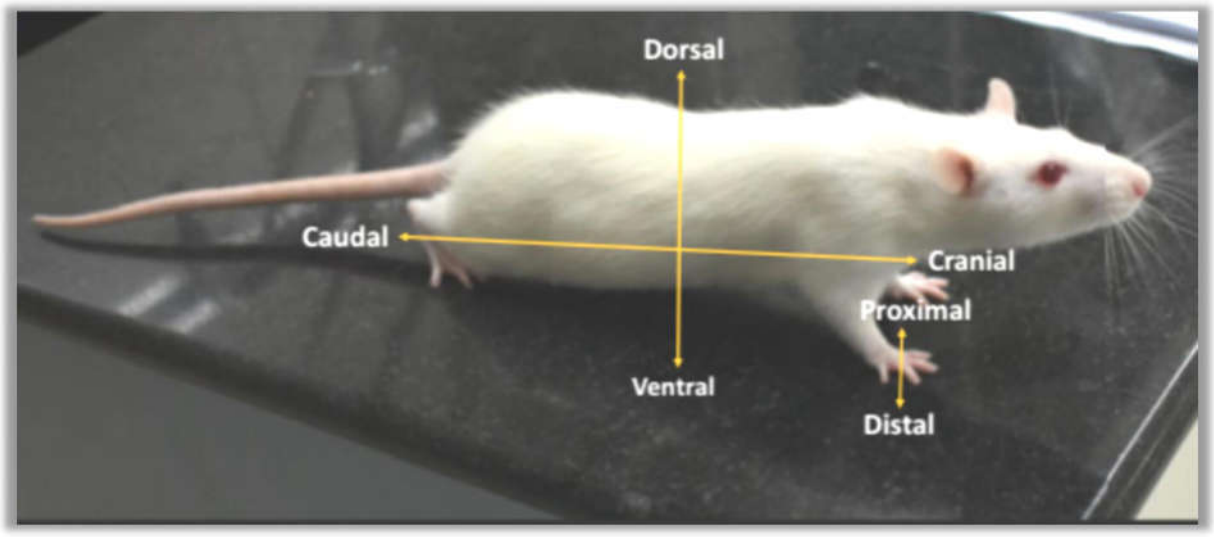

Figure 17: Directional terms **(Chawla and Jena, 2021)**

IV.4. Anatomical and physiological features

The laboratory rat is commonly used as an experimental model in biomedical research. Characteristics such as short life span, ease of breeding, short generation time, and requirement of smaller space have made laboratory rats as the most commonly used experimental animals along with mice in the field of basic and applied research **(Chawla and Jena, 2021)**.

This section briefly summarizes the following rat's anatomical and physiological characteristics: Nutrition, digestive system, and reproduction.

IV.4.1. Nutrition

The rat is a good animal model for studying nutrition because it is sensitive to a variety of nutrient deficiencies. Vitamin A, vitamin E, vitamin K, riboflavin, and thiamine deficiency can cause infertility, skin disease, or bleeding. Rats can store fat-soluble vitamin B12 effectively, produce vitamin C, and supply most of its needs for vitamin B by eating fecal matter. In addition, the rat is commonly used for studying calcium and phosphorus metabolism (**Liu and Fan, 2017**). The food given to the animals should be free from any type of contamination and should have high nutrition value. The food should be easily palatable and convenient, accessible to the animals at all times, or as specified in the animal study protocol. Importantly, the food should be available in proper and sufficient amount so that it helps in the proper growth of the animals, particularly during the reproduction as well as the lactation phase (**Damron, 2013**).

IV.4.2. Digestive system

The rat dental formula is 2(1 1/1, C 0/0, PM 0/0, M 3/3) = 16. The incisors are well developed and grow continuously. Rats have three pairs of salivary glands in the head and neck region **(Chawla and Jena, 2021)**. The esophagus is a distensible and muscular tube like other mammals that connect the pharynx and stomach. The esophagus transports food toward the stomach aided by the peristaltic movement (**Wilson and Reeder, 2005**). The stomach lies in the left, anterior part of the abdominal cavity, its anterior surface is overlapped by the liver and the left costal margin. To the left the stomach is in contact with the spleen. Visceral peritoneum covers the anterior and posterior surfaces of the stomach except for two narrow strips along the greater and lesser curvatures where an enveloping double layer of peritoneum separates to cover the anterior and posterior surfaces of the organ (**Maynard and Downes, 2019**). The terminal part of the stomach tract is connected to the duodenum at the pyloric ring. Protein digestion begins in the stomach by HCL and enzyme pepsin **(Chawla and Jena, 2021)**. The small intestine is composed of the duodenum (10 cm), jejunum (100 cm), and ileum (3 cm). The colon is composed of the ascending colon, followed by a short rectum that is confined to the pelvic canal. The liver has four major lobes (median, right lateral, left, and caudate) and is capable of regeneration

subsequent to partial hepatectomy. The rat has no gallbladder. The bile ducts from each lobe form the common bile duct that enters the duodenum (**Aitman *et al.*, 2008; Brenin, 1997; Buehr, 2008**).

IV.4.3. Reproduction

In general, rats reach puberty between 2 and 3 months of age, and are normally not bred until about 3 months of age. Females are continuously polyestrous, spontaneous ovulators with an estrous cycle length of 4–5days. Outbred stocks regularly achieve conception rates greater than 85%, while a lower rate is common in inbred strains. Nonfertile matings and cervical stimulation can induce a pseudopregnancy of 12–14days duration (**Colby *et al.*, 2019**). Rat gestation is 19–23 days (an average of 21 days) with a litter size of 6–12 pups (**Liu and Fan, 2017**).

IV.5. Common routes of injection and oral dosing procedures

Compared with conventional administration routes, laboratory animal administration routes can be divided into three types: transdermal administration, enteral administration, and parenteral administration (**Liu and Fan, 2017**).

The routes for the administration of substances include intravenous (i.v.), intraperitoneal (i.p.), intramuscular (i.m.), subcutaneous (s.c.), intragastric (i.g.), inhalatory, and through drinking of water. These routes allow the administration of exact amounts of substances in solution or suspension. The inhalatory route is the exception, and it is useful in the case of gaseous and volatile substances (anesthetics, hydrogen, oxygen, etc.) (**Rigalli and Di Loreto, 2016**).

Figure 18: Subcutaneous injection (**Sobhi, 2015**)

Figure 19: Gastric gavage.

Figure 20: Intraperitoneal injection (IP).

Figure 21: Intravenous injection.

Figure 22: intramuscular injection.

IV.6. Blood collection

Blood may be collected from many different sites in the rat (Table 05). Survival blood collection sites include the tail, jugular, saphenous, and dorsal metatarsal veins; vena cava, and orbital plexus. Specific nonsurvival techniques would include open thoracic and abdominal puncture of vasculature, the heart, and decapitation. Serial blood samples may be collected through the above survival techniques or through the use of indwelling jugular or femoral catheters (**Sharp and La Regina, 1998**).

Table 05: Blood Collection Site and Blood Capacity of rats (**Liu and Fan, 2017**)

	Blood Collection Site	**Blood Capacity (mL)**	**Measures of Blood Collection**
Partial blood collection	Caudal vein	0.3–0.5	
	Caudal artery	0.5–1.0	
	Saphenous vein	0.1–0.3	
	orbital venous plexus	0.5–5.0	Anesthesia
Whole blood collection	Jugular vein	3.0–5.0	Anesthesia, operation
	Decollation	5.0–10.0	
	Heart	3.0–5.0	Anesthesia, operation

EXPERIMENTAL PART

I. *In vitro* experiments

I.1. Plant material

The aerial part of *Hammada scoparia* (HS) was collected in November 2021 from the district of Abadla, Bechar region. The collected plant was washed with water and dried within a solar dryer in the Research Unit in Renewable Energies in Saharan Medium (URER.MS) of Adrar as described by **Loumani *et al.* (2020)**. After that, plant was chopped in mortar and pestle and then, grinded in a household electric grinder.

Figure 23: Dryer

I.2. Reagents and solvents

All reagents and solvents used in our study are listed in the table below.

Table 06: List of reagents and solvents

Reagents , solvents	Formula
Acetic acid	CH_3COOH
Ferric chloride	$Fecl_3$
Ferric chloride	$FeCl_2$
Ammonia/Ammonium hydroxide	NH_3 / NH_4OH
Sulphuric acid	H_2SO_4
Ethanol	CH_3-CH_2-OH
Potassium iron cyanide	$C_6FeK_3N_6$
Catechols	$C_{15}H_{14}O_6$
Chloroform	CH C_{l3}

Reagents , solvents	Formula
Acetic anhydride	$C_4H_6O_3$
Potassium hydroxide	KOH
Gallic acid	$C_7H_6O_5$
Carbonates de Sodium	Na_2CO_3
Methanol	CH_3OH
Ascorbic Acid,	$C_6H_8O_6$
Vanillin	$C_8H_8O_3$
Zoletil$_{100}$	$C_{12}H_{17}NOS$
DPPH	$C_{18}H_{12}N_5O_6$

I.3. Measuring moisture using a convection oven

I.3.1. Principle

Water is measured in a sample by determining the loss in weight for the sample after it has been dried in a convection oven. The method requires only a small amount of homogeneous sample and can measure an effective range of 0.01% to 99.99 %water.

I.3.2. Procedure

Moisture was measured according the method of **Wrolstad *et al.* (2005)** as follow:

a. Pyrex Petri dishes were dried for at least 1 h at 105°C. After that, dishes were cooled for 30 min in a desiccator before using;
b. Empty dried dishes (with cover) were weighed to nearest 0.1 mg.
c. After addition of 3 g of homogeneous sample to dish, its weight, with cover, was measured to nearest 0.1 mg;
d. Dish with sample was placed into oven at 105°C for 4 h;
e. Dish with dried sample was removed and cooled 30 min in a desiccator;
f. Cooled dish with dried sample was weighed;
g. Dish with sample was returned to oven, for another hour, cooled, and reweighed.
h. If weight has not changed, test is done. If weight is lower, drying continued for 1h periods and reweighed until constant weight is achieved.
i. Moisture was calculated as the percent loss in weight after drying with the following

$$\textbf{Moisture content (\%)} = \frac{W2 - W3}{W2 - W1} \times 100$$

Where:

W1 = weight of cooled covered dish

W2 = weight of covered dish with sample before drying

W3 = weight of covered dish with sample after drying

Figure 24: Pyrex Petri dishes with samples in a desiccator

I.4. Preparation of plant extract

In the present study, HS powder was infused in boiling distilled water at the ratio of 5% (w/v) for 15 min at room temperature (25 ± 2 °C) with constant stirring. The mixture was centrifuged at 9000 rpm for 30 min and the supernatant was collected, and then evaporated under reduced pressure in a rotary evaporator at 45°C to dryness using (Nahita rota-vapor). The dried extract was resuspended in methanol. This crude extract was subjected to further quantitative phenolics assessment.

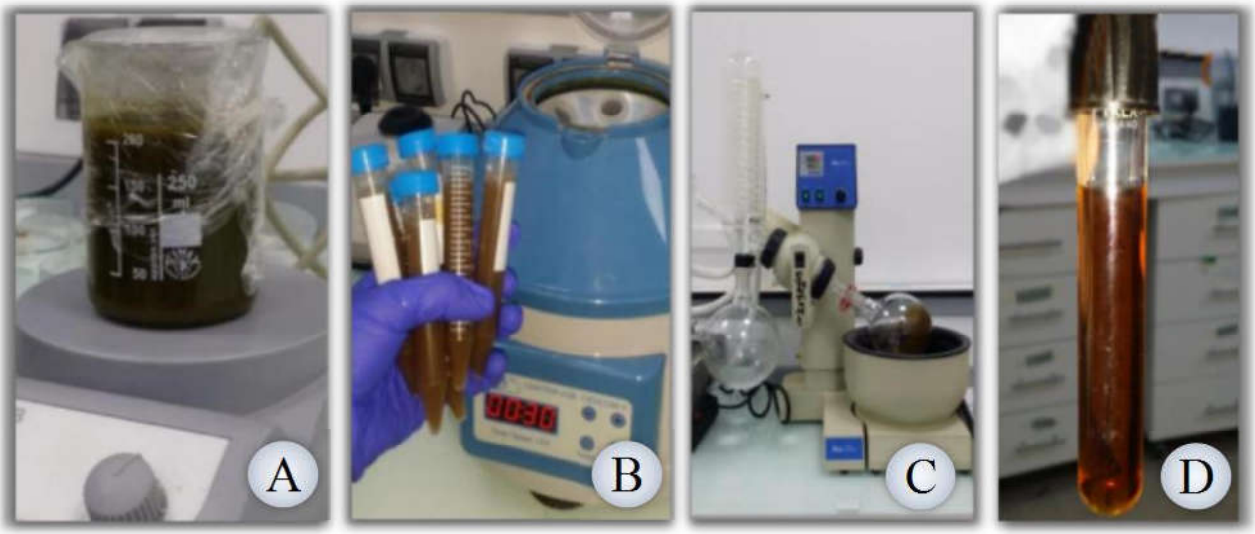

Figure 25: Extraction steps: (**A**): infusio; (**B**): centrifugation; (**C**): evaporation, (**D**): crude extract.

I.5. Qualitative tests for preliminary phytochemical screening

The presence of phytoconstituents such as glycosides, flavonoïdes, steroids and saponines were confirmed by employing the following standard procedures.

I.5.1. Phenols

Equal quantity of aqueous ferric chloride (1%) was mixed with potassium iron cyanide (1%). The equal amount of the reagent and plant extract was mixed. The appearance of blue-green color indicates a positive result **(Rissala *et al.*, 2019).**

I.5.2. Flavonoïdes

The detecting solution was prepared by mixing 10 mL of ethanol (50%) with 10 mL of potassium hydroxide (50%), and then 5 mL of this solution was added to 5 mL of the plant extract. The appearance of yellow color was an indicator of the presence of flavonoïdes (**Risala *et al* ., 2019**).

I.5.3. Tannins (Gallic tannins, Catechic tannins)

One milliliter of extract was mixed with 10 mL of distilled water and filtered. Ferric chloride ($FeCl_3$) 1% reagent (3 drops) was added to the filtrate. A bleu–black or green precipitate confirmed the presence of the Gallic tannins or catechol tannins respectively (**Karumi *et al.*, 2004**).

I.5.4. Saponins

This method was done according to the method described by (**Harbone, 1984**). Two methods detected saponins: 3 mL of the extract were put in a tube then shaken vigorously for 2min, the formation of more or less important foam (more than 1cm in height) indicates the presence of saponoside. 5 mL solution of plant powder was added to 1-3 mL of 3% ferric chloride solution. The development of white precipitate shows a positive effect (**Risala *et al*, 2019**).

I.5.5. Terpenoids (Salkowski test)

To each 0.5 g of the extract 2 mL of chlorofrom was added. Concentrted H_2SO_4 (3mL) was carefully added to form a layer. A reddish brown colouration of the interface (**Ayoola *et al*,. 2008**).

I.5.6. Steroids

One mL of a solution of plant powder participated in a few drops of chloroform, and then a drop of acetic anhydride and a reduction of concentrated sulphuric acid were added, brown precipitate

appeared which represents the presence of terpenes. The appearance of a dark blue color after few minutes indicates the presence of steroids (**Risala *et al*, 2019**).

I.5.7. Glycosides

I.5.7.1. Cardiac glycoside (Keller-Killiani test)

To 0.5 g of extract diluted to 5 mL in water was added 2 mL of glacial acetic acid containing one drop of ferric chloride solution. This was underlayed with 1 mL of concentrated sulphuric acid. A brown ring at the interface indicated the presence of a deoxysugar characteristic of cardenolides. (**Ayoola *et al*,. 2008**).

I.5.7.2. Anthraquinone glycoside (Borntrager's test)

To the extract solution (1mL) , 5% H_2SO_4 (1mL) was added. The mixture was boiled in a water bath and then filtered. Filtrate was then shaken with equal volume of chloroform and kept to stand for 5 min. Then lower layer of chloroform was shaken with half of its volume with dilute ammonia (10%). The formation of rose pink to red color of the ammonia cal layer gives indication of anthraquinone glycosides (**Joshi *et al.*, 2013**).

I.5.8. Alkaloids

A volume of 1.5 mL of aqueous extract was mixed whith 0.5 mL of HCL à 1%. A few drops of **Wagner** reactive will added, the development of brown precipitate indicate the present of alkaloids (**john *et al.*, 2015**).

I.5.9. Reducing sugars

Five mL of extract was mixed with a volume of Fehling and boiled in a water bath 100 °C. The appearance of red precipitate induct the presence of Reducing sugars (**Fehling, 1849**).

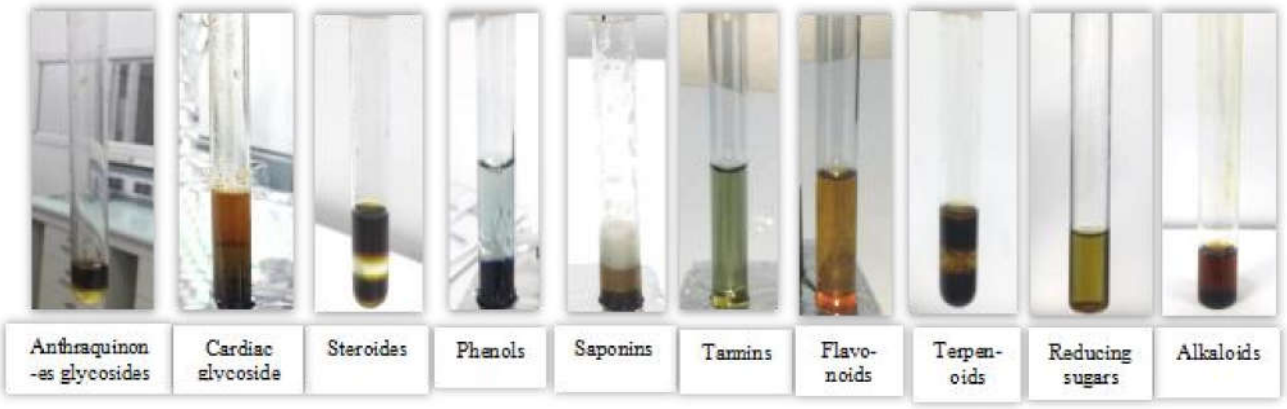

Figure 26: Tests of phytochemical screening.

I.6. Phytochemical analysis

I.6.1 Determination of total phenolics by Folin-ciocalteu colorimetry (TPC)

✓ **Principle:**

Folin-Ciocalteau (FC) colorimetry is based on a chemical reduction of the reagent, a mixture of tungsten and molybdenum oxides. The products of the metal oxide reduction have a blue color that exhibits a broad light absorption with a maximum at 765 nm. The intensity of light absorption at that wavelength is proportional to the concentration of phenols (**Giusti, 2005**).

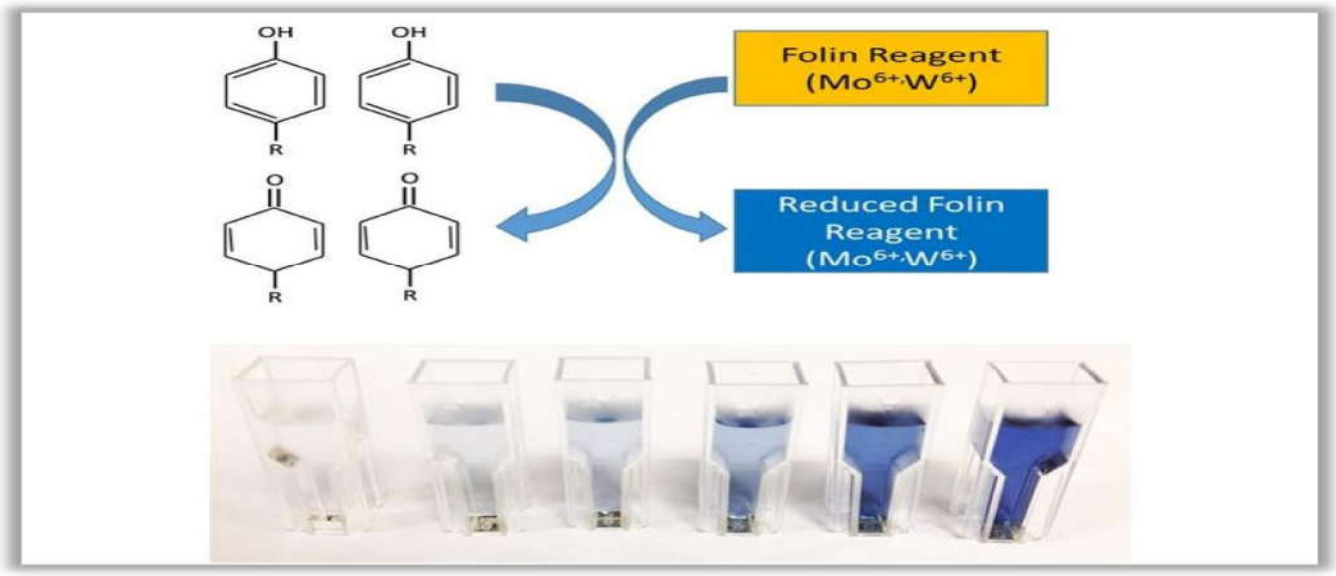

Figure 27: Determination of polyphons contents by Folin- Ciocalteu.

✓ **Procedure:**

The total phenolic content of the extract was determined by the Folin–Ciocalteu(1927) method as follow:

- ✧ To 500 µL of the extract of each sample we added: 2500 µL Folin-ciocalteu (diluted 10x) plus 2000 µL Na_2CO_3 at 7.5%
- ✧ the well stirred mixture is incubated in the dark for 1 hour at 20°C.
- ✧ The reading of the absorbance is made against a blank at 765nm with a UV-Visible spectrophotometer.

For calibration curve, 3 mg of gallic acid are weighed, and then mixed in 10 ml of 99.6% methanol; it is the stock solution with a concentration of 0.3 mg/ml:

- ✧ From this stock solution, the following dilutions were prepared: 0.21 – 0.15 – 0.105 – 0.075 – 0.06 – 0.045 – 0.024 mg/ml.
- ✧ Then 500 µL of each concentration are treated with the same procedure as that of the samples.

Figure 28: Increasing of (GA), a satantadrd for estimation of (TPC)

I.6.2. Determination of Flavonoids contents (TFC)

✓ **Principle:**

To determine total flavonoid content from crude extract, an assay based on the aluminium chloride colorimetric and sodium hydroxide method. Aluminum trichloride forms a yellow complex with flavonoids, and sodium hydroxide forms a pink complex that absorbs in the visible range of 510 nm (**Ardestani and Yazdanparast, 2007**).

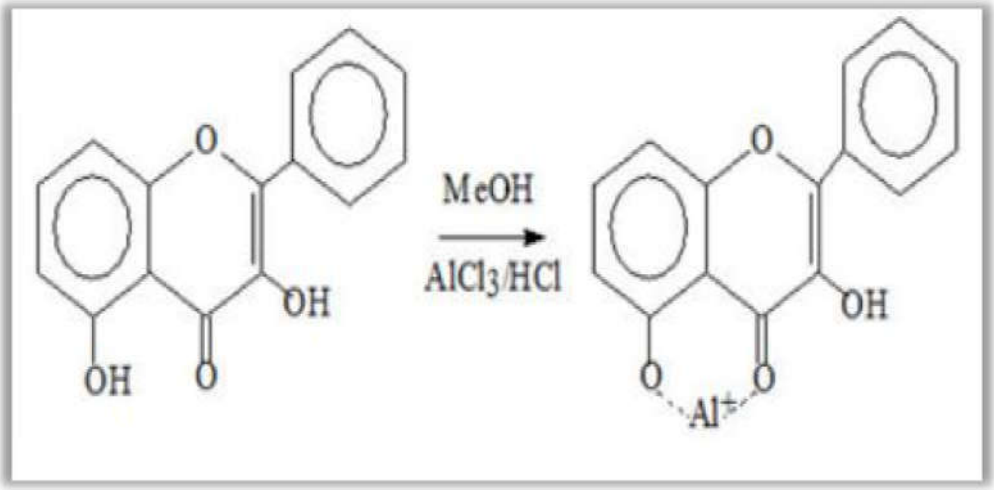

Figure 29: Reaction of 5-hydroxy-flavonol with AlCl3/HCl

✓ **Procedure:**

Total flavonoids content was assayed by colorimetry as follows:

- ✧ 700 µL of crude extract were put in a test tube, to which were added 2000 µL of distilled water, and then 150 µL of 15% $NaNO_2$.
- ✧ After two consecutive intervals of 6 min, 150 µl ($AlCl_3$, $6H_2O$) at 10% and 2000 µL NaOH at 4% were added.
- ✧ The tubes are incubated for 15 min at room temperature.
- ✧ The absorbance was measured at 510 nm.

Standard catechin calibration curve has been established as follows :

- ✧ Stock solution of catechin at 0.4 mg/mL was prepared by dissolving 4 mg catechin in 10 mL of methanol. From this stock solution, we prepared dilutions of different concentrations: (0.36-0.28-0.2-0.12-0.08-0.04) mg/mL
- ✧ 700 µL of each concentration was treated similarly to samples, and then absorbances were measured at 510 nm.

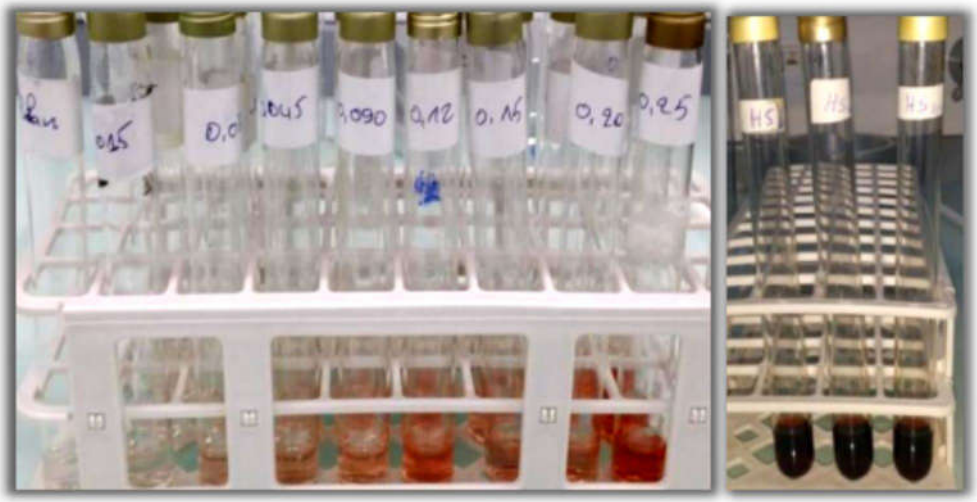

Figure 30: Increasing of (catechin), a satantadrd for estimation of (TFC)

I.6.3. Determination of condensed tannins (Vanillin Assay)

The total tannin content was measured using the modified vanillin assay described by **Sun *et al.*, (1998)**. A total of 3 mL of 40% methanol vanillin solution and 1.5 mL of concentrated H_2SO_4 were added to 50 µL of syitably diluted sample. The mixture was kept for 15 min, and the absorbance was measured at 500 nm against methanol as a blank. The amount of total condensed tannins was expressed as milligrams of catechin equivalent par gram of dry weight (mg of CE/g of DW) through the calibration curve with catechin Triplicate measurements were taken for all samples.

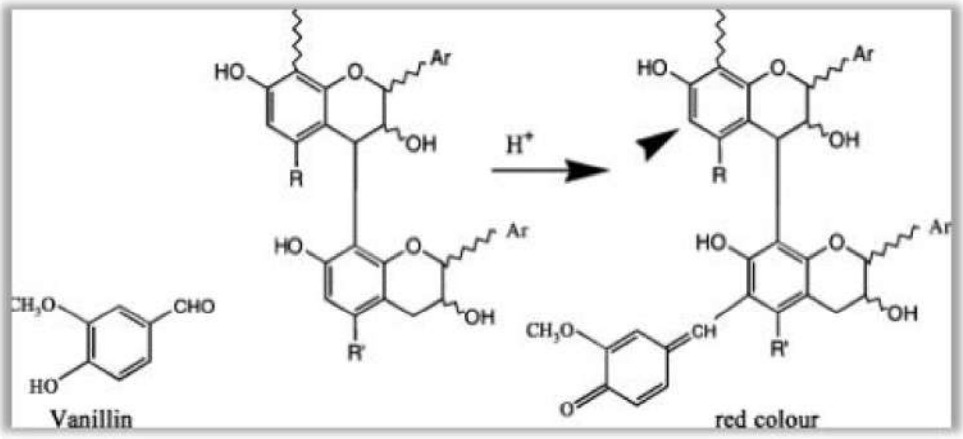

Figure 31: Chemistry of the vanillin assay for condensed tannins

Figure 32: Increasing of (vanillin), a reference for estimation of (Tannin).

I.6.4. DPPH antioxidant power assay

The DPPH (2,2-diphenyl-l-picrylhydrazyl) assay uses the stable DPPH free radical. It has an extra electron that is delocalized on the whole molecule and does not dimerize as other free radicals do (**Molyneux, 2004**). This method is measured at ambient temperature to avoid thermal degradation. Electron delocalization generates an intense purple color with maximum absorption (λ max) at 515 nm. If the radical is reduced, the purple color and absorption at λ max decrease, with depends on the concentration of the antioxidant. The DPPH assay involves mixing the sample of interest with a DPPH radical solution (50 µM) at 40:1 proportion (0.1 mL of sample with 3.9 mL of radical solution) using methanol as solvent (**Brand-Williams *et al.*, 1995**). The mixtures are incubated for 5-30 minutes, and the absorbance is read at 55-520 nm. Radical scavenging percentage is calculated as follows:

% inhibition of DPPH radical = ((Abs initial-Abs final)/ initial Abs)* 100

Where Abs initial is the absorbance before the reaction and Absorbance after the reaction. The mechanism of action of the DPPH assay is mixed HAT and SET (**Apak *et al.*, 2016**).

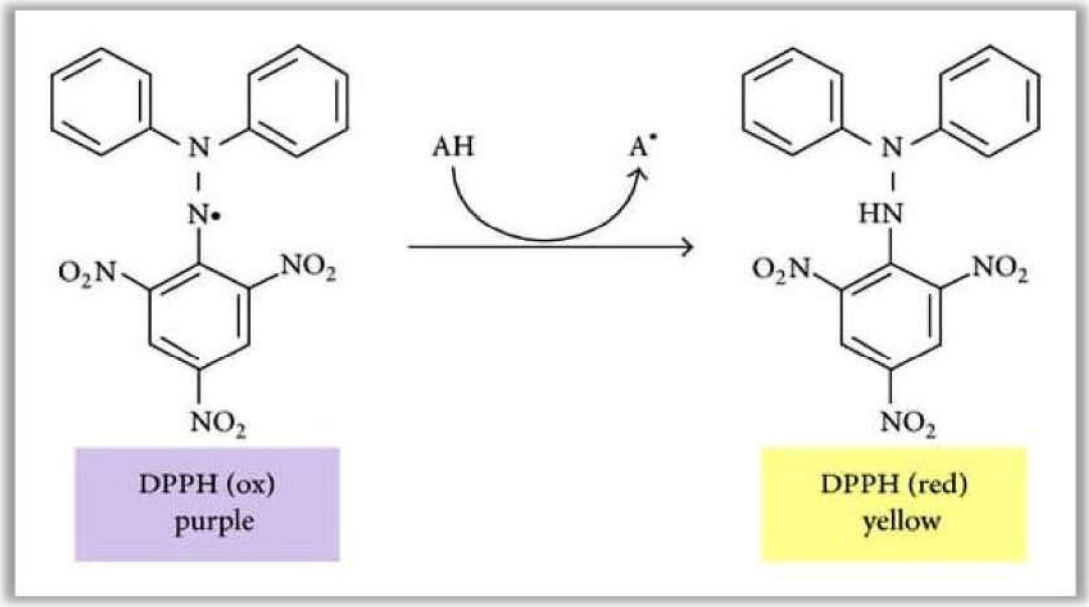

Figure 33: DPPH assay. The decolouration reaction brought by the radical scavenging module (active agent).

Figure 34: Increasing of (DPPH) a satantadrd for estimation of antioxidant power assay.

II. *In vivo* experiments

II.1. Preparation of carrageenan

λ-Carrageenan, type IV (Sigma, USA) Carrageenan is a polysaccharide isolated from two species Girgartina aciculaire and G. pistillata, which grow together in the sea (**Lokesh *et al.*, 2014**).

500 mL sterile 0.9% saline were poured into a 1-liter beaker with a stir bar. 2.5 g (0.5%) carrageenan powder were added to the beaker. Heat the solution to 90 ◦C with stirring, but do not allow the solution to boil. Heating the mixture helps to dissolve the carrageenan. It should take less than an hour to dissolve all of the powder. Pour the solution into a clean 1-liter glass bottle equipped with a cap and sterilize by autoclaving. Cool the solution to room temperature and aliquot into sterile, 100-mL capped bottles. This solution is stable for at least a week when stored at 4°C following preparation (**Fehrenbacher *et al.*, 2008**).

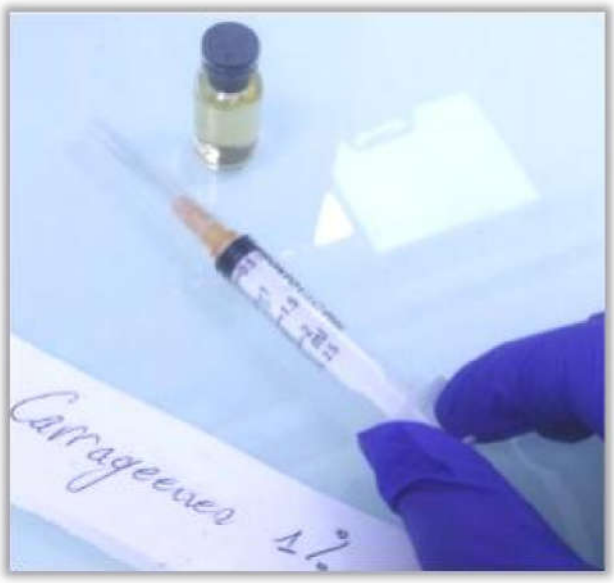

Figure 35: Carrageenan 1%

II.2. Animals and treatments

Experiments were performed on healthy Wistar Albino rats stock were housed in polypropylene cages, with not more than four animals per cage and maintained at standard environmental conditions (12 hrs dark/light cycles; temp 23±2°C, 35-60% humidity, air ventilation) and were fed with standard pellet diet (supplied by the Industrial Society of Concentrates (Ain-Fezza, Tlemcen) and water, allowed free access to diet and water and received human care according to the guidelines of National Institute of Health (**NRC, 1996**).

Experiments were performed on 20 female Wistar Albino rats stocks (160-200 g), The rats were acclimatized to laboratory conditions ,weighed, marked and subjected to fasting for 16 h overnight before the experimental schedule. Than they were divided into 5 groups:

- ✧ Healthy control group (n=4)
- ✧ One hour before carrageenan (100ul:1%) injection ,each group was treated as follow:
- ✧ Untreated group (n=4): Solution of NaCl 0.9%
- ✧ Reference group (n=4): Rats treated intra-peritoneally with an anti-inflammatory diclofenac (5mg/kg).
- ✧ Oral administration group (n=4): The aqueous extract to be tested of *Hammada scoparia* infusion (HSI) is administered to rats by gavage (2000 mg/kg).
- ✧ Intravenous administration group (n=4): The aqueous extract to be tested of HSI is administered to rats by the intravenous route (1000 mg/kg).

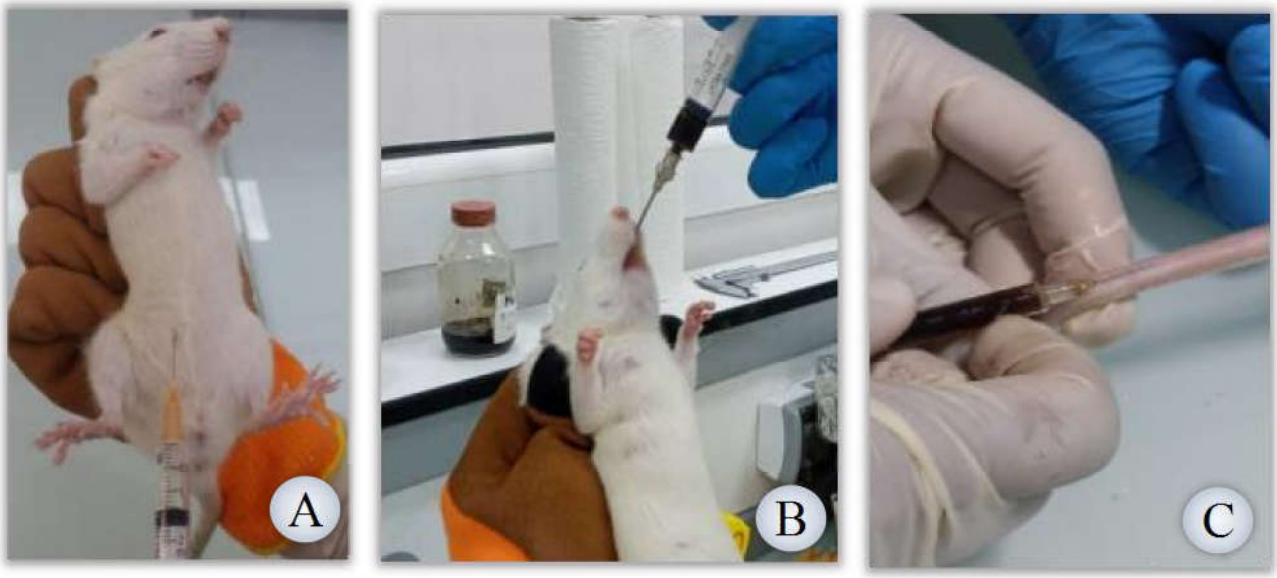

Figure 36: Treatments administration (A): intraperitoneal injection; (B): Gastric gavage (C): Intravenous injection.

II.3. Induction of inflammation

A solution of carrageenan in saline injected into the hind footpad of rats induces an acute swelling of the paw that becomes maximal 3 h after the injection. This model has long been used to assess the anti-inflammatory properties of agents such as non steroidal anti-inflammatory drugs (NSAIDs) that inhibit prostaglandin production. This protocol is a method to elicit and measure carrageenan-induced foot pad edema (**Fehrenbacher *et al.*, 2012**).

Paw swelling, or footpad edema, is a convenient method for assessing inflammatory responses to antigenic challenges and irritants (**Winter *et al.*, 1962; Otterness and Moore, 1988**).

✓ **Procedure :**

✧ Rat is placed in a temporary animal restraint.

✧ 1% carrageenan solution was loaded into a repeating pipettor and attach a 27-G, 1.25-in needle to the combitip. The needle is inserted, bevel down, through the callus, at an anglenearly parallel with the footpad and inject 100 µl of solution. A new needle was used for each animal.

✧ The needle is inserted to a depth of 1 mm into the callus to deliver an accurate and uniform amount of carrageenan into the subplantar site. The uninjected left hind paw serves as the control.3- Return the rat to its cage after injection. The injection was performed for each animal in the experimental group.

II.4. Edema Measurement

The measurements of the volumes of the left hind paw of each rat were carried out before the induction of the edema and at each 1 h, 2 h, 3 h, 4 h, 5 h and 6 h after the injection of carrageenan. The volume of the paw was measured using a vernier caliper. The volume of the edema at a given time (VT) is obtained by the following equation:

$$VT = V_t - V_0$$

V_0 : Initial volume of the paw before injection of carrageenan to cause edema.

V_t : Volume of the paw at time t after injection of carrageenan.

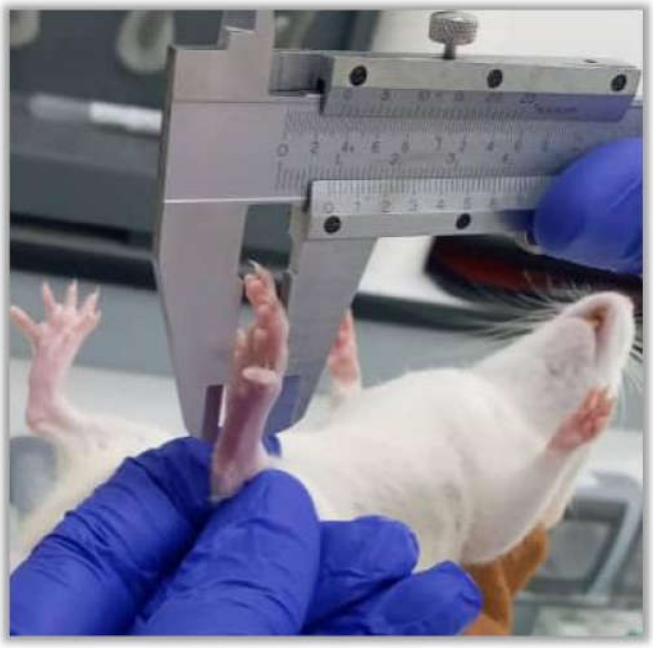

Figure 37: Edema Measurement (vernier caliper).

The development of oedema it evaluated by the determination of augmentation pourcentage (%AUG) with the next formula (**John, K. *et al.*, 2021**):

$$\%AUG = \frac{Vt - V0}{V0} \times 100$$

The anti-inflammatoiry activity evaluate by par the calcul of inhibition pourcentag (%INH) of paw with the formula (**John, K. *et al.*, 2021**):

$$\%INH = \frac{\%AUG_{TM} - \%AUG_{TT}}{\%AUG_{T}} \times 100$$

V_t : Volume of paw at times(t).

V_0: Initial volume de paw.

$\%AUG_{TM}$: Percentage of augmentation of carrageenan group.

$\%AUG_{TT}$: Percentage of augmentation of treated groups.

II.5. Sacrifice and blood draw

It is important that blood sample collection from experimental animals should be least stressful because stress will affect the outcome of the study. Furthermore After 6 hours of experimentation ,each rat received a specific volume of zoletil anesthesia depending to the weight to reduce pain (analgesia). Blood was collected carefully by a euthanizing cardiac puncture via the diaphragm) an open heart from aortic vein (churigical) using a 21G needle and a 10 mL syringe .

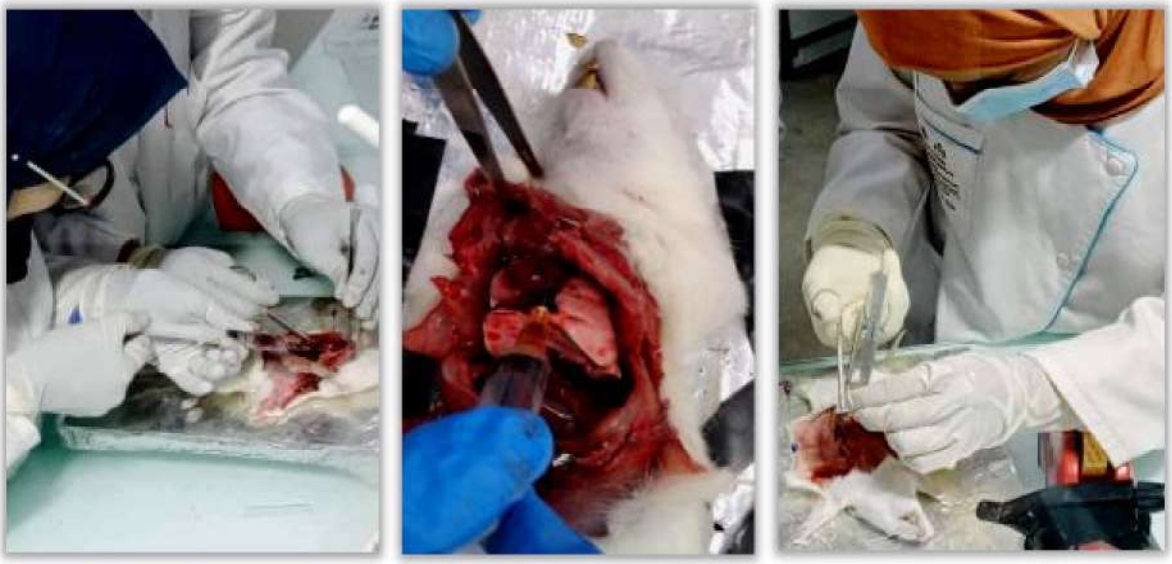

Figure 38: Sacrifice and blood draw.

The blood was immediately distributed between microtainers containing Ethylenediamine Tetra-acetic Acid (EDTA) for the hematological analysis and Lithium Heparin which was centrifuged for 15 min at 3000 rpm and served for the biochemical analysis . Even a small error in the collection procedure may lead to a lot of variation in the results.

Figure 39: Blood samples: (A) EDTA tubes (total blood) (B) Heparin tubes (erythrocyte and serum) (C) dry tubes (serum).

II.6. Analysis of inflammatory markers

II.6.1. Complete Blood Counts (CBC)

By definition the CBC or the hemogram is the quantitative and qualitative cytological study of the circulating blood. It is therefore a blood diagram which analyzes the number, the proportion, the morphology and the variations of the erythrocytes, leukocytes and platelet.

II.6.2. Biochemical analyses

C-reactive protein (CRP) and albumin were assessed in serum using biochemical kits.

II.7. Statistical analysis

The results are expressed as mean±SEM. The significance of the differences between the control and the treatment was established by the Student's t test for independent samples ($P<0.05$).

RESULTS AND DISCUSSION PART

I. *In vitro* study

I.1.Moisture content

Moisture content affects the processability, shelf life, functionality and quality of a product. It is therefore imperative to determine this parameter with precision to guarantee the quality of products in the pharmaceutical and chemical sectors (**Ronald *et al.*, 2005**).

The percentage of *Hammada scoparia* moisture was 4.84%.

I.2. Phytochemical screening

The aqueous extract of HSI in distilled water at the ratio of 10% (w/v). The results of the phytochemical screening carried on the extracts of HSI are mentioned in **Table 5**. Analysis of these results shows that the studied extracts are rich in phenolic compounds including flavonoïdes, gallic and catechic tannins. The extract of HSI contains also reducing sugars, alkaloids, saponins, terpenoids and sterols. Moreover, we observed positive reactions of cardiac and anthraquinones galycosides. The presence of different phyto-constituents in leaf and stem extracts may be responsible for the medicinal properties of HSI. For example, alkaloids have been reported as, anti-inflammatory antimicrobial. Similarly, sterols derived from plants are known to have a cardiotonic effect and also possess antibacterial and insecticidal properties. The presence of phenolic compounds provides pharmacological activities such as anti-cancer, antioxidant, antimicrobial and anti-inflammatory (**Nounah, 2019**).

Table 07: Phytochemical screening of *hammada scoparia* extract:

Test	Interferences
Phenols	+++
Flavonoides	+++
Tannins:	
Gallic tannins	+++
Catechic tannins	+++
Saponins	+++
Terpenoids	+++
Steroils	+
Glycosides	
Cardiac galycosides	+
Anthraquinones glycosides	+
Alkaloids	+++
reducing sugars	+

(+) = Present; **(++)** = Abundant; **(+++)** = Very abundant; **(-)** = Absent

I.3. Contents in phenolic compounds

Powder of HSI was infused in boiling water at the ratio of 5% (w/v). After water evaporation and dry extract weighing, the yield of extraction was estimated to be 16 %.

I.3.1. Total polypenols continent (TPC), total flavonoids continent (TFC) and continent tannin compounds (CTC)

Based on the absorbance value of the extract solution and by comparison with the standard solution, the results of the colorimetric analysis of the total polyphenols, flavonoids, and condensed tannins are expressed in milligram equivalent (standard) per gram of dry plant matter (mg standard E/g DM), using the equation of the linear regression of the calibration curve plotted from the corresponding standard (gallic acid,and catechin).

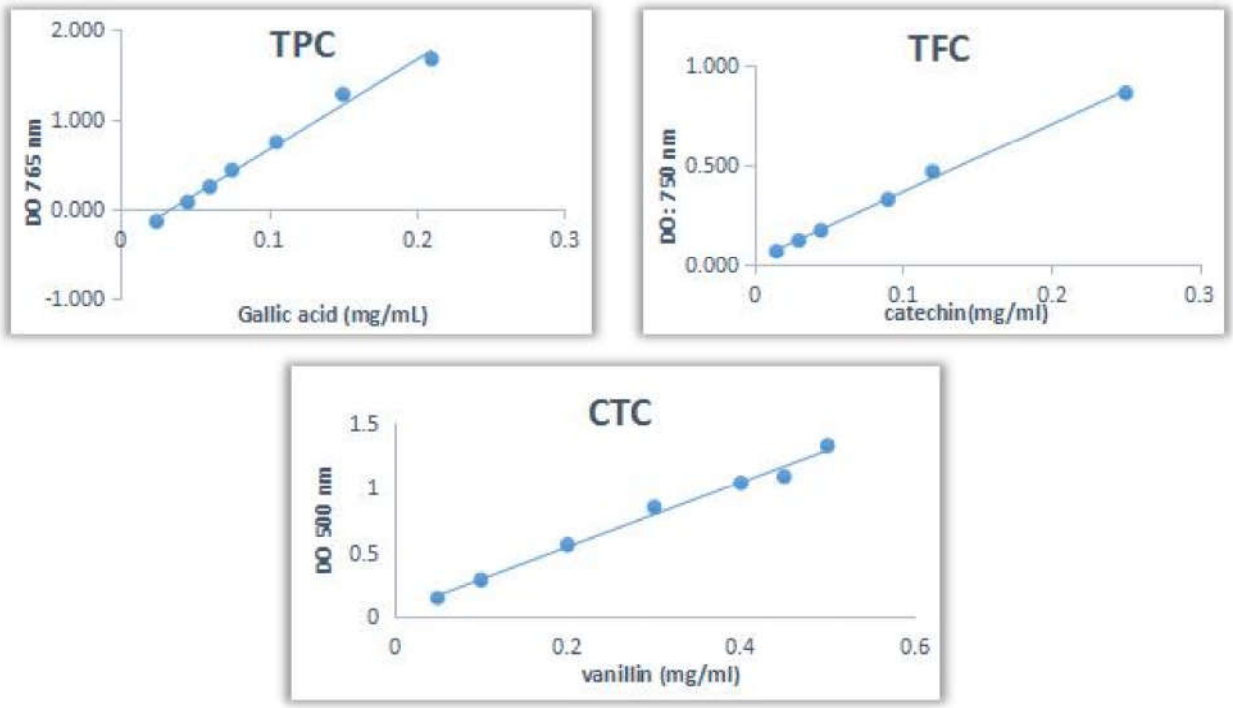

Figure 40: Calibration of curve: (**A**): Total polypenols continent; (B): total flavonoids continent; (**C**) and continent tannin compounds.

Our results showed that HSI is rich in **TPC, TFC, and CTC with amounts of** 3,95 ± 0.015 mg GAE/g DM, 2,66 ± 0.21 mg CE/g DM, and 1,70 ± 0.12 mg CE/g DM, respectively. Indeed, **Lakhdar *et al.*, (2021)** estimated values of (3.81±0.21 µg EAG/mg DM; 228.67 ± 10.87 µg EQ/mg; 1,1 ± 0.13 µg CE/mg) for **TPC, TFC, and CT,** respectively. According to a study conducted in Algeria, **Belhadj *et al.* (2015)** found that HSI has **TPC:** 4,163± 0,028 mg EAG/g DM, **TFC:** 0,139± 0,003 mg EQ/g DM and **CTC:** 1,641±0,017 mg CE/g DM. Also, **Rached *et al.* (2015)** showed that HSI contain 37.31 mg EAG/g DM and 12.3 mg RE/g DM. Of **TPC,** and **TFC** respectively.

I.4. Antioxidant capacity of HS crude extract

The free radical-scavenging activity was investigated using the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH.) test. We measured the capacity of extracts or antioxidant molecules, such as ascorbic acid and Gallic acid, to scavenge the free radical DPPH, causing a change of the initial violet solution to a yellow colour. This is due to the formation of diphenylpicrylhydrazine by donation of hydrogen atom or an electron (**Tepe *et al.*, 2005**). This activity can be evaluated by determination of the IC_{50} values, which correspond to the concentration of HSI samples that are able to scavenge 50% of free radicals present in the reaction mixture, where high IC_{50} values indicate low antioxidant activity.

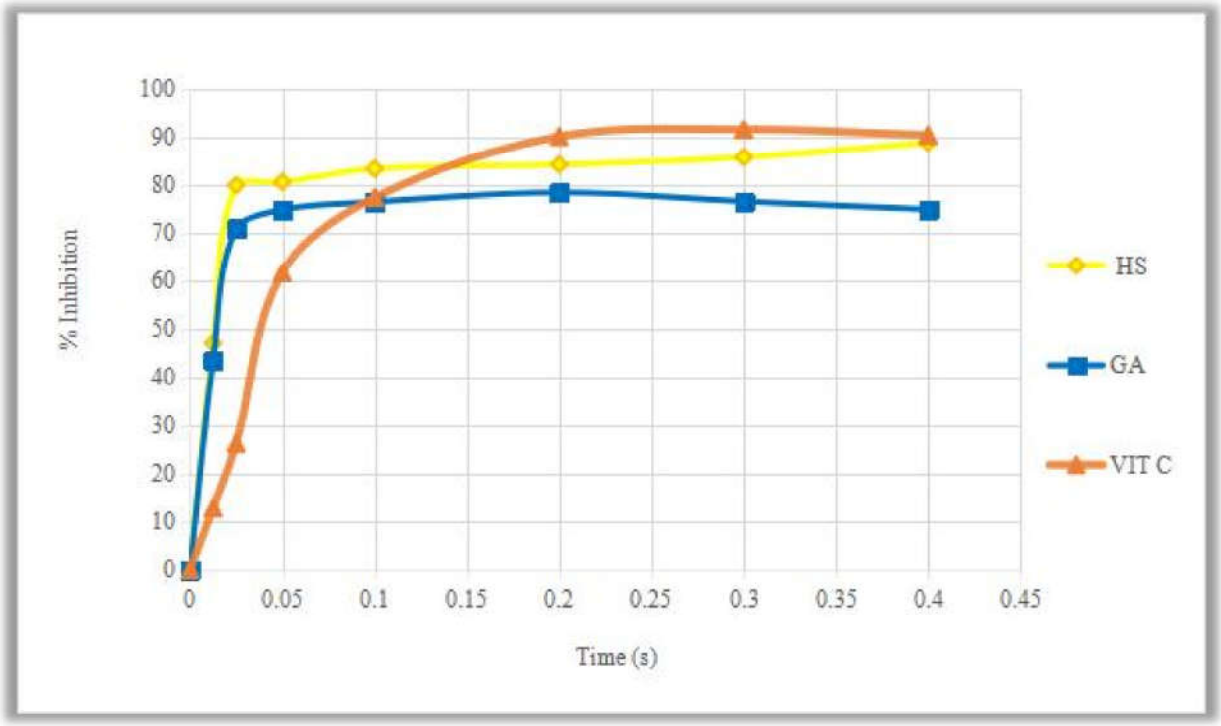

Figure 41: Inhibition percentage of free radical (DPPH•) of HS extract and references curve.

Table 08: The IC_{50} inhibition of the DPPH•

IC_{50}	**(IC_{50} mg/mL)**
Gallic acid	0,0133± 0.0006
Vitamin C	0,0417 ±0.0014
HSI	0,0135±0.0019

As shown in graph ,the aqueous extract exhibited a scavenging activity with an important decrease of DPPH free radicals versus that of gallic and ascorbic acid. In addition, the results showed that the scavenging ability of HSI extract was at the same level or even lower in comparison to the gallic acid followed by the ascorbic acid, where the IC_{50} was 0.0135 mg/mL, **0.0133 mg/mL** and **0.0417mg/mL** respectively. **Arabshahi and Urooj, (2007)** indicate that the antioxidant molecules, such as Phenolic acids, Flavonoids, and Tannins, reduced and decolourise DPPH.due to their hydrogen donating ability. According to that we suggest the contribution of phenolic compounds of HS extracts in the antiradical activity.

In fact, free metal ions, as well as highly reactive hydroxyl radical are known to increased by the formation of ROS. To the opposite, **Mishra *et al.*, (2013)** indicated that polyphenols are able to chelate metal ions like Fe_2^+, Cu_2^+, and free radicals which lead to a reduction of highly oxidizing free radicals. Polyphenols can inhibit NOX (NADPH oxidase) causing a reduction in the generation of O_2• during infections consecutively in endothelial cells in THP1-monocytes (**Deby-Dupont *et al.*, 2005; Petrônio *et al.*, 2013**), while they upregulate other endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase, peroxidase (Px) and glutathione (GSH). **Bouaziz et al., (2016)**, indicated that the N-methylisosalsoline showed a high capacity for scavenging DPPH free radicals. This alkaloid was demonstrated to be present in HS extract (**Zerriouh, 2014**).

According to that we suggest that the antioxidant activity of *H. scoparia* in scavenging DPPH free radicals may be expressed by the ability of their polyphenols to inhibit multiple enzymes involved in reactive oxygen species ROS production.

I.4.1. kinetic

Use of DPPH• provides an easy and rapid way to evaluate the anti radicalar activities of antioxidants, also to build plausible models of reactions (**Berset, 1997**).

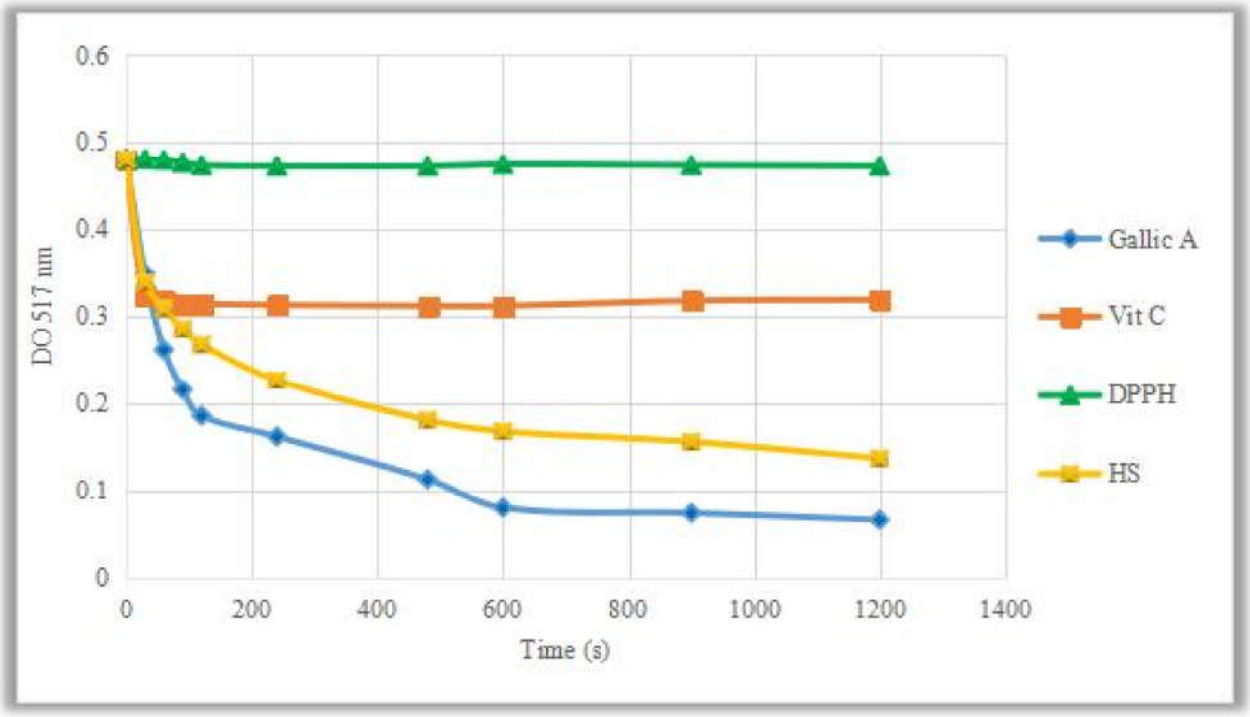

Figure 42: Kinetic reduction of DPPH• of HS extract curve.

The absorbance was read at 517 nm during 20 min. Monitoring the kinetics of the reaction enabled us to identify the extract which reacts rapidly with the DPPH•. We have noticed that the violet color of the medium changes as a function of time, and the decrease in absorbance is proportional to the rate of neutralization of the DPPH•. From the analysis of the curves above, it turns out that in the begining of reaction, the aqueous extract of HS reacts quickly and similarly to the Gallic acid then with increasing order of reaction rates the Gallic acid react quickly with DPPH•,then the extract and vitamin C. (**Berset, 1997**).

II. *In vivo* study

II.1. Carrageenan-Induced Inflammation

II.1.1. Paw thickness

To demonstrate the effect of *H. scoparia in vivo,* we measured the inflammatory edema of the left hind paw of rat induced by Carrageenan.

Table 09: Results of anti-inflammatory activity. Carrageenan induced rat paw edema

Groups	Paw Thickness of Wistar Rats (mm)							
	Dose	**0h**	**1h**	**2h**	**3h**	**4h**	**5h**	**6h**
Cg	1%	2,33±0,57	4,03± 0,57	4,06±0,02	4,23±0,23	4,3±0,43	4,2±0,26	4,1±0,2
D	5 mg/kg	2,3±0,52	3±0.00	3,63±0,47	4,3±0,67	3,9±0,1	2,97±0,06	2,73±0,23
G	2000 mg/kg	2.1±0,08	2,98±0,05	3,9±0,25	3.87±0,29	3,3±0,42	2,96±0.1	2,7±0,22
IV	1000 mg/kg	2,07±0,05	3,27±0,25	3±0,52	2,92±0,05	2,9±0,05	2,73±0.1	2,6±0,16

Cg: Carrageenan; **D:** Diclofenac; **G: G**astric gavage; **IV:** Intravenous

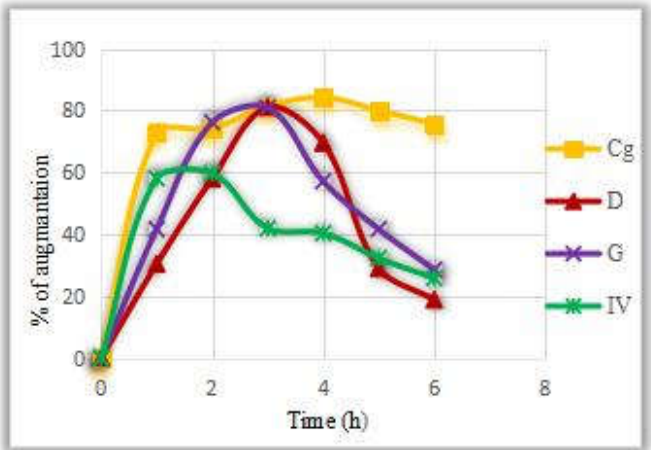

Figure 43: Augmentation parentage of paw edema.

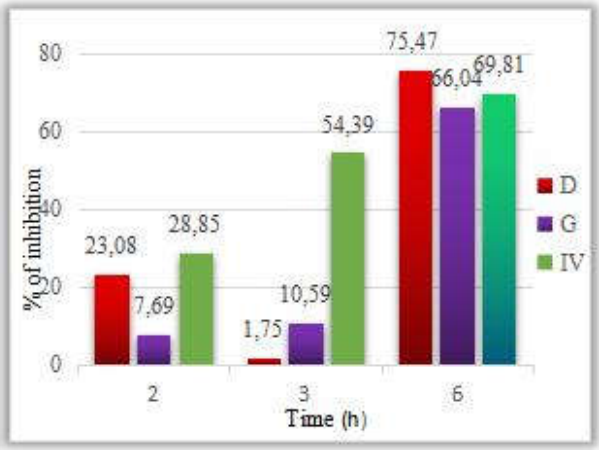

Figure 44: Inhibition percentage of paw edema.

The injection of carrageenan produced a significant (P>0,001) and rapid increase in the volume of the injected paw, with no disappearance, indicating that the acute inflammatory response was successfully induced. At t = 0, the untreated group paw thickness was 2,33± 0,57 mm reaching its maximum at 4 hours with 4,3±0,43 mm . This level of inflammation was maintained for about 6h and subsequently declined to remain 4,1±0,2 mm. This value correspondent with percentage of augmentation (AUG%) of 72,85% at the first hour and 84,28% at the 4 h until it reached 75,72% at 6 h (see the graph).

The Effect of the extract administering orally at dose of 2000 mg/kg and the reference drug, diclofenac, (5mg/kg) on carrageennan induced paw oedema showed a significant Inhibition 3h after carrangeenan injection (*P*>0,043), then starts to decline till 6 hours , from (3,8±0,29 to 2,7±0,22 mm, with percentage of inhibition from 10.53% to 66.04% and from 4,16±0,67 to 2,73±0,23 mm, with (INH%) 1.75 %to 75.47% respectively. Diclofenac activity was similar to the administering orally extract (2000mg/kg).

While the intravenously dose (1000mg/kg) of the extract showed its highest significant Inhibition at 2 h (*P*>0,007) from 3,3±0,52 to 2,6±0,16 mm, with (INH%) 28.85% to 69.81% . This results has shown us also that HSI extract may be more potent than the reference drug, diclofenac, and the extract orally administration, where the anti-inflammatory (anti oedematogenic) effect of the extract was most effective with its lowest dose administered intravenously

The course of acute inflammation is biphasic. First phase starts with the release of histamine, serotonin, and kinins to increase the vascular permeability up to 2 h. The maximum inflammation is seen approximately three hours post the carrageenan injection, after which it begins to decline. Following that the prostaglandins act from 3 hours to six hours, which results in the migration of leucocytes into the inflamed site (**Castro *et al.*, 1768; Di-Rosa, 1971**). All the mediators appear to be dependent upon an intact complement system for their activation and release (**Giroud and Willoughby, 1970**), giving rise to edema formation. It has been shown that Prostaglandins, in particular PG2 potentiates the effects of histamine and bradykinin, and activates C3 and C5 fractions of complement, causing an increase in the hydrostatic pressure from which a passage of a large amount of water and electrolytes, and increased permeability capillary, which allows non-blood passage of weighty substances high molecular levels. Histamine released locally by mast cells is responsible of this retraction of endothelial cells which swell and globalize by liquid penetration (**Diebold *et al.*, 1995**).

The carrageenan-induced paw edema model in rats is known to be sensitive to cyclo-oxygenase (COX) inhibitors and has been used to evaluate the effect of non-steroidal anti-inflammatory agents. As with all NSAIDs, diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) with relative equipotency. However, Diclofenac is among the most effective inhibitors of prostaglandin E2 (PGE2) production and has been reported to be 3 to 1000 times more potent on a molar basis compared with other NSAIDs in its ability to inhibit COX activity (**Ku *et al.*, 1986**).

Hammada scoparia shows a significant, inhibition of inflammation, which is comparable to the standard drug, diclofenac sodium. As Phytochemical tests showed the aquoues extract of H.s is rich in phenolic compounds, they might act either through inhibition of prostaglandin or one of the transmitters released before the second phase of carrageenan oedema or both collectively.

Furthermore, evidence indicate that polyphenols have the ability to inhibit phospholipase A2 (PLA2), cyclooxygenase (COX) and lipoxygenase (LOX) leading to a reduction in the production of prostaglandins (PGs) and leukotrienes (LTs) and inflammation antagonism (**Laughton *et al.*, 1991**; **Lindahl and Tagesson, 1997**).

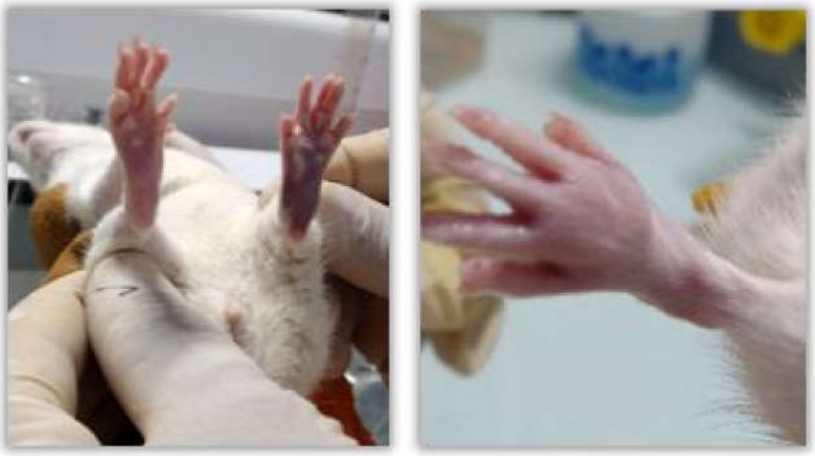

Figure 45: Carrageenan effect on edema progression.

II.2. Haematology and Biochemical analysis

A summary of the results obtained in these tests is presented in bar graphs

II.2.1. Product reaction on blood leukocytes

Acute inflammation is characterized by coordinated activation of several signalling pathways that regulate the expression of mediators and cytokines with pro and anti-inflammatory functions **(Leyva-López *et al.*, 2016; Ambriz-Pérez *et al.*, 2016**).

An inflammatory condition involves induction of edema and recruitment of cells, predominantly neutrophils, to the site of inflammation, driven by several mediators of different origins controlling its phases from onset to resolution (**Doherty *et al.*, 1985; Kolaczkowska *et al.*, 2009**).

Recent studies have shown that the inflammation induced by carrageenan involves cellular migration, plasma exudation, and the production of mediators, such as nitric oxide, prostaglandin E2, interleukins IL-1β, IL-6, IL-10 and tumoral necrosis factor (TNF-α) (**Loram *et al.*, 2007**). These mediators are able to promote the recruitment of leukocytes in various experimental models. Evidence suggests these pro-inflammatory cytokines help propagate the extension of a local or systemic inflammatory process (**Mizgerd *et al.*, 2001**).

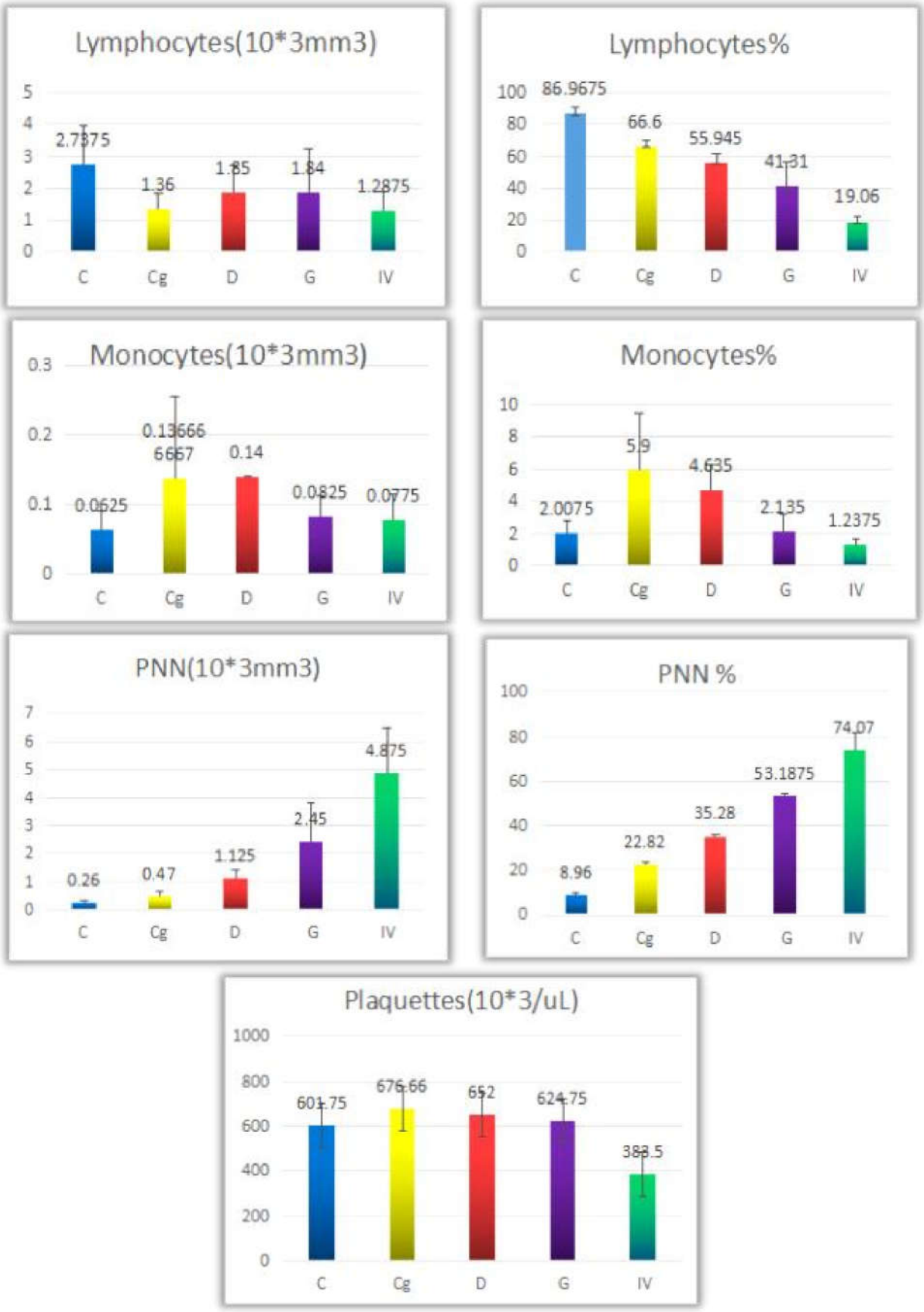

Figure 46: CBC results: (**C:** Control; **Cg**: Carrageenan; **D:** Diclofinac; **G:** Gastric gavage, **IV:** Intravenous).

Graphs bars have shown that the injection of Carrageenan on sub-plantar paw of rat induced an increase in monocytes, neutrophils and platelet levels in untreated oedematous rats, while lymphocytes level decreased compared to the healthy controls. On other hand, compared to the untreated group, both gastric gavage (200mg/kg) and intravenous (1000mg/kg) extracts showed the same effect on cells migration as the reference drug, diclofenac, where monocytes, lymphocytes and platelets levels in blood were reduced, excepted for neutrophils whose levels increased , that with some differences in potential of effect where the extract administered intravenously was more potent than the both.

According to these results, we suppose that the ability of *H. scoparia* extract to suppress the 'prostaglandin phase ' may be correlated directly with their ability to suppress leukocytes migration into the inflamed tissue.

As previous results showed that *H. scoparia* is rich on polyphenols, flavonoids and tannins, in addition to their significant anti-inflammatory effect on paw edema induced by carrageenan. These phenolic compounds were seemed to be better inhibitors of leukocyte migration (**Middleton *et al.*, 2009**). Concerning polyphenols for example, evidence indicate that they can repress macrophages by inhibiting cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), thus they reduce the production of TNF-α, interleukine-1-beta (IL-1-β) and IL-6 expression (**González *et al.*, 2011**), which are crucial in Growth regulation, cell activation, differentiation, and homing of the immune cells to the sites of infection (**Turner, 2014**).In addition to their anti-oxidant characteristics such as ROS (reactive oxygen species) scavenging and toll-like receptor (TLR) suppression contributes to the regulation of inflammatory signaling (**Santangelo *et al.*, 2007; Malireddy *et al.*, 2012**).

Moreover, flavonoids, as quercetin, isoquercitrin and rutin, play an important anti-inflammatory effect by influencing cytokines' secretion. They are found able to suppress or inhibit the expression of various pro-inflammatory cytokines and chemokines such as TNFα, IL-1β, IL-6, IL-8, MCP-1, RANTES, MIP-2 and PGE2 by inhibiting the activation of NF-kB pathway in multiple cell types (**Sato *et al.*, 1997; Lyu *et al.*, 2005; Comalada *et al.*, 2006**). MCP-1, is membre of C-C chemokine familly, one of the key chemokines that regulate migration and infiltration of monocytes and macrophages (**Cochran *et al.*, 1983**). RANTES, a CC-chemokine also, is a chemoattractant for basophils, eosinophils, and T lymphocytes (**Baggiolii *et al.*, 1999**). MIP-2 is a major CXC-chemokine involved in the migration of PMNs to the sites of inflammation. It is elicited that all PMNs produce large amounts of MIP-2 (**Matzer *et al.*, 2001**).

According to the analysis of **Bourogaa *et al.*, 2011**, quercetin is present in the aqueous extract of *Hammada scoparia*. This metabolite has been reported to reduce paw edema induced by carrageenan (**Paradkar *et al.*, 2004**). In human mast cells for example, quercetin prevents the degradation of Iκ Bα, as well as the nuclear translocation of p65 resulting in reduction of TNFα, IL-1β, IL-6 and IL-8 (**Min *et al.*, 2007**). It can also modulate chromatin remodeling by blocking the recruitment of an histone acetyl transferase called CBP/p300 to the promoters of interferon-inducible protein 10 (IP-10) and macrophage inflammatory protein-2 (MIP-2) genes in primary murine small intestinal epithelial cell. As a result, it inhibits the expression of these pro-inflammatory cytokines (**Ruiz *et al.*, 2007**).

Thomas and Filho (1985), indicated that **a**pproximately, 90% of the cells present in the exudate inducing by carrageenan were polymorphonuclear leukocyte (PMNL).

Furthermore, it is probable that neutrophils are the targets of anti-inflammatory effects of flavonols, since they contribute toward the majority of exudate cells and are known to produce the inflammatory mediators assessed (**Morikawa *et al.*, 2003**).

Selloum *et al* (2001), reported that rutin (flavonols) have significant inhibitory effect on neutrophil chemotaxsis and degranulation by preventing polymorphonuclear migration towards fMet-Leu-Phe (neutrophil chemotactic factor) and partial inhibitory effect on degranulation of fMet-Leu-Phe neutrophils. Inhibition of this chemokine and others factors as TNF-a and granulocyte–macrophage colony-stimulating factor (GM-CSF), inhibit the metalloproteinase involved in the cleavage of L-selectin, the responsible for PMN rolling over endothelial cell surface (**García-Vicuña *et al.*, 1997**). This flavonols was reported to be present in *H. scoparia* extract (**Ben salah *et al.*, 2002**).

Tannins also are known to possess anti-inflammatory effect by the inhibition of prostaglandin synthesis (**Alcaraz and Ferrandiz, 1987**). It is probable that the anti-inflammatory actions of these agents are due to an effect on leukocyte migration and antagonism of the phlogistic actions of mediators of inflammation. Tannins may do so by their well-known astringent properties causing precipitation of cell membrane proteins (**Thomas and Filho, 1985**).

Therefore, the inhibitory effect of HS extract against the influx of leukocytes in the paw edema induced by carrageenan might be attributed to the suppression of the effect of pro-inflammatory cytokines and chemokines involved in cellular migration.

We propose this effect may be due to the presence of phenolic compounds which may regulate the immunity by interfering with immune cell regulation, pro-inflammatory cytokines' synthesis, and gene expression. They may have contributed to the inactivation of NF-κB and arachidonic

acids pathway or inhibition of leukocytes rolling through a rapid induction of L-selectin, contributing as well to their anti-inflammation properties.

II.2.2. Product reaction on blood CRP and albumin levels

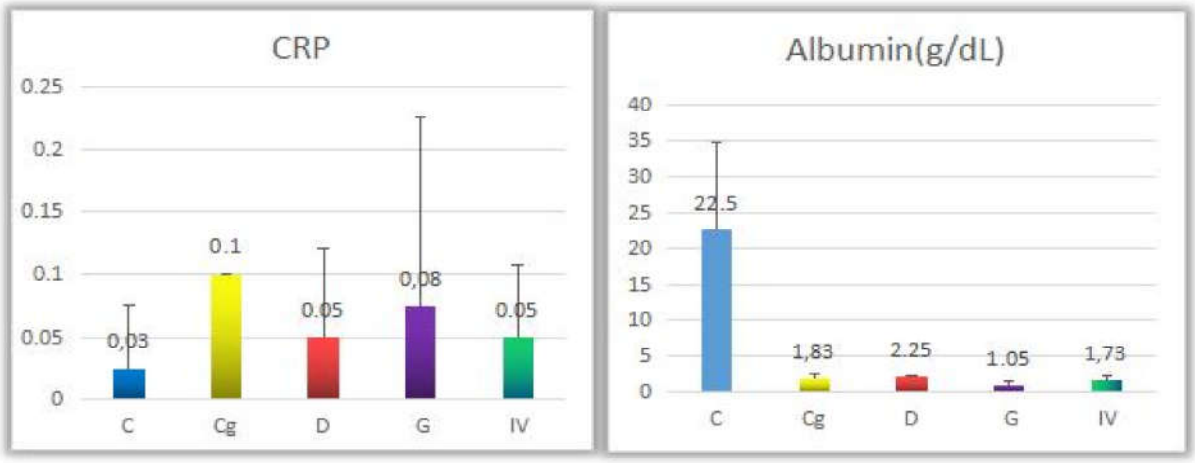

Figure 47: CRP and Albumin results (**C:** control; **Cg:** carrageenan; **D:** Diclofenac; **G:** Gastric gavage; **IV:** intravenous).

Hepatic protein production also is stimulated by pro-inflammatory cytokines level in blood, the production of CRP for example is mainly under the control of IL-6. However, IL-1 and TNF-α can also contribute to hepatic synthesis and secretion of CRP (**Yudkin *et al.*, 2000; Jialal *et al.*, 2004**). The inhibition of this cytokines by polyphenol and specifically IL-6 may be the main responsible for the low level of CRP in blood rats treated, where, clinical trials have shown the ability of polyphenol to reduce IL-6 and C-reactive protein expression (**Fitó *et al.*, 2008**).In other hand, albumin secretion is stimulated by a decrease in osmotic pressure (**Evans, 2002**), but it can also be affected by pathophysiological changes such as during an infectious or inflammatory disease, where the secretion may be reduced because of pro-inflammatory cytokines secretion.

Over production of ROS can prompt tissue injury that might initiates the inflammatory process (**Willcox *et al.*, 2004; Geiszt and Leto, 2004**). Therefore, the classical antioxidant actions of polyphenols undoubtedly contribute to their anti-inflammatory roles by interrupting the ROS-inflammation cycle. Polyphenols is proposed to be useful as adjuvant therapy for their potential anti-inflammatory effect, associated with antioxidant activity, and inhibition of enzymes involved in the production of eicosanoids. They are known for their antioxidant activities they scavenge a wide-ranging selection of ROS as we see previosely, they can scavenge radicals and chelate metal ions (**Heim *et al.*, 2002**). They inhibit also phospholipase A2 (PLA2), cyclooxygenase (COX) and lipoxygenase (LOX) leading to a reduction in the production of prostaglandins (PGs) and leukotrienes.

Conclusion

Conclusion

The inflammatory response is triggered by an array of chemical mediators released in the affected tissue. These mediators act and interact to induce changes in blood micro vessels, tissue cells and blood cells. Sometimes these changes can be harmful, due to the aggressiveness of the pathogenic agent. The scientific community is constantly working to find new more effective therapies with few side effects.

In our study we were interested to the anti-inflammatory effect of *Hammada scoparia* (HS) aerial part. This plant represents a potential source of bioactive molecules. The phytochemical analysis based on specific tests showed the presence of phenols, flavonoïds, saponins, tannins, glucosides, steroids, terpenoids and alkaloids in the aqueous extract of HS aerial part. The assessment of polyphenols revealed that the HS contains high levels of polyphenols up to (**3, 95 GAE mg/g**). We found that the extract of HSI has notable antioxidant activity compared to the gallic acid, and vitamin C, where the **IC_{50}** was **0,0135µg/mL**. The mountains of the DPPH radical scavenging kinetic revealed that the HSI reacts as fast as gallic acid.

In addition, the anti-edematous activity of the plant has confirmed the anti-inflammatory properties of the plant since it significantly reduces the edema paws of rats. The present study indicated that the *H. scoparia* exhibited anti-inflammatory effects on carrageenan-induced oedema in rat paw at both **1000** and **2000 mg/kg** doses. In this regards, we noticed that the administration of HS intravenously in a low dose (**1000 mg/kg**) was more potent than the high dose (**2000 mg/kg**) administred orally. This low dose was also more significant than the reference drug, diclofenac, at (**5 mg/kg**).

The anti-inflammatory effect of HSI was also confirmed by the hematological and biochemical analysis which showed a significant decrease in leukocytes and inflammatory proteins levels in blood for carrageenan-administrated rats treated with HSI In addition, the plant was found to exert an effect during the early and acute stages of inflammation induced by carrageenan. The anti-edematogenic activity was seemed to be associated with the inhibition of mediators such as PGE, inhibition of cell migration to the site of inflammation, and its interference in levels of proinflammatory cytokines (TNF-α and IL-1β).

The findings of our study argue the use of *H. scoparia* in folk medicine to treat inflammation. However, the isolation of plausible compounds responsible for anti-inflammatory effect is worthy to be conducted for future investigations

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Index

Instruments:

	
Figure 01: Agitator magnetic	**Figure 02:** Vortex
	
Figure 03: Centrifuge	**Figure 04:** Ultrasonic cleaner

Figure 05: Rotary evaporator (Nahito)

Figure 06: Spectrophotometer

Figure 07: Balance

Figure 08: Electric hot plate

Figure 09: Dissection kit

Figure 10: Vernier caliper

Chemical and reagents:

Figure 11: Diclofinac

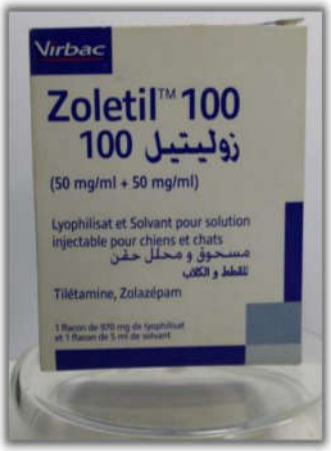

Figure 12: Zolatil

Figure 13: Carrageenan

الملخص

عادة ما تكون الإستجابة الإلتهابية مفيدة، لكنها قد تكون في بعض الأحيان مؤذية كذلك. ترتبط الأدوية المضادة للإلتهاب بآثار جانبية خطيرة. نتيجةً لذلك تزايدَ الإهتمام بالنباتات الطبية الطبيعية ذات الخصائص المضادة للإلتهاب. يعتبر الرمث (HS) من أشهر النباتات المستوطنة (شجيرات رعوية صحراوية) ومعروف جيدًا بنشاطه المضاد للإلتهابات. لذا كان الغرض من هذه الدراسة هو تقييم النشاط المضاد للإلتهاب لمنقوع الجزء الهوائي من نبات الرمث في الجسم الحي. لتحقيق هذا الهدف، قمنا أولاً بإجراء فحص كيميائي للمستخلص المائي الخام لـهذا النبات قبل إجراء فحوصات لونية للمركبات الفينولية (البوليفينول، الفلافونويد والعفص المكثف). بعد ذلك قمنا بتقييم القوة المضادة للأكسدة لهذا المستخلص عن طريق إختبار ال DPPH . تم تقييم التأثير المضاد للإلتهاب لنبات الرمث بحقن الكاراجينان (1%) في مخلب الجرذان ويستار (Wistar Rats) وتتبعها لمدة 6 ساعات تَمّ خلالها قياس الوذمة. في نهاية التجربة تم تشريح الفئران وتقديم عينات الدم للتحاليل الكيميائية الحيوية الخاصة بأمراض الدم والبلازما. كشفت الإختبارات الكيميائية النباتية عن تنوع المُستَقلَبَات الثانوية (بوليفينول، تربنويدات، الأكلويدات.. الخ) في النبات المدروس. أظهرت فحوصات مستويات المركبات الفينولية أن الرمث يحتوي على نسبة كبيرة من البوليفينول تقدر ب **3.95ملغ/غ**. أشار إختبار **DPPH** إلى أن للمستخلص المائي للنبات المدروس نشاط فعال ضد الأكسدة حيث قدر تركيز المادة الموافق للتثبيط النصفي(IC_{50}) بـ **0.0135 مغ/ملل**، كما أنه يتفاعل بسرعة مثل حمض الغاليك. أكدت نتائج الدراسة على النماذج الحيوانية المخبرية النشاط المضاد للإلتهاب لنبات الرمث حيث سجلنا في الفئران المعالَجة بالمستخلصات االمائية بجرعة**2000 ملغ/كغ** و **1000ملغ/كغ** تثبيطاً واضحاً لحجم الوذمة مقارنة بالحيوانات غيرالمعالجة, بنسب تصل إلى **66.04%**و **69.81%** على التوالي في الساعة السادسة. ومن هذا نستنتج أن الخاصية المضادة للإلتهابات لنبات الرمث ترتبط بالقوة المضادة للأكسدة للمُستَقلَبَات الثانوية وخاصة البوليفينول. إضافة إلى أن هذه النتائج تدعم بشكل واضح الإستخدام التقليدي لهذا النبات كمركبات بديلة خاصة في معالجة الأمراض الإلتهابية.

الكلمات المفتاحية: الرمث, منقوع, كاراجينان, مثبط الاكسدة , الكيمياء النباتية, جرذان ويستار, الإلتهاب

Abstract

The inflammatory response is generally beneficial process but can lead to a harmful overeaction. The anti-inflammatory drugs are associated with numerous side effects. Therefore, there is an increasing interest in medicinal plants with anti-inflammatory proprieties.*Hammada scoparia*(HS) is an endemic plant (shrubs and subshrubs) which is well known for its anti-inflammatory activity. Hence, The objective of this work was to evaluate *in vivo* the anti-inflammatory activity of the infusion from HS aerial part. To achieve this goal, phytochemical screening was carried out before the colorimetric assays of the phenolic compounds (polyphenols, flavonoids, and condensed tannins). Then, we evaluated the antioxidant activity of HS crude extract by the DPPH scavenging test. The anti-inflammatory activity of HS was assessed by injection of 1% carrageenan in the hind paw of Wistar Albino rats and evaluated for 6 hours during which the edema was mesured (*in vivo*). At the end of the experimentation, the rats were sacrificed and the drawed blood was served to the hematological and biochemical analysis. The phytochemical screening revealed the diversity of secondary metabolites (polyphenols, terpenoids, alkaloids…etc) present in the studied plant. Polyphenols assessement indicates that the extract is rich in polyphenols(up to **3.95 mg/g GAE**). We found that the HSI has a potent antioxidant activity with an **IC50** value of **0.0135µg/mL** and reacts as fast as gallic acid. The *in vivo* study confirms the anti-inflammatory activity of *Hammada scoparia*. Moreover, we noted that rats treated with **2000 mg /kg** and **1000 mg/kg** of HSI exhibited a very significant inhibition of the edematous paws increase compared to the untreated rats, where it reached **66.04%** and **69.81%** respectively at the 6 hour. We can conclude that the anti-inflammatory property of HSI would be linked to the antioxidant power of its secondary metabolites, particularly polyphenols. Therefore, these results clearly support the traditional use of this plant as alternative compounds in the control of inflammatory diseases.

Keywords: *Hammada scoparia,* infusion, phytochemistry, anti-oxidant, Wistar rats, carrageenan, inflammation

Résumé

La réponse inflammatoire est un processus habituellement bénéfique, mais Parfois elle peut être néfaste. Les anti-inflammatoires sont associés à des effets secondaires graves. Par conséquence, on s'intéresse aujourd'hui de plus en plus aux plantes avec des propriétés anti-inflammatoires. *Hammada scoparia* (HS) est une plante endémique (arbuste), bien connue pour son activité anti-inflammatoire. L'objectif de ce travail était d'évaluer *in vivo* l'activité anti-inflammatoire de l'infusion de la partie aérienne de *Hammada scoparia*. Pour atteindre cet objectif, tout d'abord, nous avons procédé un criblage phytochimique de l'extrait aqueux de HS avant de faire des dosages colorimétriques des composés phénoliques (polyphénols, flavonoïdes, et tanins condensés). Ensuite, nous avons évalué le pouvoir antioxydant de l'extrait brut de HS par le test au **DPPH**. L'effet anti-inflammatoire de HSI a été évalué en utilisant la méthode de l'œdème plantaire provoquée par la carragénine chez les rats Wistar à 1%. L'expérimentation *in vivo* s'est déroulée pendant 6 h durant laquelle l'œdème a été surveillé. A la fin de l'expérimentation animale, les rats sont sacrifiés et les paramètres hématologique et biochimiques plasmatiques ont été dosés. Les tests phytochimiques ont révélé la diversité des métabolites secondaires (polyphénols, terpenoids, alcaloïdes...etc) dans la plante étudiée. Les dosages des composés phénoliques ont montré que *Hammada scopaaria* contient une teneur considérable en polyphénols estimée à **3.95 mg EAG /g MS**. Le test au **DPPH** a indiqué que l'extrait aqueux de HS a un pouvoir antioxydant puissant avec un IC_{50} estimé à **0.0135 mg/ml** et réagit rapidement comme l'acide gallique. L'étude *in vivo* a confirmé l'activité anti-inflammatoire du *Hammada scoparia*. D'ailleurs, nous avons enregistré chez les rats traités avec les extraits aqueux de HS au dose **2000 mg/kg** et **1000 mg/kg** une inhibition très importante des volumes des pattes œdémateux par rapport aux rats non traités atteignent jusqu'au **66.04%** et **69.81%** respectivement au 6 ème heur. Nous pouvons conclure que la propriété anti-inflammatoire du HSI serait liée au pouvoir antioxydant de ses métabolites secondaires, particulièrement les polyphénols. Par conséquent, ces résultats soutiennent clairement l'utilisation traditionnelle de cette plante comme composés alternatifs particulièrement dans le contrôle des maladies inflammatoires.

Mots clés: *Hammada scoparia,* infusion, anti- oxidant, phytochimique, Wistar rats, carragénine, inflammation.