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Theme

Exploring the therapeutic potential of *Bassia muricata* and *Suaeda mollis* plants: *In Vitro* and *In Vivo* anti-skin cancer induced by DMBA and anti-diabetic induced by alloxan

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إهداء

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ ﴿وَآخِرُ دَعْوَاهُمْ أَنِ الْحَمْدُ لِلَّهِ رَبِّ الْعَالَمِينَ﴾ (يونس :10)

الحمد الله حبا وشكرا وامتنانا على البدء والختام
لم تكن الرحلة قصيرة ولا الطريق محفوفا بالتسهيلات لكنني فعلتها فالحمد لله الذي يسر البدايات وبلغنا النهايات بفضله وكرمه
اهدي بكل حب بحث تخرجي:

الى نفسي الطموحة لقد ظننت انني لا أستطيع ولكن من قال انا لها نالها وان ابت اتيت بها رغم عنها

الى من زين اسمي بأجمل الألقاب من دعمني بلا حدود واعطاني بلا مقابل الى من علمني ان الدنيا كفاح وسلاحها العلم والمعرفة داعمي الأول في مسيرتي وسندي وقوتي وملاذي بعد الله فخري واعتزازي **أبي الغالي (الهاشمي)**

الى التي تعجز كل الكلمات عن وصفها الى من علمتني الأخلاق قبل الحروف الى التي كانت النور في عتمتي الي التي كان دعائها سر نجاحي الى معلمتي وسيدتي العظيمة **أمي الحبيبة (ناديه)**

الى سندي وأبي الثاني الى من مهد لي كل العقبات الى الذي لم يبخل بشيء من أجل دفعي الى طريق النجاح **عمي الغالي "لطفي"**

الى ملهمي نجاحي وضلعي الثابت صانع قوتي وصفوة ايامي وسلوة اوقاتي الى الشمعة التي تنير لي الطريق الى سندي وخير معين **أخي العزيز (طه)** وابنه **(سند)**

الى ملائكة رزقني الله بهن لأعرف من خلالهن طعم الحياة الى من خففتن عني مشقة هذه الأيام **أخواتي (جمينة ومنى) وزوجة أخي (أشواق)** ادامكن الله لي وجعلني واياكن من الباريات

الى من جمعتهم معي صلة الرحم الى عائلتي **"خليفي "و"قادي "**

الى صاحب الفضل الكبير لك مني كل عبارات الشكر والتقدير أستاذي وموجهي الأول البروفيسور **شمسة احمد الخليفة** حفظك الله ورعاك وادامك بالصحة والعافية

اليكن يامن بذلتن ولم تنتظران العطاء اليكن اهدي أجمل عبارات الشكر والامتنان أستاذاتي **غرايسة نورة وعزي منال**

ولن أنسي بالذكر أستاذاتي **زمولي نوال والعايب إبتسام وكرطي أميرة** على كل دعم ونصيحة منحتموني إياها في وقت من الأوقات فجزاكن الله خير الجزاء

الى رفيقاتي المشوار وصاحبتا الفضل العظيم صديقات الرحلة والنجاح اللاتي قاسمنني لحظاته **أحلام ورانيه** حفظكن الله

شكرا لكل من ساعدني وساندني على طوال رحلتي الدراسية
وفي الختام اسال الله التوفيق والنجاح

إخلاص

إهداء

بســـــم الله الرحمـــن الرحيـــم

(وَآخِرُ دَعْوَاهُمْ أَنِ الْحَمْدُ لِلَّهِ رَبِّ الْعَالَمِينَ) [يونس: 10]

اللهم لك الحمد قبل ان ترضى ولك الحمد إذا رضيت ولك الحمد بعد الرضاء، اللهم لك الشكر لأنك وفقتني على اتمام هذا العمل المتواضع رغم كل الصعوبات وتحديات.

إني طلبت العلم لوجه الله تعالى وذلك فضل الله يأتيه من يشاء، اللهم نويت هذا العمل وكل خطوة فيه عبادتا لك اللهم اجعله شفيعا لي لا عليا عند اليوم الاكبر.

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الى ذلك الرجل العظيم سيدي وعزوتي وقدوتي الاولى وتاج راسي الى الذي بذل كل ما بوسعه ولم يبخل "ابـــي: **السيد الاشهب مصباح** " اطال الله عمرك وامدك بالصحة والعافية.

الى حبيبتي وعزيزتي وجميلتي ووردة قلبي الى الشمعة التي تنير طريقي لمن رضاها يخلق لي التوفيق " امـــي" غاليتي اطال الله في عمرك بالصحة والعافية.

قَالَ الله **(سَنَشُدُّ عَضُدَكَ بِأَخِيكَ وَنَجْعَلُ لَكُمَا سُلْطَانًا فَلَا يَصِلُونَ إِلَيْكُمَا بِآيَاتِنَا أَنْتُمَا وَمَنِ اتَّبَعَكُمَا الْغَالِبُونَ)** [القصص - 35] الى

أحبتي وضلعي الثابت الى من استمد منهم القوة "إخوتـــي"كل باسمه واختص بذكر **"محمد ايمن"** اثبك الله وجزاك عني خير الجزاء وأصلح حالك وولدك ومالك و "اخواتـــي وزوجة اخـــي "كل باسمها حبيبات قلبي حفظهن الله ووفقهن الى ما يحب ويرضى

وخاصتا ضراعي الايسر ورفيقة ومؤنسة دربي صاحبة البسمة **"عبير"**.

الى من سبقونا الى دار الحق الى من ذكراهم في قلوبنا " اجـــدادي" رحمهم الله وغفر ذنوبهم.

واذكره بأطيب الذكر استاذي ومؤطري وموجهي الاول البروفسور " **شمسة احمد لخليفة** " واستاذاتي " **عزي منال** " " **غرايسة نورة**" حفظهن الله.

الى من قبلوا مني كل السؤال ولم يبخلوا بالإجابة استاذاتي " **ابتسام العايب**" " **بوضبية وفاء**" "**زموري نوال**" " **كرطي اميرة**" " **شنة جهاد** "رعاكم الله بحفظه وجعلكم ذخرا للعلم.

الى رفيقاتي في هذا العمل زميلاتي ومؤنساتي في هذا الطريق الى من شاركوني أصعب وأجمل اللحظات " **موساوي احلام**" "**خليفي اخلاص**"

جاءت كما ارادها الله، الخير فيما اختاره الله انت رب الخير لا تأتني الا بالخير، اللهم رضيت بقدرك وخيرك.

✍ *Rania*

إهداءِ

ۦ ﴿وَأَنْ لَيْسَ لِلإِنسَانِ إِلَّا مَا سَعَى وَأَنَّ سعْيَهُ سَوْفَ يُرَى﴾ ۦ النجم: 39

الحمد الله ملأ السموات والارض وما بينهما نشكره سبحانه وتعالي علي منحه نعمة العقل والامل والصبر والصلاة والسلام علي اشرف المرسلين وبعده.

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أهديك هذا الانجاز الذي لولاك لم يكن. أهديك مراحلي وانجازاتي كلها فالفضل والثناء للمولي ولكفاحك لأجلي وعطائك الذي يضمد تعبي. كنت لي الأم والأب اكتفيت بك عن العالم اجمع يا خير عوض وأعظم سند. كنت لي النور في دربي الشاق مضينا معا طريقا لم يكن محفوفا بالسهولة. ها أنا اليوم أهديك علما وشهادة تخليتي عنها في سبيل رعايتي وتعليمي ممتنة لأن الله اصطفاك من البشر أما لي.

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اشكر كل من مد لي يد العون من قريب او من بعيد ... أخص بالذكر الدكتورة **العايب ابتسام، زمولي نوال، كرطلي اميرة** وفقهن الله

الي من سعتهم ذاكرتي ولم تسعهم مذكرتي الي من حفظهم القلب ونسيهم القلم.

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Résumé

Ces dernières années, l'utilisation de plantes pour la prévention et le traitement du cancer et d'autres maladies a attiré davantage d'attention en raison de la diversité de leurs constituants phytochimiques et de la diminution de leurs effets indésirables. Cette étude examine les propriétés antioxydantes, anti-inflammatoires, antibactériennes et anticancéreuses de deux plantes du désert d'El Oued, en Algérie, *Bassia muricata* et *Suaeda mollis*, de la famille des Chénopodiacées, et leurs effets thérapeutiques contre le diabète et le cancer de la peau.

Les analyses de la composition chimique ont identifié des composés actifs tels que les polyphénols, les flavonoïdes, les alcaloïdes, les terpènes et les saponines. Grâce à des études d'efficacité in vitro, les deux plantes ont présenté d'importantes activités antioxydantes, anti-inflammatoires et antibactériennes. Le test de cytotoxicité MTT contre les cellules de cancer du sein MCF-7 et les cellules de cancer du poumon A549 a révélé que *S. mollis* présentait une toxicité sélective envers les cellules de cancer du sein, tandis que *B. muricata* présentait des effets cytotoxiques plus larges contre les cellules MCF-7 et A549.

Pour évaluer les effets antidiabétiques, 25 rats Wistar albinos mâles ont été divisés en cinq groupes (n = 5) : groupes témoins, diabétiques non traités et groupes diabétiques traités avec *B. muricata* (20 mg/kg) ou *S. mollis* (75 mg/kg).et les groupes diabétiques traités à l'acarbose (12 mg/kg). Le diabète a été induit à l'aide d'Alloxan (150 mg/kg). Le traitement a amélioré de manière significative la glycémie ($p < 0,001$) et les taux de lipides ($p < 0,01$) et a renforcé les activités des enzymes antioxydantes. L'analyse histologique a montré que les extraits protégeaient les tissus du pancréas, du foie, des reins et de la rate des dommages causés par le diabète, avec des réductions significatives des taux de MDA ($p < 0,001$).

Les effets anti-cancer de la peau ont été évalués à l'aide du cancer de la peau induit par le DMBA chez le rat. Quarante-deux rats Wistar albinos mâles ont été divisés en sept groupes (n = 6) : groupes témoins, traités au DMBA, traités à l'acétone et traités au DMBA traités avec des extraits alcaloïdes de *B. muricata* ou de *S. mollis* (2 mg/kg) par voie orale ou par voie topique). Les extraits ont réduit de manière significative le stress oxydatif ($p < 0,001$) et amélioré les paramètres biochimiques, notamment des réductions des activités des enzymes hépatiques (GOT et GPT, $p < 0,05$). L'examen histologique a montré une réduction des anomalies tissulaires par rapport au groupe DMBA uniquement.

Ces résultats suggèrent que *B. muricata* et *S. mollis* possèdent un potentiel thérapeutique important en tant qu'agents naturels pour gérer le diabète et prévenir le cancer

de la peau. Des recherches supplémentaires sont recommandées pour optimiser leur sélectivité et leur efficacité pour des applications cliniques potentielles.

Mots clés : Diabète, Cancer de la peau , Stress oxydatif , DMBA ,Alloxan ,*Bassia muricata* , *Suaeda mollis*

الملخص

في السنوات الأخيرة، اكتسب إستخدام النباتات للوقاية من السرطان والأمراض الأخرى وعلاجها مزيدًا من الاهتمام نظرًا لتنوع مكوناتها الكيميائية النباتية وتأثيراتها الضارة الأقل. تبحث هذه الدراسة في الخصائص المضادة للأكسدة، والمضادة للالتهابات، والمضادة للبكتيريا، والمضادة للسرطان لنبتتين صحراويتين من الوادي، الجزائر، *Bassia muricata* و*Suaeda mollis*، من عائلة *Chenopodiaceae*، وتأثيراتها العلاجية ضد مرض السكري وسرطان الجلد.

حددت تحليلات التركيب الكيميائي المركبات النشطة مثل البوليفينول والفلافونويد والقلويدات والتربين والصابونين. من خلال دراسات الفعالية المختبرية، أظهر كلا النباتين أنشطة كبيرة مضادة للأكسدة ومضادة للإلتهابات ومضادة للبكتيريا. السمية الخلوية كشفت مقايسة MTT ضد خلايا سرطان الثدي MCF-7 وخلايا سرطان الرئة A549 أن *S. mollis* أظهرت سمية انتقائية تجاه خلايا سرطان الثدي، في حين أظهرت *B. muricata* تأثيرات سامة للخلايا على نطاق أوسع ضد خلايا MCF-7 وخلايا A549.

لتقييم التأثيرات المضادة لمرض السكر، تم تقسيم25 ذكرًا من فئران ويستار البيضاء إلى خمس مجموعات (العدد = 5): مجموعة السيطرة، ومجموعات مرضى السكري غير المعالجين، ومجموعات مرضى السكري المعالجة بـ *B. muricata* (20 مجم / كجم) أو *S. mollis* (75 مجم / كجم) ومجموعات مرضى السكري المعالجة بالأكاربوز (12 ملغم / كغم). تم إحداث مرض السكري باستخدام الألوكسان (150 ملغم / كغم). أدى العلاج إلى تحسين ملحوظ في نسبة الجلوكوز في الدم ($P < 0.001$) ومستويات الدهون ($P < 0.01$) وتعزيز أنشطة الإنزيم المضاد للأكسدة. أظهر التحليل النسيجي أن المستخلصات تحمي أنسجة البنكرياس والكبد والكلى والطحال من التلف الناتج عن مرض السكري، مع إنخفاض كبير في مستويات MDA ($P < 0.001$).

تم تقييم التأثيرات المضادة لسرطان الجلد باستخدام سرطان الجلد الناجم عن DMBA في الفئران. تم تقسيم اثنين وأربعين من فئران ويستار البيضاء الذكور إلى سبع مجموعات (العدد = 6): مجموعة السيطرة، والمجموعات المغلفة بـ DMBA، والمعالجة بالأسيتون، والمغلفة بـ DMBA، والتي تم علاجها بمستخلصات قلوية من *B. muricata* أو *S. mollis* (2 ملغم / كغم عن طريق الفم أو موضعياً). المستخلصات خفضت بشكل كبير الإجهاد التأكسدي ($P < 0.001$) وتحسين المعلمات البيوكيميائية، بما في ذلك التخفيضات في أنشطة إنزيم الكبد (GOT وGPT، $P < 0.05$). أظهر الفحص النسيجي إنخفاضًا في تشوهات الأنسجة مقارنةً بمجموعة DMBA فقط. تشير هذه النتائج إلى أن *B. muricata* و *S. mollis* يمتلكان إمكانات علاجية كبيرة كعوامل طبيعية لإدارة مرض السكري والوقاية من سرطان الجلد. يوصى بإجراء مزيد من الأبحاث لتحسين انتقائيتها وفعاليتها للتطبيقات السريرية المحتملة.

الكلمات المفتاحية: مرض السكري، سرطان الجلد، الإجهاد التأكسدي، DMBA، الألوكسان، *Bassia muricata* ، *Suaeda mollis*

ABBREVIATIONS LIST

A1: Absorbance 1

A2: Absorbance 2

A549: human lung carcinoma

Abs: Absorbance

AlCl3: Aluminum chloride

ALP: Alkaline phosphatase

ATP: Adenosine triphosphate

B.m: Bassia muricata

BHT: Butyl hydroxy toluene

CAT: Catalase

CCD-1079Sk: human normal skin fibroblast cells

DMBA: 7,12-Dimethylbenz(α)anthracene

DMSO Dimethyl sulfoxide

DNA: Deoxyribonucleic Acid

DPPH: 2,2-diphenyl-1-picrylhydrazyl.

DTNB: 5,5'-dithiobis-2 nitro benzoic acid.

EDTA: Ethylenediamine tetraacetic acid.

Fe $^{+3}$: Ferric ion.

$FeCl_3$: Ferric chloride test

FRAP: Ferric-tripyridyltriazine

GOT: Glutamate-oxaloacetate-transaminase

GPT: Glutamate-pyruvate-transaminase

GSH: Glutathione

H2 PO4: Phosphoric acid

H_2O_2: Peroxyde d'hydrogène

HCL: Hydrogen chloride.

HCT: Hematocrit

HDL: Hight density lipoproteins (lipoprotéines de haute densité)

HGB: Hemoglobin.

HLA: Human leukocyte antigens

IC50: Inhibitory concentration 50

IP: Inhibition percentage

KH2PO4: phosphate buffer

LDH: Lactate dehydrogenase.

LDL: Low density lipoproteins

MCF-7: human breast cancer cells

MCH: Mean corpuscular Hemoglobin.

MCHC: Mean Corpuscular Hemoglobin Concentration.

MCV: Mean corpuscular volume

MDA: Methylene dioxyamphetamine

MTT : 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide

Na2CO3: sodium carbonate

Nacl: sodium cloride.

O $^{\cdot -}$: Superoxide radical.

O^{2-}: Oxygen radical.

OH$^{\cdot -}$: Hydroxyl radical

OH$^{\bullet}$: Radical hydroxyle O2 Oxygène singulet.

PBS Sodium Phosphate Buffer

PLT: Platelets

RBC: Red blood cell count.

RNS: Reactive Nitrogen Species

ROS: Reactive Oxygen Species

S.m: Suaeda mollis

SPF: Sun protected factor

T1DM : Type 1 Diabetes Mellitus

T2D : Type 2 Diabetes

TBA : Thiobarbituricacid :L'acide thiobarbiturique

TCA: Trichloroacetic acid.

TG: Triglycérides

WBC: White blood cell

γ-GCS: γ-glutamylcysteine synthetas

FIGURES LIST

TABLES LIST

Summary

Introduction

Introduction

Medicinal plants have been playing an essential role in the development of human culture. As a source of medicine, Medicinal plants have always been at forefront virtually all cultures of civilizations. Medicinal plants are regarded as rich resources of traditional medicines and from these plants many of the modern medicines are produced. For thousands of years medicinal plants have been used to treat health disorders, to add flavor and conserve food and to prevent diseases epidemics. Active compounds produced during secondary vegetal metabolism are usually responsible for the biological properties of some plant species used throughout the globe for various purposes, including treatment of infectious diseases (Dar et al., 2017). Medicinal plants have proved their sole role in coping with a number of deadly diseases including cancer (Vashist & Jindal, 2012).

Medicinal plants are receiving much attention nowadays to meet the public concern of replacing synthetic medicine with those from natural origins, The growing problem of the appearance of new diseases rises up the necessity for finding replacements from natural origins (Ghanem & El-Magly, 2008).

The species *Bassia muricata (L.)* A *Chenopodiaceae* family and locally known as Ghabitha. It is distributed in the dry regions in Arabian Desert, North Africa, and Iran This medicinal plant whose leaves and aerial part have been reported to have medicinal significance in the traditional system of medicine it is used for diarrhea and skin diseases, specifically to treat dermatosis،pustules, boils, and infected wounds , antidiabetic Also mentioned that it is used as an antipyretic, analgesic, and against spasticity, studies have proven that it possesses antioxidants, antimicrobials, and insecticidal properties(Gheraissa et al., 2022).

Suaeda mollis is a halophyte plant, it grows in harsh conditions. Conditions that encourage the biosynthesis of a wide range of biologically active metabolites possessing blood sugar-lowering, anti-inflammatory, blood lipid-lowering, cardioprotective, antioxidant, antimicrobial, and anticancer activities (Amin & Musa, 2016).

Diabetes mellitus is a common metabolic disorder characterized by chronic high blood sugar levels, leading to both microvascular and macrovascular complications. These complications include limb loss, blindness, ischemic heart disease, and end-stage renal

disease. Diabetes is broadly classified into two categories: type 1 diabetes and type 2 diabetes. Both types result from complex interactions between genetic and environmental factors, but their pathogenesis differs. Type 1 diabetes occurs due to the immune-mediated destruction of beta cells in the islets of Langerhans, the site of insulin production and secretion. Generally, the disease manifests in childhood and adolescence (although it can occur at any age) and is characterized by an absolute insulin deficiency. Therefore, individuals with type 1 diabetes require insulin therapy to control hyperglycemia and maintain life (Cobelli et al., 2009).

Despite significant improvements in patient health, especially over the past 25 years, a cure for type 1 diabetes remains elusive. Additionally, despite advances in technology, blood sugar control for most people with type 1 diabetes is not optimal, and many cannot access modern treatments due to the high costs of even basic care (DiMeglio et al., 2018).

Diabetes is one of the pathological conditions that are always accompanied by oxidative stress, that is, With the preponderance of oxidative reactions over the anti-oxidative protection of tissues. Glucose oxidation is the main source of free radicals (Ebuehi et al., 2010).

Oxidative stress is caused by exposure to reactive oxygen intermediates, such as superoxide anion (O.*-), hydrogen peroxide (H_20_2), and hydroxyl radical (HO*), which can damage proteins, nucleic acids, and cell membranes. Increasing evidence suggests that the cumulative damage caused by reactive oxygen species contributes to numerous diseases (Storz & Imlayt, 1999).

Skin cancers are by far the most common malignancy of humans, particularly in the white population. The growing incidence of cutaneous malignancies has heralded the need for multiple treatment options. Although surgical modalities remain the mainstay of treatment, new research and fresh innovation are still required to reduce morbidity and mortality (Simoes et al., 2015).

7,12-Dimethylbenz(α)anthracene (DMBA) is a well-known carcinogen and immunosuppressor utilized in rodent models for studying tumor development (Al-Asady & Ghaleb, 2020). DMBA generates free radicals on the applied area of the skin leading to development of epidermal neoplasia, which is comprised of one irreversible tumor initiation step and another reversible but accumulative tumor promotion (Das et al., 2010).

The aim of the present work is in vitro evaluation of Chemical, biological and in vivo activities of *Bassia muricata, Suaeda mollis* plant extracts against diabetes and skin cancer.

First part

Bibliographic synthesis

Chapter I

Bassia muricata & *Suaeda mollis*

1. Bassia muricata

1.1. Generality

The *Chenopodiaceae* family comprises 1700 species distributed in about a hundred genera. The members of *Chenopodiaceae* are mostly adapted for arid to semiarid and/or saline habitats. This family has a cosmopolitan distribution, and comprises herbs or shrubs, rarely small-trees or lianas. The presence of various alkaloids, flavonols, flavonoids and triterpenoid saponins has been reported in the Chenopodiaceae (Mohammedi et al., 2019).

The species *Bassia muricata (L.)* Asch. is a sandy annual plant that belongs to the *Chenopodiaceae* family and its synonyms are *Salsola muricata L.*, or *Kochia muricata L.*, and locally known as Ghabitha. It is distributed in the dry regions in Arabian Desert, North Africa, and Iran (Abd-ElGawad et al., 2020). It is one ofthe important plants that used in traditional medicine where it used as analgesic, antipyretic, and nephritic as well as it has several biological activities such as antioxidant, antibacterial molluscicidal, and insecticidal activities (Cherrada et al., 2024).

1.2. Botanical description

Bassia muricata belongs to the *Chenopodiaceae* family. It is a decumbent as woody annual ‹separated from the base, up to 80 cm in tallness (Al-barri et al., 2021). differ widely in habit, lower branches decumbent. Leaves sessile ‹linear-narrow elliptic, 10-20 mm long and 1.5-2.0 mm wide, with acute-attenuate tips. Inflorescence spicate, with 1-3 sessile flowers in the axils of leaf like bracts. Fruiting perianth with radiating spines, spines longer than the disc. Seeds orbicular, pale dark brown. Flowers exposed with loose hairs, stigma 1-1.8 mm (Turki et al., 2006). The plants have a pronounced tendency towards a cushion like appearance, due to the numerous ‹almost vegetative shoots, which are densely covered with small, glaucous needle like leaves ‹4−7 mm in size (Figure 01) (Al-barri et al., 2021). The species is a common sandy herb growing in Egyptian and Algerian deserts (Mohammedi et al., 2019).

Figure 01. Different parts of *B. muricata*: A. Longitudinal section of a flower; B. Cross section of flower (Quezel & Santa, 1962)

1.3. Geographic distribution

The genus *Bassia* comprises about 20 species, distributed in the western Mediterranean to eastern Asia (El Mokni & Iamonico, 2019).

Geographic range of *Bassia muricata* grows in sandy habitats and on the edges of desert roads (Turki and al., 2006). In North Africa, the eastern Mediterranean region, Sinai, Saudi Arabia, Palestine, Iran, Iraq, Egypt, Syria, PakistanAlgeria, Cyprus, Egypt, Ethiopia, Gulf States, Kuwait, Lebanon, Libya, Mali, Mauritania, Morocco, Oman, Sinai, Tunisia, Western Sahara and Yemen. (G.Schweinfurth and auct. 1867)

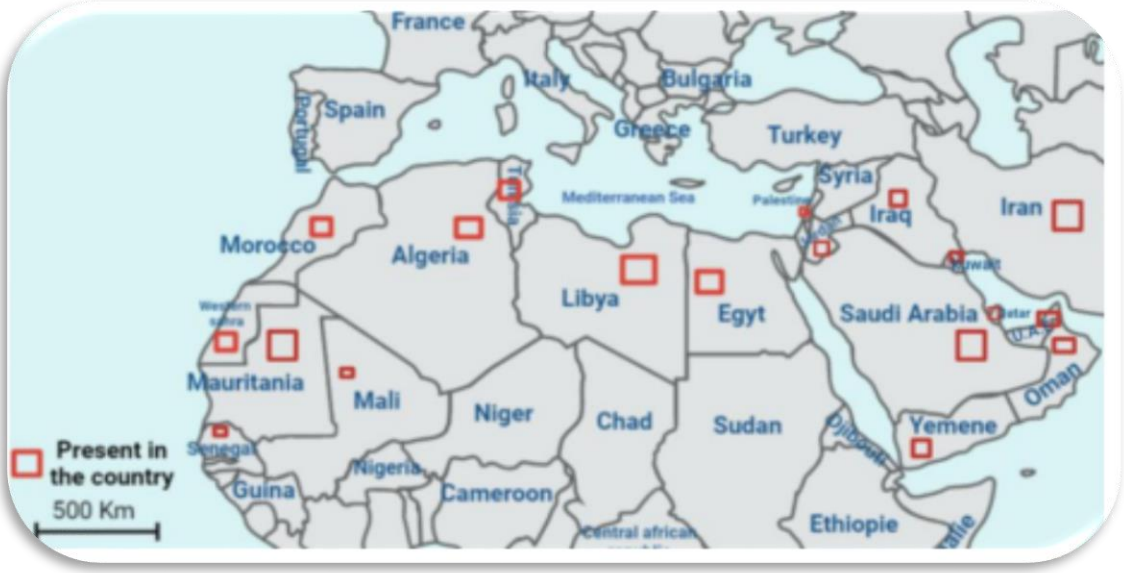

Figure 02. The geographical distribution of *B. muricata* (Gheraissa, 2023)

1.4. Taxonomical Classification

Taxonomic of *B. muricata* is presented in table 01 below according Cronquist, A, (1981).

Scientific name: *Bassia muricata (L)*

French name: Bassia fact file

Arabic Name: غبيثاية، الحليبة

Table 01. Classification of *Bassia muricata*

Taxonomical Rank	Taxon
Kingdom :	Plant
Under Kingdom :	Tracheobionta
Division :	Spermatophyta
Phylum :	Magnoliophyta
Class :	Magnoliopsida
Under the class :	Caryophyllidae
Order :	Caryophyllales
Family :	*Chenopodiaceae*
Genus :	*Bassia*
Species :	*Bassia muricata*
Synonyms :	*Salsola muricata L . ,Kochia muricata L.*

1.5. Chemical constituents

Chemically, the *B. muricata* plant contains: triterpenoidal saponins, tannins, sterols, phenolics (coumarin, p-coumaric acid, gallic acid, p-catechuic acid, salicylic acid, ferulic acid), favan-3-ol(catechum), favonoids (kaempferol, kaempferol-3-O-α-L-rhamnoside, rutin, myricetin, qurcetin-3-O-α-L-rhamnoside, qurcetin-3-O-β-D-glucoside,3′-methylquerctein,3-O-[α-L-arabinopyranosyl(2→1)-L-α-arabinopyranosyl)]-3′-methylquercetin)، flavonoid glycosides (quercetin-3-O-sophoroside ، quercetin-3,7-O-β-diglucopyranoside) and two acetylated favonoid glycosides (cafeoyl and feruloyl) (Al-Obeidyeen et al., 2023).

1.6. Therapeutic uses

B. muricata is regarded as a significant herb in traditional medicine, where it is utilized as a diuretic, antipyretic, anti-inflammatory, and antispasmodic (Al-Obeidyeen et al., 2023). It is used to treat skin conditions, acne, boils, infected wounds, diarrhea, and rheumatic and

renal illnesses. It also possesses varying degrees of anti-inflammatory, antispasmodic (Chemsa et al., 2016), and hypotension properties . It has several biological properties, including antibacterial, molluscicidal, insecticidal, and antioxidant properties. It is also utilized as an antidiabetic (Gheraissa et al., 2022).

2. Suaeda mollis

2.1. Generality

Genus *Suaeda*, known as seablites also referred to as seepweeds, belong to the *Chenopodiaceae* family and are annual herbaceous succulent plants. Out of the approximately 100 species, only 27 have been thoroughly examined and documented thus far. These species are found all over the world, primarily on saline-alkaline environments like wasteland and the beach. In the regions where it grows, Genus *Suaeda* is frequently utilized as animal feed or green food (Wang et al., 2022).

Suaeda mollis L. à member of the plant family *Chenopodiaceae*, is a native lignified halophytic shrub grown throughout arid rangelands of Mediterranean basin particularly in salt marshes and coastal dunes (Nedjimi, 2018). It possesses a number of morphological features allowing it to cope with both drought and variable habitats including salinity (El Ghazali, 2020).

2.2. Botanical description

Succulent perennial shrubs that reach a height of 50 cm, they are mainly glabrous, heavily branched from the base, and develop slowly. Initially pale green, the stems eventually turn grey and split. Young leaves and branches are turning black from drying. Older leaves are flat on the upper side and obovate to oblong to elliptical. All or most of the leaves are obovate to globular, spreading or directed downward. The upper leaves gradually shrink in size and are dark green. The inflorescences consist of two to five flowered axillary clusters in lax or rather dense, leafy spikes that are terminal or branched, or the spikes are laxly paniculated. Bisexual flowers with scarlet bracts, Seeds vertical with spiral embryos (Figure 03) (El Ghazali, 2020).

Figure 03. *Suaeda mollis L*. (original photo)

2.3. Geographic distribution

Suaeda (l.) Forsk., succulent perennial halophytes belonging to the *Chenopodiaceae* family a shrub that grows widely in both terrestrial and coastal swamps and is highly salt-tolerant (Oueslati et al., 2012). It is commonly seen in dry desert regions with few water sources and an extremely salinized atmosphere (Oueslati et al., 2023).It is primarily located in Middle East and Africa (Othman & Ali, 2021), It grows in the Mediterranean Basin's arid pastures (Nedjimi, 2018) and in the central areas of Saudi Arabia (Al-Omar, 2021). It can also be found in Tunisia's north, middle, and south. In salt flats or salt depressions, S. mollis is thought to be an obligate halophyte (Oueslati et al., 2012).

Figure 04. Geographical distribution of *Suaeda mollis L.*in the world (G.Schweinfurth and auct. 1867)

2.4. Taxonomical Classification

Taxonomic of *S. mollis* is presented in table 02 below according Quzel and santa, (1961).

Scientific name: *Suaeda mollis (L)*

Table 02. Classification of *Suaeda mollis*

Taxonomical Rank	Taxon
Kingdom :	Plant
Under Kingdom :	Tracheobionta
Division :	Spermatophyta
Phylum :	Spermatophyta
Class :	Caryophylladae
Under the class :	Caryophyllales
Order :	Caryophyllales
Family :	*Chenopodiaceae*
Genus :	*Suaeda forsk*
Species :	*Suaeda mollis Desf*
Synonyms :	*S. vermiculata B. et T., Salsola mollis Desf*

2.5. Chemical constituents

Chemically ,Phenols, flavonoids, alkaloids, saponins, and sterols are present in significant concentrations in the *Suaeda mollis* plant (Al-Omar et al., 2021). In addition, it has antioxidants and the three primary flavonoids quercetin, quercetin-3-O, and kaempferol-3-O(acetyl)-hexoside-pentoside (Mohammed et al., 2022). *S. mollis* had good levels of calcium, potassium, and cobalt (Nedjimi, 2018).

2.6. Therapeutic uses

The *S. vermiculata*, an edible halophyte, is traditionally well-known for its hepatoprotective activity. Several biological activities : antimicrobial, antioxidant, anti-inflammatory, hepatoprotective, and antidepressant activities, have been reported for the plant extracts and/or its essential oils (Mohammed et al., 2022).and used by desert nomads to treat

jaundice (Mohammed et al., 2020).It is also used as a herb to lower blood sugar levels, treat asthma and respiratory diseases, and can be used in the manufacture of nutritional supplements. It is traditionally used as fuel when burned and as fodder for camels and sheep (Mohammed et al., 2019).

Chapter II

Diabetes, Skin Canser & Oxydative stress

1. Diabetes

1.1. Definition

Diabetes represents a group of metabolic disorders characterized by chronic hyperglycemia. The underlying cause typically involves either impaired insulin secretion, impaired insulin action, or commonly, both (Petersmann et al., 2019). It also includes a variety of heterogeneous disorders that share the common feature of high blood sugar levels (Roden, 2016).

Diabetes presents with multi-system complications, including microvascular (such as retinopathy, nephropathy, neuropathy) and macrovascular (like ischemic heart disease, stroke, peripheral vascular disease (Forouhi & Wareham, 2010).

Diabetes is defined as having blood sugar levels higher than 1.26 g/L (7.0 mmol/L) after two testing sessions following an 8-hour fast : or having diabetes symptoms (weight loss, polyuria, and polydipsia) in conjunction with blood sugar levels higher than or equal to 2 g/L (11.1 mmol/L) in venous plasma : or higher than or equal to 2 g/L (11.1 mmol/L) in venous plasma two hours following an oral dose of 75 g glucose (Ozougwu et al., 2013).

1.2. Diabetes classification

1.2.1. Type 1 diabetes

Diabetes is now understood as an autoimmune disorder involving the destruction of insulin-producing pancreatic β-cells. It varies in age of onset, severity, and response to therapy, often categorized into type A (with serological autoimmune response) and type B (idiopathic) (Eisenbarth, 2007). Recognition of Type 1 Diabetes Mellitus (T1DM) dates back to 1979, with significant strides in understanding its pathophysiology made in the 1960s and 1970s. This includes discoveries like insulitis, correlation with HLA genes, and detection of autoantibodies. The pathophysiology involves targeted β-cell destruction, implicating both humoral and cellular immunity, with autoantibodies against pancreatic islets being key diagnostic markers. Various autoantigens are utilized for diagnosis (Ziegler & Nepom, 2010).

Although the exact causes of this damaging process are unknown, inherited vulnerability in combination with environmental triggers such as chemicals, viruses, or specific dietary factors seem to be responsible.

High blood sugar levels combined with symptoms such as frequent urination, extreme thirst and dry mouth, weariness, loss of energy, and persistent hunger are indicative of type 1 diabetes (BENM'HAMED & BELKAID, 2019).

1.2.2. Type 2 diabetes

T2D, a major cause of diabetes, accounts for 90% of cases. It's caused by impaired insulin production by islet β cells and insulin resistance. Ageing, obesity, and physical inactivity contribute to insulin resistance. Pancreatic islets enlarge to counteract it, but insulin resistance can lead to long-term complications like atherosclerosis (Berbudi et al., 2020).

It is a complex disorder characterized by high blood sugar, nocturia, and increased thirst. Despite its complications, it often leads to early death, necessitating strict treatment guidelines (Hacene, 2022). The prevalence of type 2 diabetes is rapidly increasing. It is expected to rise to 693 million by 2045. High blood sugar in people with type 2 diabetes usually leads to significant side effects such as retinopathy, kidney failure, and cardiovascular disease (Wu GuangJie et al., 2020).

While the exact cause of type 2 diabetes remains elusive, it is believed to result from a intricate interplay of genetic predisposition and environmental factors. The likelihood of developing the condition is higher for individuals with close relatives affected by it, indicating a familial pattern." (Ali, 2013) In the early stages of type 2 diabetes, the pancreas produces more insulin to manage rising blood sugar levels. However, over time, its ability to produce insulin declines, leading to elevated blood sugar levels. This process, known as insulin resistance, is a critical aspect of type 2 diabetes (Johnson, 2021).

1.3. Pancereas

The pancreas is a gland with two functions: it secretes vast amounts of fluid rich in sodium and bicarbonate through its tiny pancreatic ducts, which are lined with epithelial cells, and it produces and releases inactive digesting enzymes through its exocrine tissue, which is made up of acinar cells (Jun et al., 2017).

The endocrine system comprises five distinct cell types within the pancreas (Figure 05), each releasing different hormones (Röder et al., 2016).

- α cells, responsible for producing glucagon and constituting 15-20% of total islet cells.

- β cells, which produce amylin, C-peptide, and insulin, making up 65-80% of total cells.
- Gamma cells producing pancreatic polypeptide (PP), representing 3–5% of total islet cells.
- Delta cells producing somatostatin, constituting 3-10% of total cells; and epsilon cells producing ghrelin, comprising less than 1% of total islet cells.

In all animals, the majority of the pancreatic islets are made up of beta cells. With a diameter ranging from 13 to 18 micrometers, these polygonal cells have over 10,000 secretory granules, each of which may hold 8 to 9 micrograms of insulin (1.6 to 1.8 insulin amol) (Rorsman & Ashcroft, 2018).

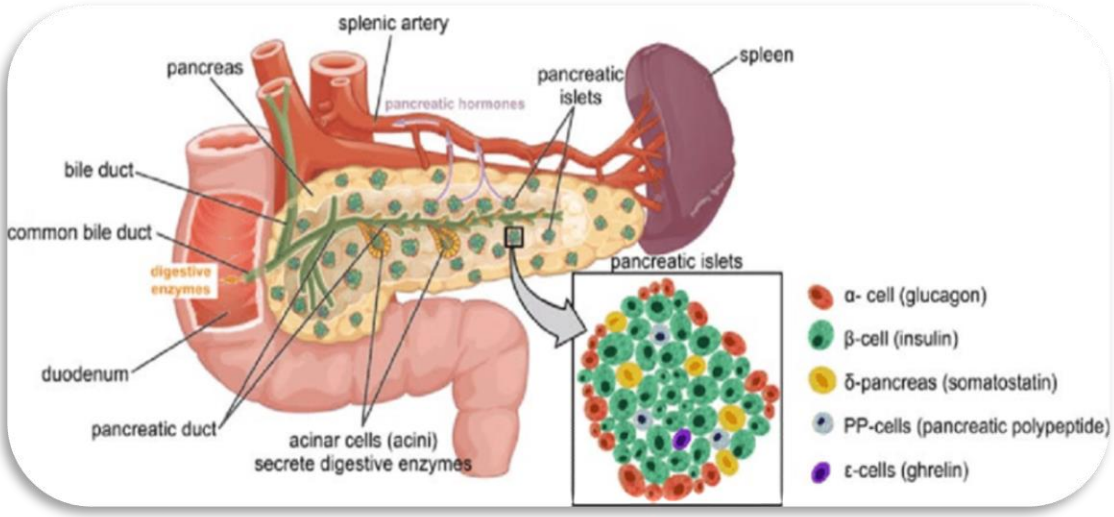

Figure 05. Anatomical organization of the pancreas (Mühlemann, 2018)

1.4. Insolin

1.4.1. Definition

Insulin is a polypeptide hormone derived from the Latin word insula, which means "island" because it is produced from the islets of Langerhans. Which was discovered by Banting and Best in 1921-1922 at the University of Toronto (Ahmad, 2014).

Insulin, a vital peptide hormone, plays a central role in regulating carbohydrate metabolism. Its deficiency leads to a rapid increase in blood sugar levels, resulting in a dangerous metabolic condition known as diabetes, insulin synthesis is regulated by blood glucose concentration. Higher glucose levels stimulate its production. Insulin consists of two peptide chains: A chain with 21 amino acids and B chain with 30 amino acids, linked by

two disulfide bridges. The intra-A chain disulfide bridge (Figure 06) is essential for maintaining insulin's spatial structure (Lenzen, 2021).

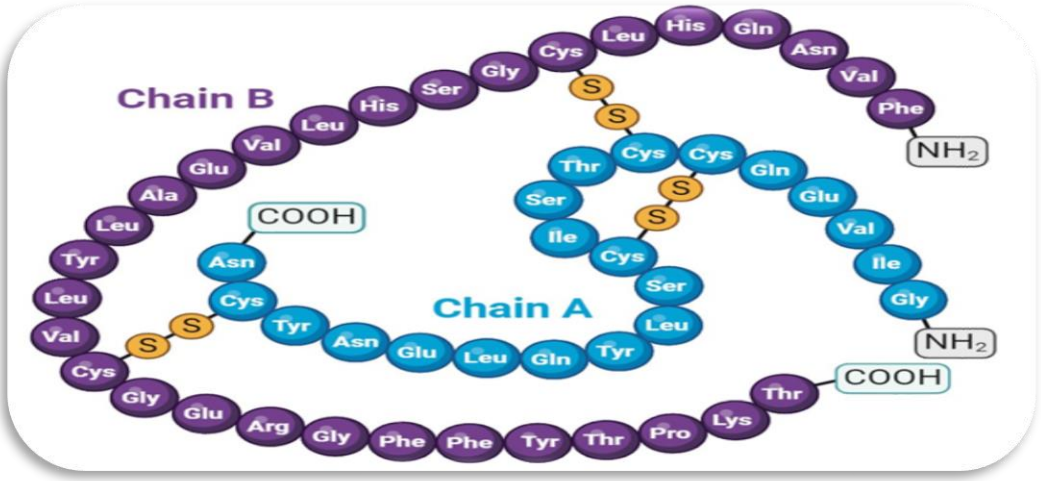

Figure 06. Schematic diagram of human insulin. Series A is shown in blue, and Series B is shown in purple. Intra- and interchain disulfide bridges between cysteine residues are shown in yellow (Wang et al., 2024)

1.4.2. Insulin secretion

Elevated glucose levels stimulate Ca2+ influx into the b-cell and ATP-dependent sequestration, together with exogenous ionic transport (Komatsu et al., 2013). Glucose enters pancreatic beta cells through GLUT2 and is converted to glucose 6-phosphate (G6P) by glucokinase (GK). G6P generates ATP, increasing the ATP/ADP ratio (Figure 07). This elevation inhibits ATP-sensitive potassium channels, leading to membrane depolarization. Closure of KATP channels causes calcium influx through L-type Ca2+ channels, leading to insulin release (Kostov, 2019).

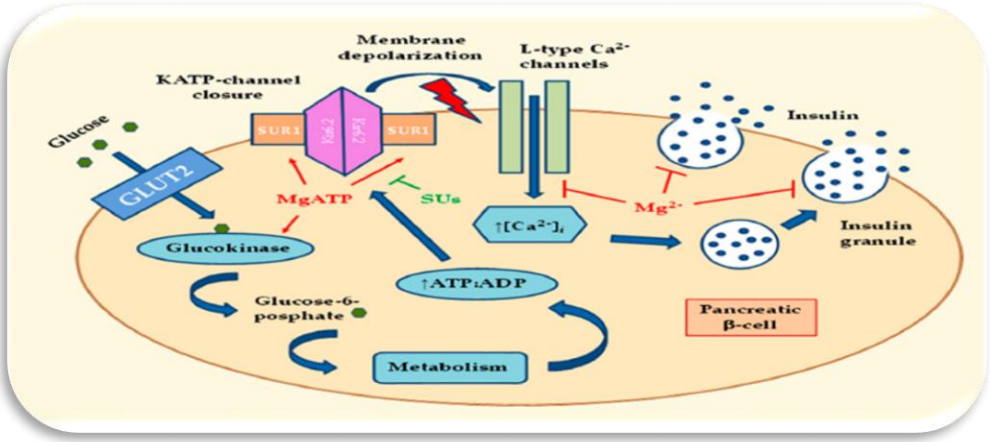

Figure 07. The insulin secretion from pancreatic beta cells (Kostov, 2019)

1.4.3. Mode d'action of insulin

Insulin acts by attaching to and activating its cell-surface receptor, which is made up of two disulfide-bonded a subunit and two b subunits, joined to form a heterotetrameric complex, a2b2. Insulin attaches itself to the extracellular a subunits and then sends a signal through the plasma membrane to activate the b subunit's intracellular tyrosine kinase domain (Pessin & Saltiel, 2000).

Since insulin is the sole hormone that regulates blood sugar, it is essential to the metabolism of glucose. Glucose transporters are translocated to GLUT4 upon receptor contact. Muscle cells and adipocytes' plasma membranes improve capture. Sugar or its reserve in the form of glycogen (glycogénèse) is broken down to release glucose and serums (Gautheron, 2021).

1.5. Diabetes Mechanism

1.5.1. Type 1 diabetes mechanisms

Type 1 diabetes is marked by the immune system's identification of β cell proteins as autoantigens, which are then targeted by auto-reactive CD4+ and CD8+ T-helper cells as well as autoantibodies. Some notable autoantigens linked to this condition include insulin, glutamic acid decarboxylase 65-kDa (GAD65), islet antigen 2 (IA-2) (Rodrigues Oliveira et al., 2023), zinc transporter 8 (ZnT8), non-specific islet cell antibodies (ICAs), islet mitochondrial autoantigen imogen-38, pancreatic duodenal homeobox factor 1 (PDX1), islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), heat shock protein 60 (hsp60), and islet cell antigen 69 (ICA69). An overview of the autoimmune processes in type 1 diabetes mellitus (T1DM) is depicted.

It is suggested that the infiltration of the islets by dendritic cells, macrophages, and T lymphocytes contributes to the loss of β-cells. Autoreactive T cells targeting β-cell autoantigens like insulin, GAD65, ZnT8 (Rodrigues Oliveira et al., 2023), and IA-2 have been identified. Although the exact trigger for these autoreactive responses is difficult to determine, it is well-known that Antigen-Presenting Cells (APCs) process these autoantigens. Within the pancreatic islets, APCs such as β cells, macrophages, and dendritic cells (DCs) are involved. These cells present the autoantigens via "diabetes-associated" HLA molecules to naive T cells, aiding in the priming and proliferation of pathogenic T cells and the production of autoreactive CD4+ T cells. The activated CD4+ T cells then produce cytokines that activate

cytotoxic CD8+ T cells specific to β cells. These activated T cells migrate to the pancreatic islets through the bloodstream, where they activate macrophages and other T cells, leading to β-cell destruction (Xie et al., 2014).

As the number of β-cells diminishes, the remaining β-cells experience increased stress, potentially leading to apoptosis. This stress can be induced by various mechanisms, including heightened endoplasmic reticulum (ER) stress due to the accumulation of misfolded or unfolded proteins (Engin, 2016).

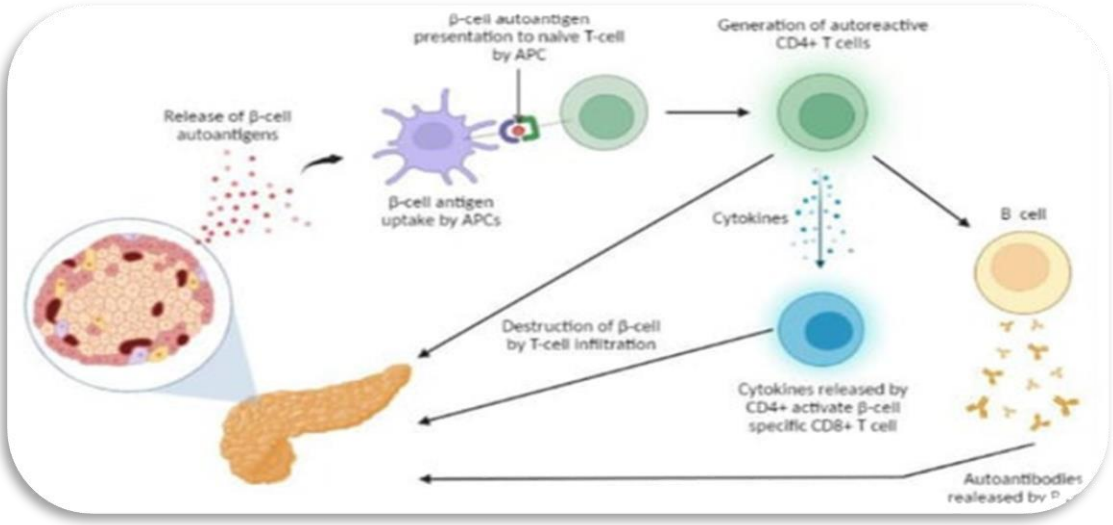

Figure 08. Physiopathology of T1DM (Rodrigues Oliveira et al., 2023)

1.5.2. Type 2 diabetes mechanisms

A. Mechanisms of insulin resistance

The term "insulin resistance refers to the decreased sensitivity of the liver, skeletal muscle, and adipose tissue to the actions of insulin R (da Silva Rosa et al., 2020). This is due to the inability of the muscles to absorb glucose and the liver to produce more glucose internally, which leads to high blood sugar during periods of fasting and after eating (Castro et al., 2014). It is a major cause of diseases such as metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), atherosclerosis, and type 2 diabetes (Lee et al., 2022).

High amounts of fatty acids, which are released into the bloodstream by adipose tissue, are involved in its implementation. An isoform of protein kinase C is then upregulated in peripheral tissues as a result of the oxidation of these fatty acids to glycerol and ceramides. The IRS-1 receptor on the amino acids serine and threonine is phosphorylated by this kinase. It has the effect of preventing the tyrosine phosphorylation necessary for the release of

insulin. This prevents vesicles carrying the GLUT4 transporter from translocating, which prevents circulating glucose from entering the cells (Figure 08), Because of the promotion of hyperglycemia, the pancreas will adjust by increasing insulin production (Shulman, 2000).

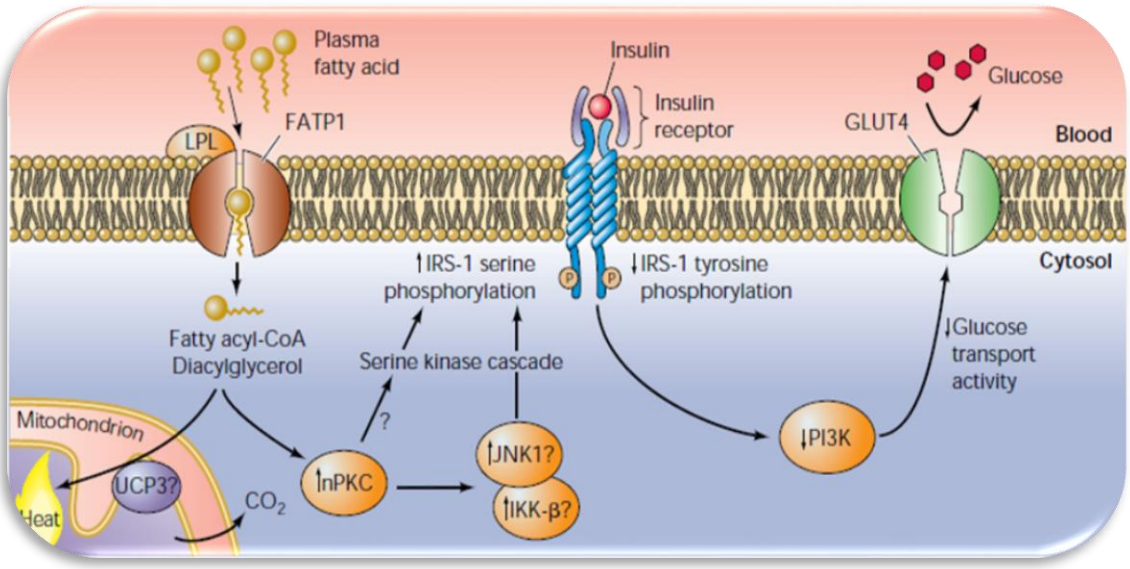

Figure 09. Mechanisms of insulin resistance (Shulman, 2004)

B. Mechanisms of insulin secretory deficiency

High levels of cytokines and chemokines found in the islets of type 2 diabetics again place inflammation at the center of the pathogenic processes. Type 2 diabetes is accompanied by a quantitative and qualitative defect in insulin secretion that evolves towards a progressive reduction of this secretion underpinned by phenomenon of apoptosis of the cells of the pancreas. By blocking the production of gene transcription factors, leading to a decrease in insulin gene expression (Anne,2012).

1.6. Risk factors

Scientific literature outlines several risk factors associated with the development of type 2 diabetes. These include:

- Age: Individuals aged 40 years and above are at higher risk.
- Family History: Having a first-degree relative with type 2 diabetes increases susceptibility.
- Ethnicity: Belonging to high-risk populations such as indigenous, Hispanic, Asian, or African communities elevates the risk.

- Glucose Intolerance: A history of glucose intolerance or abnormal fasting glycemia is a significant risk factor.
- Complications: Presence of microvascular or macrovascular complications linked to diabetes indicates heightened risk.
- Vascular Risk Factors: Exposure to factors like dyslipidemia, hypertension, overweight, and abdominal obesity increases susceptibility.

Additional risk factors may include a history of gestational diabetes, giving birth to a high-birth-weight baby, certain medical conditions (e.g., polycystic ovary syndrome, acanthosis nigricans, psychiatric disorders, HIV infection, sleep apnea syndrome), and the use of medications that can affect blood glucose levels (e.g., glucocorticoids, antipsychotics, highly active antivirals) (Linggabudi et al., 2022).

1.7. Diabetes complications

Diabetes can lead to life-threatening health complications due to poorly absorbed glucose, causing damage to tissues and increasing the risk of premature death. Long-term complications include vision loss, renal failure, peripheral neuropathy, and autonomic neuropathy (Figure 10). Diabetic patients also have an increased incidence of cardiovascular, peripheral arterial, and cerebrovascular diseases, hypertension, and abnormalities in lipoprotein metabolism (Bouharkat, 2022).

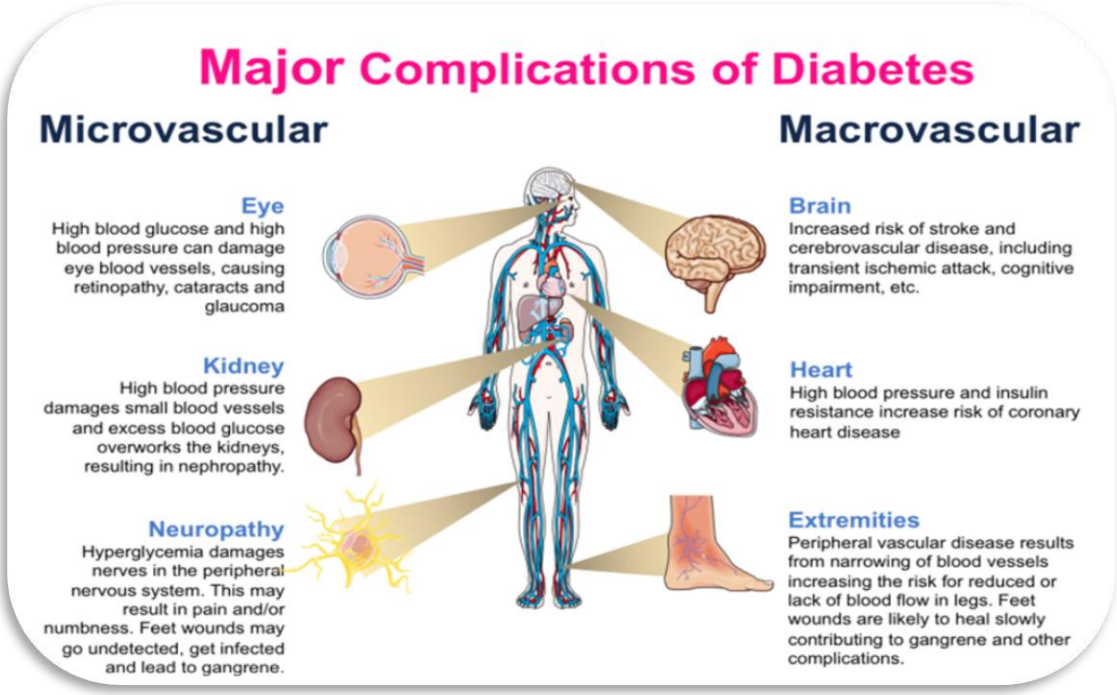

Figure 10. Chronic complications of diabetes (Al-Hmmamy, 2020)

1.7.1. Microvascular Complications

Glycemic management and the occurrence and development of microvascular problems are continuously correlated. The primary microvascular consequences caused by chronic hyperglycemia are diabetic nephropathy, neuropathy, and retinopathy (Nguyen et al., 2012).

A. Diabetic retinopathy

It is a major cause of vision loss, as it is characterized by swelling of the basement membrane of blood vessels, loss of alveoli, and the formation of aneurysms in the microvascular system as a result of sugar accumulation (Ahmad & Hoda, 2020).

Hyperglycemia leads to many overlapping physiological processes. These processes include non-enzymatic glycation assembly, protein kinase C (PKC) activation, inflammation, and oxidative stress, all of which lead to the development of microvascular and retinal damage in the eye (Eshaq et al., 2017).

B. Diabetic nephropathy

It is one of the most serious complications of diabetes and has become the leading cause of advanced-stage kidney disease. It affects more than one third of patients with type 1 diabetes, and its effect reaches 25% of all patients with type 2 diabetes. Which contributes significantly to increasing disease and mortality rates (Parveen et al., 2016).

Hyperglycemia is the primary factor for kidney damage associated with DN, because it activates and deactivates various metabolic pathways. It also exacerbates glucose oxidation and production of reactive oxygen species (ROS) within mitochondria, leading to increased oxidative stress (Sun et al., 2013).

C. Diabetic neuropathy

It is a type of nerve fibrosis characterized by its effect on sensory and motor nerves. This fibrosis is associated with changes in the metabolism and microvascular process resulting from hyperglycemia and cardiovascular risk factors. Its prevalence in cases of diabetes can reach 50%, depending on the duration and age of the patient (Alam et al., 2017).

The increased oxidative stress that comes with diabetes mellitus is one of the processes by which hyperglycemia induces neuronal damage (Boyer, 2016).

1.7.2. Complications Macrovasculaires

- **Atherosclerosis**

Diabetes accelerates the development of atherosclerosis, leading to widespread vascular issues, including cardiovascular diseases. This is attributed to chronic elevation of blood sugar levels, lipid disturbances, and insulin resistance. These factors contribute to the formation of fatty deposits in arteries and increase the risk of heart diseases. Lipid abnormalities, such as high cholesterol and triglyceride levels, along with reduced levels of heart-friendly cholesterol, are among the significant contributors. Insulin resistance and the prevalence of small, dense low-density lipoprotein particles exacerbate blood lipid levels, raising the risk of heart diseases in diabetic individuals (Hasheminasabgorji & Jha, 2021).

1.7.3. Acute Complications

- **Hyperosmolar coma**

Hyperosmolar hyperglycemic syndrome (HHS) is a clinical condition arising from complications of diabetes mellitus. This clinical condition was previously called a non-ketotic hyperglycemic coma; non-ketotic hyperosmolar hyperglycemic syndrome, and non-ketotic hyperosmolar coma (KHONK). Current HHS diagnostic criteria include plasma glucose levels >600 mg/dL and an increase in effective plasma osmolality >320 mosm/kg in the absence of ketoacidosis. Hyperosmolar hyperglycemic syndrome (HHS) usually occurs with lower insulinopenia levels compared to diabetic ketoacidosis (DKA), but its pathophysiology is considered the same. The mortality rate in Hyperosmolar hyperglycemic syndrome (HHS) can be up to 20% which is about 10 times higher than the death seen in diabetic ketoacidosis. Clinical outcomes and prognosis in HHS are determined by several factors: age, degree of dehydration, and the absence or absence of other accompanying diseases (Linggabudi et al., 2022).

- **Diabetic ketoacidosis**

Diabetic ketoacidosis is a serious condition that results from a buildup of acidic products produced by the body. It is especially for diabetics. It is an acute metabolic event that almost always results from an error that could have been corrected. In short, diabetic ketoacidosis is the culmination of a profound dysfunction in the diabetic condition (French et al., 2019).

It is a severe metabolic complication of diabetes characterized by hyperglycemia, hyperketonemia, and metabolic acidosis. It is primarily observed in patients with type 1 diabetes and presents with symptoms such as nausea, vomiting, and abdominal pain. If left untreated, it can lead to cerebral edema and coma, which is potentially life-threatening. The diagnosis of diabetic ketoacidosis is confirmed by the presence of hyperglycemia with ketosis and ketonuria, as well as an increased anion gap indicating metabolic acidosis. Treatment includes rehydration, insulin administration, and prevention of hypokalemia (Malone et al., 1992).

1.8. Diabetes treatment

1.8.1. Treatment of Type 1 Diabetes

Exercise combined with appropriate medications and medical nutrition has been the cornerstone of treatment for T1DM patients for many years. Athletes with T1DM benefit from exercise in the same ways as their healthy counterparts. These include improvements in health-related quality of life, lowering blood pressure, improving lipid abnormalities, improving insulin sensitivity, requiring less insulin, lowering hemoglobin A1c (HbA1c) levels, enhancing endothelial function, improving insulin requirements, and improving cardiorespiratory fitness (Horton & Subauste, 2016). Insulin therapy is the cornerstone of care; The hormone is broken down in the stomach and cannot be taken orally, so daily injections are necessary. The patient learns to adjust the insulin dose based on his physical activity and diet (Church & Haines, 2016).

1.8.2. Treatment of Type 2 Diabetes

A. Pharmacological

Involves a staged approach. Initially, lifestyle modifications are recommended. If glycemic targets are not met, treatment with metformin, an oral hypoglycemic agent, is advised as monotherapy according to French recommendations from the Haute Autorité de Santé (HAS). If glycemic goals are still not achieved, dual therapy is recommended, typically involving a combination of metformin and a sulfonylurea. In cases where glycemic levels continue to rise, a third medication is added, such as an oral hypoglycemic agent (e.g., alpha-glucosidase inhibitors, gliptins, or glifozines) or an injectable medication (e.g., insulin or Glucagon-like peptide-1 [GLP-1] analogues). In the final stage, patients may require a

combination of intermediate or long-acting insulin along with rapid-acting insulin (Association, 2014).

B. Non -pharmacological

Lifestyle modifications play a crucial role in the management of diabetes across all age groups, with particular emphasis on the elderly population. The Diabetes Prevention Program highlights the significance of lifestyle changes, especially for individuals under 60 years old, who exhibited improved glycemic control over time. This improvement is attributed partly to their enhanced ability to adapt to lifestyle modifications compared to younger age cohorts (Marín-Peñalver et al., 2016).

Diabetic patients are advised to maintain a balanced and varied diet, incorporating a source of carbohydrates at each meal (while considering the glycemic index of foods), and to avoid excessive fat intake as well as alcohol consumption.

Smoking is the primary risk factor for cardiovascular diseases, premature death, and microvascular complications, which is why diabetic patients should not use tobacco (Association, 2004).

2. Skin Canser

Cancer tops the list as the primary contributor to mortality in economically advanced nations and takes second place in developing countries. This burden of cancer is on the rise in economically developing regions due to factors like population aging and expansion, coupled with a growing inclination towards cancer-related lifestyle behaviors. These behaviors include smoking, physical inactivity, and the adoption of diets that mirror Westernized patterns (Jemal et al., 2011).

In terms of mortality, cancer currently ranks as the second leading cause of death worldwide, resulting in approximately 8.97 million deaths, following ischemic heart disease. However, projections suggest that by 2060, cancer is poised to surpass ischemic heart disease and become the primary cause of death, with an estimated ~18.63 million deaths anticipated globally (Mattiuzzi & Lippi, 2019).

According to the World Health Organisation (2018), one-third of people are falling in skin cancer. Approximately 232,000 people were diagnosed with skin cancer in 2012 as for every Cancer Research UK (2018). An expected 100,350 novel cases of persistent skin cancer will be identified in the U.S. in 2020, among 6,850 deaths expected to outcome from the analysis. Melanoma records for less than 1% of skin cancer cases, however, the majority are skin cancer deaths. The whole occurrence of skin cancer is about 2.6% (1 in 38) for the European people, 0.1% (1 in 1,000) for African and Americans, 0.6% (1 in 167) for Hispanics. The former studies illustrate if skin cancer is noticed near the beginning than the endurance time for five years is 99% in the U.S. The survival time falls to 65% after the disease gets to the lymph nodes and 25% after the diseases multiply to further organs (Abbas & Baig, 2020).

2.1. Definition of skin cancer

Skin cancer is one of the mortal diseases and constantly rises day by day. The way of treatment for different types of cancer is chemotherapy. Several synthetic anticancer drugs are used but they have side effects (Abbas & Baig, 2020). Skin cancer occurs due to the uncontrolled proliferation of abnormal cells in the epidermis (Queen, 2017), the outer layer of the skin, as a result of DNA damage that remains unrepaired, causing mutations. These mutations prompt rapid multiplication of skin cells, culminating in the development of malignant tumors. Tere are two main types of skin cancer which are specified as non-melanoma skin cancer and melanoma skin cancer and the former is further categorized into

basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Non-melanoma skin cancer (NMSC) or keratinocyte skin cancer (KSC) is the most common form of skin cancer (Hasan et al., 2023).

2.2. Types of skin cancers

2.2.1. Non-melanoma skin cancer (NMSC)

NMSC skin cancer is a kind of skin cancer in which cells other than melanoma cells are affected by the cancer. The rate of occurrence of NMSC is increasing by 10% per year. the most common reason for NMSC occurrence is Ultraviolet (UV) rays have a high risk in persons with lighter shade. NMSC can also be developed due to Genetic mutation such as a mutation in certain gene families named CYP450, GST (Glutathione S-transferase), p53. Tere are several distinctive forms of NMSC which are caused by viruses such as verrucous carcinoma, Bowenoid papulosis, epidermodysplasia verruciformis, squamous cell carcinoma, Kaposi sarcoma, and the most common as well as high occurrence rate named Merkel cell carcinoma (Hasan et al., 2023).

2.2.2. Basal cell carcinoma (BCC)

Is a type of skin cancer that originates from the basal layer of the epidermis and its appendages. It is primarily caused by mutations in cells triggered by exposure to ultraviolet radiation, commonly occurring on areas of the skin exposed to the sun, such as the nose, ears, face, and backs of hands. However, it can also manifest anywhere on the body. BCC typically progresses slowly and rarely spreads to other parts of the body. This type of cancer is more prevalent among individuals of Caucasian descent, with men having a 30% higher incidence rate compared to women. The lifetime risk of developing BCC is estimated to be 30%. Additionally, the incidence of BCC tends to increase with age and proximity to the equator. It's worth noting that around 40% of individuals diagnosed with BCC develop another lesion within five years. This highlights the importance of regular skin examinations and sun protection measures to reduce the risk of developing additional lesions and to catch any potential recurrences early (Linares et al., 2015).

2.2.3. Squamous cell carcinoma (SCC)

Ranks as the most prevalent form of skin cancer across much of the globe. While it can manifest in any region of the body, it typically arises from pre-existing cutaneous dysplasia rather than emerging de novo. The vast majority of cutaneous squamous cell

carcinomas stem from solar (actinic) keratoses and generally exhibit low aggressiveness. However, lesions originating de novo or from scar keratoses, chronic radiation keratoses, tar keratoses, thermal keratoses, or on mucosal surfaces tend to possess greater malignant potential.SCC represents a malignant proliferation of keratinocytes within the epidermis, constituting the predominant cell type in this skin layer. The progression of SCC can be significantly influenced by the patient's immunological condition. For instance, individuals undergoing chemotherapy for cutaneous T cell lymphomas face an elevated risk of developing aggressive cutaneous squamous cell carcinomas (Schwartz & Schwartz, 1988).

2.2.4. Melanoma skin cancer

An aggressive malignant neoplasm, originates from melanocytes, cells located in the basal layer of the epidermis. Exposure to ultraviolet light triggers the accumulation of genetic mutations within these melanocytes. These mutations activate oncogenes, deactivate tumor suppressor genes, and impair DNA repair mechanisms. Consequently, this process can lead to uncontrolled proliferation of melanocytes, culminating in the development of melanoma. For individuals diagnosed with cutaneous melanoma, prognosis hinges on factors such as the location and depth of the primary tumor, as well as the presence or absence of localized and distant metastatic disease.

In terms of histologic patterns, invasive cutaneous melanoma can be categorized into four major subtypes: superficial, nodular, lentigo maligna, and acral lentiginous. Each subtype exhibits distinct histological characteristics, aiding in diagnosis and treatment planning (Figure11) (Linares, Zakaria, & Nizran, 2015).

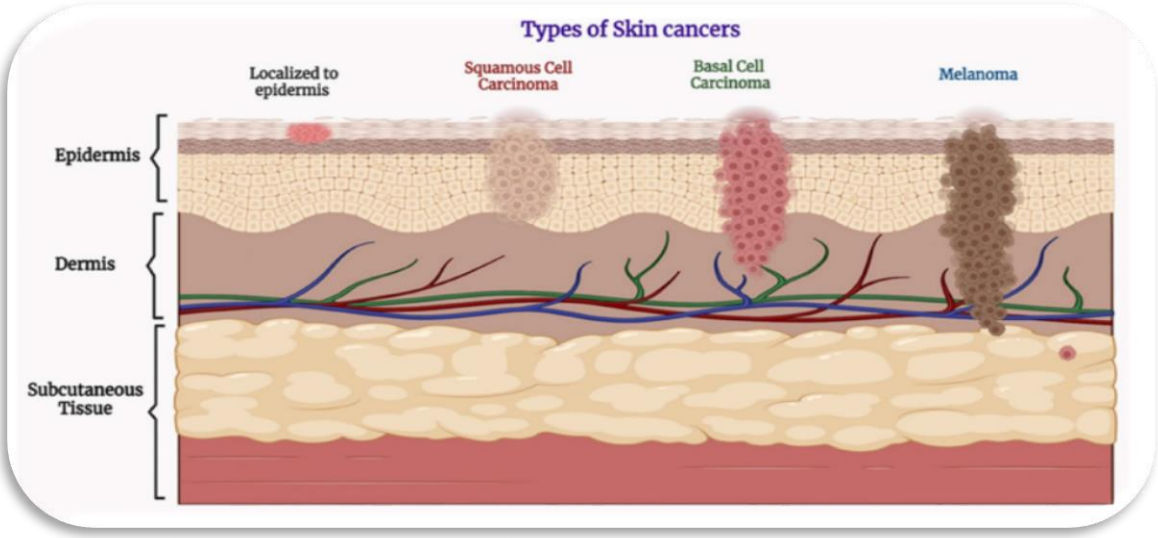

Figure 11. Different types of Skin cancers (Hasan et al., 2023)

2.3. Risk factors associated with skin cancer

There are multiple factors involved in cancer genesis. However, two major risk factors related to the pathogenesis of many cutaneous cancers are biological (non-modifiable) and non-biological (modifiable)

2.3.1. Biological factors (Non-modifiable)

The human skin is the largest and outermost organ of the body, strategically providing an interface between external and internal worlds. It provides a dynamic, mechanical, physical, and defensive barrier against external insults: infectious microorganisms, ultraviolet (UV) radiations, toxic chemicals and mechanical stresses. It also coordinates sensory perception and mediates thermoregulatory and immune responses. Biological factors which contribute in the onset of skin cancers are mainly involved in altering the protein synthesis which negatively impacts the skin cells proliferation; ultimately, results in various skin diseases including the melanoma and NMSC. There are associations between skin cancers and those viral infectious diseases like acquired immune deficiency syndrome (AIDS). It has been observed that the risk of progression of nonmelanoma skin cancer increases 3 to 5 times in AIDS patients. Moreover, it has been documented that the incidence of BCC is 11.4 times more common in HIV-infected hemophiliac individuals. The SSC in HIV patients show a high risk of metastasis. Additionally, it is considered that these viruses might be indirectly incorporated in the pathogenesis of NMSC.

Regulation of gene expressions is frequently dysregualted in diverse cancers including the melanoma and non-melanoma skin cancers. One onsuch dysregulation is the mutation in the PTCH1 gene (under an autosomal dominant condition) that leads to uncontrollable proliferation of skin cells and results in the development of multiple BCCs. Human telomerase RNA and human telomerase reverse transcriptase (hTERT) might be involved in the pathogenesis of BCC, SCC and melanomas (Khan et al., 2022).

2.3.2. Non-biological factors (Modifiable)

Environmental stressors such as exposure to air pollutants, noise and artificial lights at night are contributing to rising cancer rates. Although there are several factors associated with skin cancer but incessantly UV radiations from sunlight is the predominant etiologic agent in the development and progression of skin cancers worldwide there is a cascade of molecular mechanisms involved in UV-induced skin cancers include: activation of the p53

pathways, increased DNA damage, inflammatory responses, genetic mutations, oxidative stress, immunosuppression and apoptotic pathway induction, which remarkably modify cell physiology to arbitrate cell cycle arrest . In UVR exposure, ultraviolet A (UVA) produced reactive oxygen species (ROS), which interact with lipids and proteins molecules and subsequently producing intermediates capable of combining with DNA to make adducts and result in breakage of DNA. UVB is the most carcinogenic UVR reaching the earth's surface and induce structural damage of DNA and RNA. It initiates covalent bond formation between neighboring pyrimidines that subsequently generates genotoxic photoproducts like pyrimidine-pyrimidine adducts and cyclopyrimidine dimers that later on cause inflammatory responses and tumor genesis. While lastly, ultraviolet C (UVC) damage is repairable for DNA repair enzymes and in rare instances, is responsible for skin cancer. the relationship between diet and skin cancer: It has been observed that the reduction of tumor latency and augmentation of tumor multiplicity, diets rich in omega-6 fat endorse tumorigenesis. However, low fat diet could significantly decrease occurrence of non-melanoma skin cancers. Findings revealed that, polyunsaturated fats supply arachidonic acids as substrates for the formation of prostanoids and it can make structural or physiological modifications in immune responses to UV radiation, thus promoting the growth of skin cancer. Exposure to environmental trace elements (arsenic, selenium and zinc) confirms the risk of keratinocyte carcinoma and melanoma in humans (Figure12) (Khan et al., 2022).

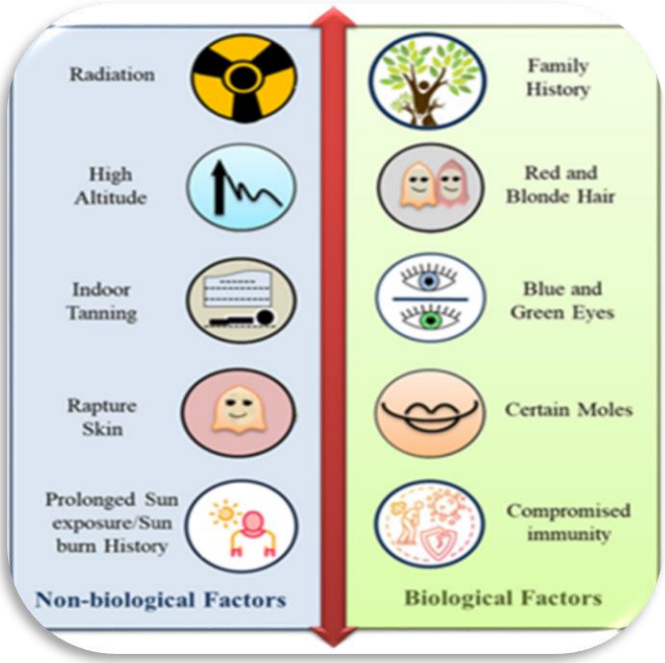

Figure 12. Biological (non-modifiable) and non-biological (modifiable) risk factors associated with the pathophysiology of many cutaneous carcinogenesis (Khan et al., 2022)

2.4. Current topical treatments of skin cancers

2.4.1. Fluorouracil

Topical 5-fluorouracil (5-FU) has been described as a treatment for malignant and non-malignant skin conditions. Acting as an agent, 5-FU enters cells using the same mechanism as uracil. The metabolism of 5-fluorouracil (5-FU) or its derivatives disrupts intracellular nucleotide pools. This disruption leads to the incorporation of false bases, specifically 5-FU, an analog of uracil, into the DNA. Consequently, this alteration interferes with the processing and functioning of RNA, ultimately resulting in DNA damage. The cytotoxic effects of 5-FU manifest primarily in rapidly proliferating cells within abnormal skin. Following the topical application of 5-FU, there is typically a progression of inflammation, erosion, and disappearance of the abnormal lesions (Hasan et al., 2023).

2.4.2. Photodynamic Therapy

Photodynamic therapy (PDT) is a rapidly advancing non-invasive treatment with notable advantages over alternatives. It uses a tumor-targeting photosensitizer, potentially requiring metabolic synthesis, activated by specific-wavelength light. The mechanisms of PDT involve the generation of singlet oxygen ($^1O_2$) through photosensitizer excitation, inducing necrotic, autophagic, or apoptotic tumor cell destruction. PDT is recognized for its therapeutic effectiveness in treating certain types of cancers, including non-melanoma skin cancers. Successful in treating BCC, Bowen's disease, and AK, PDT offers advantages such as reduced pain and improved patient tolerance, achieving excellent cosmesis (Figure13) (Kowalski et al., 2024).

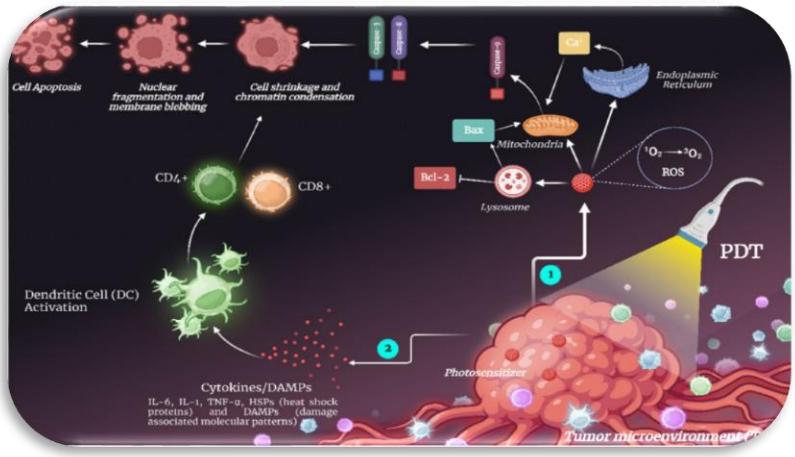

Figure 13. An illustration of the efector mechanism in photodynamic therapy (Hasan et al., 2023)

2.4.3. Laser Therapy

Laser therapy is a treatment that involves applying a focused light source of a specific wavelength to the tumor. Lasers can be used to cut, burn, or destroy tissues, which can be applied to NMSCs. The treatment of skin cancer involves the use of four main types of lasers: solid-state, diode, dye, and gas lasers. There are two laser treatments used especially for BCC: carbon dioxide laser and pulsed contrast laser(Soleymani et al., 2017).

2.4.4. Cryosurgery

Cryosurgery involves the delivery of liquid nitrogen to freeze the target tumor tissue rapidly and then thaw slowly, leading to local cellular destruction. Numerous studies have confirmed the high efficacy of cryosurgery in the treatment of BCC, there are several benefits of cryosurgery. Of those, cryosurgery is quick, cost-effective, and requires no anesthesia. Some potential adverse effects should also be acknowledged, e.g., posttreatment prolonged edema, neuropathic pain, scarring, and hypopigmentation(Ferry et al., 2020).

2.4.5. Immunotherapy

Immunotherapy is playing an increasingly crucial role in the treatment of advanced cancers. In the case of skin cancers, it is employed in locally advanced and unresectable cSCCs (cutaneous Squamous Cell Carcinomas), as well as, in BCCs resistant to hedgehog inhibitors. In NMSC immunotherapy, checkpoint inhibitors are used to assist the host immune system in more effectively combatting cancer cells by modulating the immune response and enhancing the activity of cytotoxic T cells. Despite satisfactory responses to immunotherapy in NMSCs, the associated immunerelated adverse events require monitoring. Consequently, clinical research efforts should focus on discovering a novel treatment that enhances tumor response while minimizing toxicity(Shalhout et al., 2021).

2.5. Preventing skin cancer

Primarily involves ensuring adequate protection from the sun whenever feasible. This entails: Avoiding direct sun exposure as much as possible. Wearing full-length clothing that shields exposed skin from the sun's rays. Using hats and sunglasses to further protect sensitive areas such as the face and eyes. Applying broad-spectrum sunscreen and sunblock regularly, with frequent reapplications, to guard against both ultraviolet A and ultraviolet B radiation. Steering clear of tanning beds, which emit harmful UV radiation. It's imperative to integrate discussions about skin cancer prevention into counseling sessions during all well-

child and adult wellness visits. This ensures that patients are well-informed about the importance of sun protection and can take proactive measures to reduce their risk of developing skin cancer (Dreyfuss et al., 2022).

2.6. DMBA product

7,12-Dimethylbenz(α)anthracene (DMBA) is a well-known carcinogen and immunosuppressor utilized in rodent models for studying tumor development. DMBA induces mutations through the formation of DNA adducts. Moreover, it is recognized as a potent skin carcinogen.

The carcinogenic and mutagenic effects of DMBA rely on its metabolic activation by mixed-function oxidases. The hydroxylation of DMBA at the 7-methyl position is a crucial step in its carcinogenesis. Further metabolism of DMBA results in the generation of various metabolites with varying levels of toxicity. Among these, trans-3,4-dihydrodiol-1,2-epoxide is a carcinogenic derivative of DMBA.

The metabolic byproducts of DMBA disrupt the ROS-antioxidant balance within the body by causing an overproduction of free radicals. In response, the body modulates the activities of antioxidant enzymes to mitigate the detrimental effects of increased ROS levels (Al-Asady & Ghaleb, 2020).

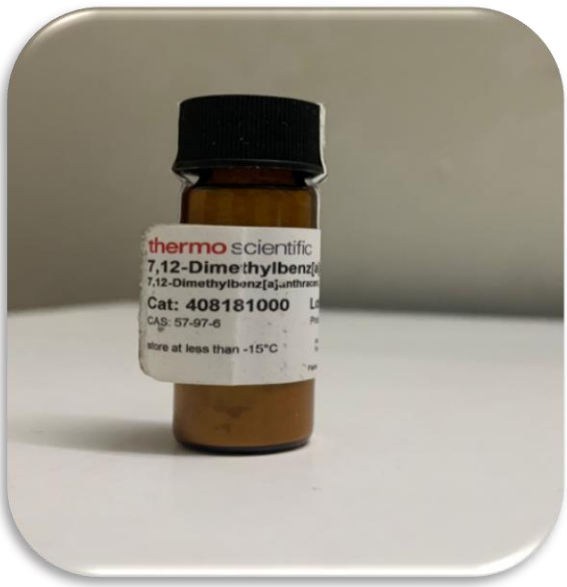

Figure 14.7,12-Dimethylbenz(α)anthracene product (original photo)

3. Oxydative stress

3.1. Definition

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant systems (Figure 15), in favour of the former (Haleng et al., 2007).Reactive oxygen species or free radicals can be produced by normal cellular metabolism and react with biomolecules like protein, lipid, and DNA to cause cellular damage and responsible for degenerative changes (Manisha et al., 2017) and to play a central role in the pathophysiology of many different disorders (Burton & Jauniaux, 2011).This situation may result dysfunction of the mitochondrial chain (ischemia–reperfusion, aging), activation of enzymatic systems (xanthine oxidase, NADPH oxidase،glucose oxidase, monoamine oxidase), a release of free iron from chelating proteins (ferritin) or a oxidation of certain molecules (glucose, hemoglobin، catecholamines, etc.). Finally, a poor diet low in antioxidants will also contribute to the appearance of oxidative stress (Pincemail et al., 2002)

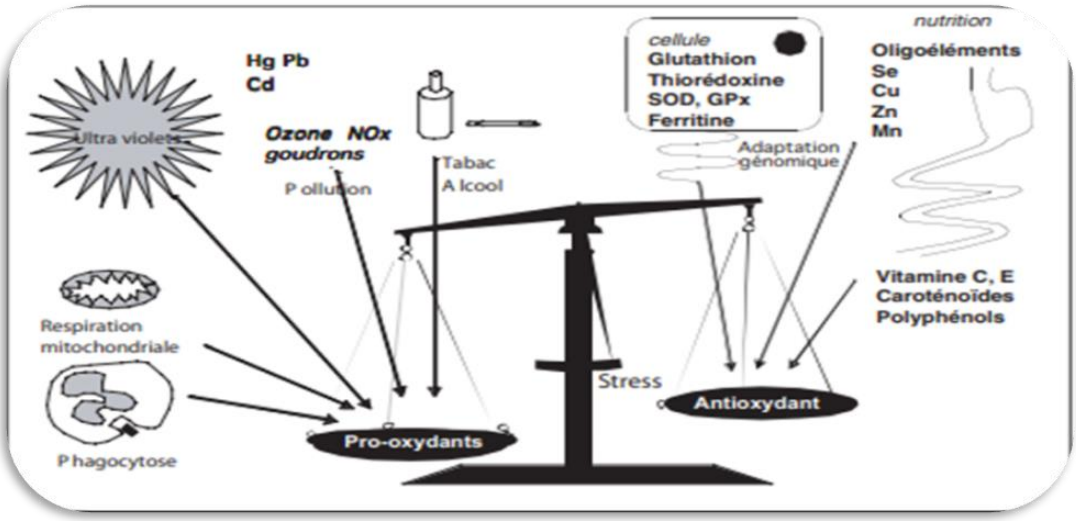

Figure 15. The balance between the pro and antioxidant systems (Favier, 2006)

3.2. Free radicals

3.2.1. Definition

Free radicals are molecular species that exist independently and contain an unpaired form of an electron in their atomic orbital.They either donate or accept an electron, therefore acting as oxidants and reductants (Chaudhary et al., 2023) which may be formed by the loss or gain of electrons from a non-radical compound.They are unstable chemical species، very reactive, and have a half-life time extremely short (Tessier & Marconnet, 1995) . Free radicals

were initially thought to be oxygen centred radicals called reactive oxygen species (ROS) but also include a subgroup of reactive nitrogen species (RNS) and are all a product of normal cellular metabolism (Ifeanyi, 2018). Reactive species include nitric oxide (NO•), alkoxy (OR-), peroxyl (ROO·), hydroxyl (OH·), hydrogen peroxide (H_2O_2), and superoxide (O_2 .-), respectively (Chaudhary et al., 2023).

3.2.2. Sources of free radicals

3.2.2.1. Endogenous sources

They are produced, in the majority, at the level of the respiratory-mitochondrial chains of the cells of aerobic organisms (Tessier & Marconnet, 1995). The plasma membrane and the endoplasmic reticulum are the main sites of free radical release. Secondary contributors to endogenous oxidant generation are enzymes, such as xanthine oxidase, membrane oxidases, nitric oxide synthases, which physiologically produce oxidants (Kirschvink et al., 2008).

3.2.2.2. Exogenous sources

Exogenous sources can be represented by radiation (X-rays and UV light), drugs, xenobiotics, toxins, air pollutants (N, NO_2), organic solvents,pesticides, tobacco smoke ,etc (Figure 16) (Ifeanyi, 2018).

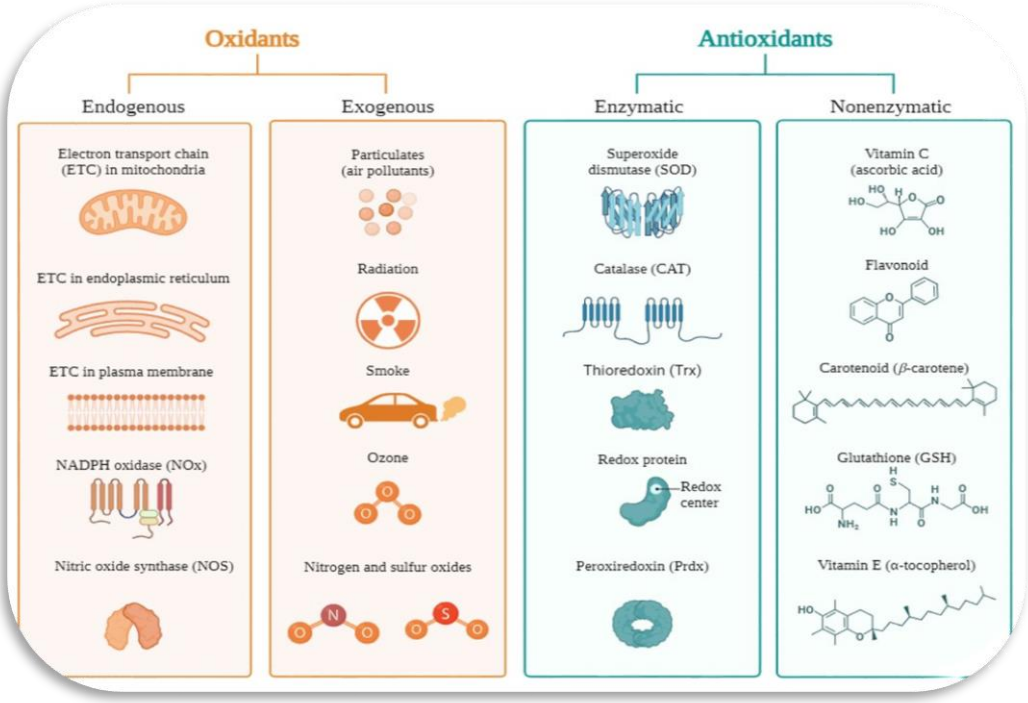

Figure 16. Sources of Oxidants and Antioxidants (Han et al., 2021)

3.2.3. Damage of Free radicals

- **Deoxyribonucleic acid or DNA**

DNA is a preferred target for free radicals. Guanine can react with OH. to form 8-hydroxy-2'-deoxyguanosine (8-OH-dG) which, instead of pairing with cytosine, will associate with adenine, resulting in mutations within the DNA leading to alterations of the genetic message involved in the onset of cancer and aging (Haleng et al., 2007).

- **Protein**

Protein oxidation affects the alteration of signal transduction mechanism ،enzyme activity,receptors, and membrane transport, heat stability, and proteolysis susceptibility, which leads to aging Proteins can be oxidatively modified in three ways :

- Oxidative modification of specific amino acid, free radical mediated peptide cleavage, and formation of protein cross-linkage due to reaction with lipid peroxidation products (amino acids : methionine, cystein, arginine, and histidine seem to be the most vulnerable to oxidation) (Burton & Jauniaux, 2011).

- ROS can damage proteins and produce carbonyls and other amino acids modification including formation of methionine sulfoxide and protein carbonyls and other amino acids modification including formation of methionine sulfoxide and protein peroxide.

- Oxidatively damaged protein products may contain very reactive groups that may contribute to damage to membrane and many cellular functions. Peroxyl radical is usually considered to be free radical species for the oxidation of proteins (Lobo et al., 2010).

- **Lipoproteins**

The oxidative attack of circulatory lipoproteins results in the production of oxidized LDL, which will be captured by specific receptors macrophages. The functioning of these receptors Without being controlled by intracellular cholesterol concentration, macrophages gradually change into spiky cells, which play a crucial role in the early stages of atherosclerosis. Furthermore, these LDL-oxidized particles are immunogens, and the formed immune complexes have the ability to activate the conventional complement pathway and cause macrophages to secrete pro-inflammatory cytokines (Haleng et al., 2007).

- **Membrane lipids**

The hydroxyl radical is capable of extracting a hydrogen from the carbons located between two double bonds of polyunsaturated fatty acids (PUFA): this is the initiation phase. The lipid radical reacts with an oxygen molecule to form a peroxyl radical (ROO•), sufficiently reactive to extract an H+to a neighboring PUFA, thus propagating the reaction. This results in an alteration of membrane fluidity which inevitably leads to cell death. The peroxides generated will be neutralized by glutathione peroxidase or will continue to oxidize and fragment into aldehydes (malondialdehyde, 4-hydroxynonenal) whose pro-atherogenic activities are well known (Haleng et al., 2007).

3.3. Antioxidant

3.3.1. Definition

Antioxidants are the substances that may protect cells from the damage caused by free radicals. Antioxidants interact with and stabilize free radicals and may prevent some of the damage free radicals might otherwise cause. The antioxidants may be exogenous or endogenous in nature (Shinde et al., 2012). Antioxidants can be said to go aboutb its defence system in three main ways: by proteins sequestering with transition metals preventing their availability for reaction with free radicals thus inhibiting their deleterious effect, making available small molecules that have the capability of scavenging free radicals and through specific mechanisms for the correction of ROS-induced DNA damage (Lobo et al., 2010).

3.3.2. Antioxidant classification

Endogenous compounds in cells can be classified as enzymatic antioxidants and non-enzymatic antioxidants (Pham-Huy et al., 2008).

-The antioxidant enzymes (directly involved in the neutralization of ROS and RNS) include Superoxide dismutase (SOD), Catalase (CAT), glutathione peroxidase (GPx), glutathione reducates (GRx) (Shinde et al., 2012).

- SOD ،the first line of defense against free radicals, catalyzes the dismutation of superoxide anion radical ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2) by reduction.
- The oxidant formed (H_2O_2) is transformed into water and oxygen (O_2) by catalase (CAT) or glutathione peroxidase (GPx).

- The selenoprotein GPx enzyme removes H_2O_2 by using it to oxidize reduced glutathione (GSH) into oxidized glutathione (GSSG).
- Glutathione reductase, a flavoprotein enzyme, regenerates GSH from GSSG, with NADPH as a source of reducing power.
- Besides hydrogen peroxide ،GPx also reduces lipid or nonlipid hydroperoxides while oxidizing glutathione (GSH) (Pham-Huy et al., 2008).

-The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. Metabolic antioxidants belonging to endogenous antioxidants, are produced by metabolism in the body, such as lipoid acid ،glutathione, L-ariginine, coenzyme Q10, melatonin, uric acid, bilirubin, metal-chelating proteins, transferrin, etc .While nutrient antioxidants belonging to exogenous antioxidants, are compounds which cannot be produced in the body and must be provided through foods or supplements, such as vitamin E, vitamin C, carotenoids, trace metals (selenium, manganese, zinc), flavonoids, omega-3 and omega-6 fatty acids, etc (Valko et al., 2007).

3.4. Free radicals and diseases

3.4.1. Cancer

Free radicals can damage DNA and cause mutagenicity and cytotoxicity and thus play a key role carcinogenesis. It is believed that ROS can induce mutations and inhibits DNArepair process that results in inactivation of 17 certain tumor repressor genes, leading to cancer (Manisha et al., 2017).

3.4.2. Inflammatory diseases

Oxidants play a significant role in the pathogenesis of a number of disorders such asinflammation, rheumatoid arthritis, asthma, psoriasis and contact dermatitis leading to oxidative stress.

3.4.3. Cardiovascular diseases

ROS can stimulate oxidation of LDL, cholesterol, cholesterol derived species, protein modifications which can lead to foam cell formation and atherosclerotic plaques and vascular thrombosis (Heart attack and Stroke).

3.4.4. Respiratory diseases

Long-term direct exposure to 100% oxygen in the lungs is known to degrade endothelium and result in pulmonary edema. Free radicals operate as a mediator in this. In addition, ROS cause COPD, ARDS, and many forms of asthma. As a result, cigarette smoke both contains and encourages the production of free radicals .ROS is the cause of the lung damage that smokers experience (Pham-Huy et al., 2008).

3.4.5. Neurological diseases

Parkinson's disease, Alzheimer's disease, multiple sclerosis, depression, and memory loss have all been linked to oxidative stress. Although oxidative stress in cells can be caused by a variety of circumstances, the neurotransmitter glutamate is the primary mediator of this process in the brain, mainly by activating its ionotrophic receptors. Damage from free radicals can also be caused by activating phospholipase A, which then releases arachdonic acid. These chemicals and ROS increase glutamate release, which feeds a vicious cycle (Shinde et al., 2012).

3.4.6. Nephropathy

Oxidative stress plays a role in a variety of renal diseases such as glomerulonephritis and tubulointerstitial nephritis ،chronic renal failure, proteinuria, uremia. The nephrotoxicity of certain drugs such as cyclosporine, tacrolimus (FK506), gentamycin, bleomycin, vinblastine, is mainly due to oxidative stress via lipid peroxidation (Pham-Huy et al., 2008).

3.4.7. Diabetes

Destruction of islets of pancreas due to accumulation of free radicals is one of the causes for the pathogenesis of insulin dependent diabetes mellitus. Excess generation of mitochondrial ROS due to hyperglycemia initiates a vicious circle by activating stress-sensitive pathways such as NF- B, p38 MAPK and Jak/STAT, polyol (sorbitol) and hexosamine pathways, PKC and AGEs. Enhanced production of AGEs, sorbitol and proinflammatory cytokines exerts positive feedback on ROS and RNS synthesis and potentiates PKC-mediated vascular dysfunction by altering gene expression as well as vascular function and structure (Figure 17) (Shinde et al., 2012).

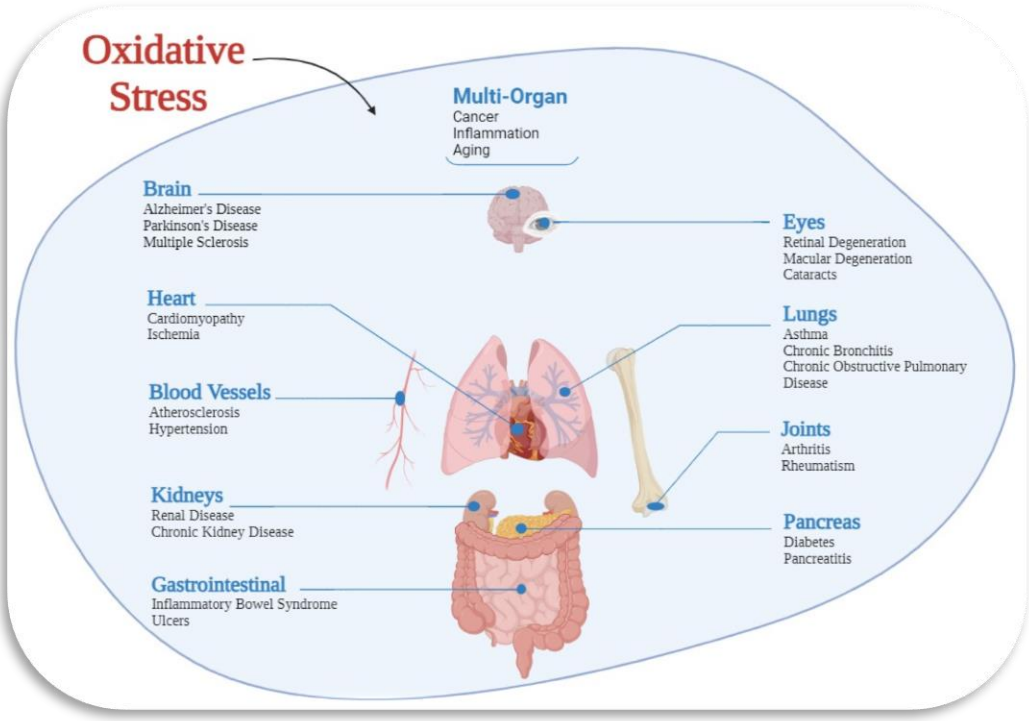

Figure 17. Oxidative stress-induced diseases in humans (Vona et al., 2021)

Second part

Experimental part

Chapter I

Materials & methods

1. Materiels

2.Methods

Chapter I.I:

Results & discussion

1. Results

2. Discussion

Conclussion

&

Prespectives

Conclusion

References

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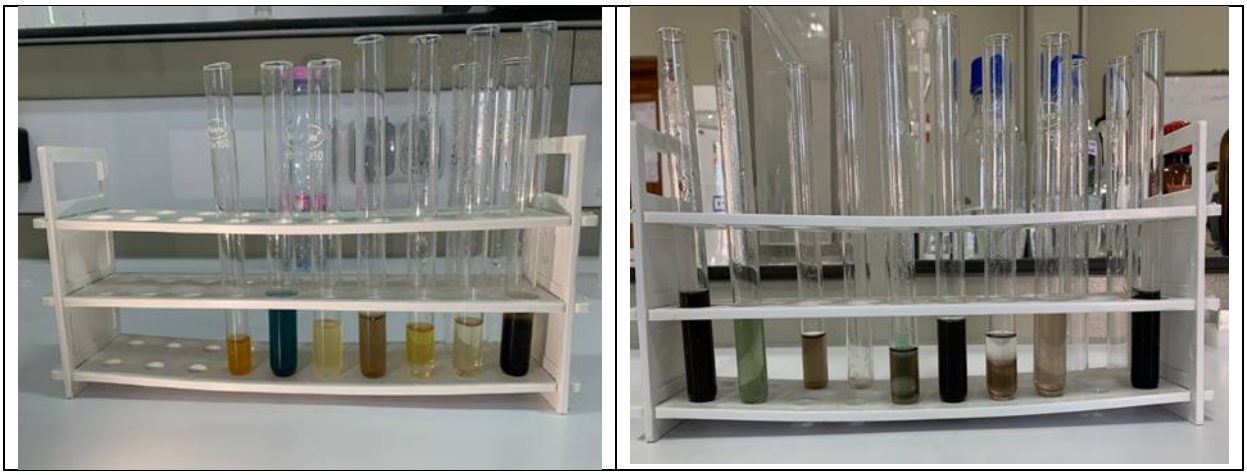
Annexes

Annexe 01



Annexe 02.

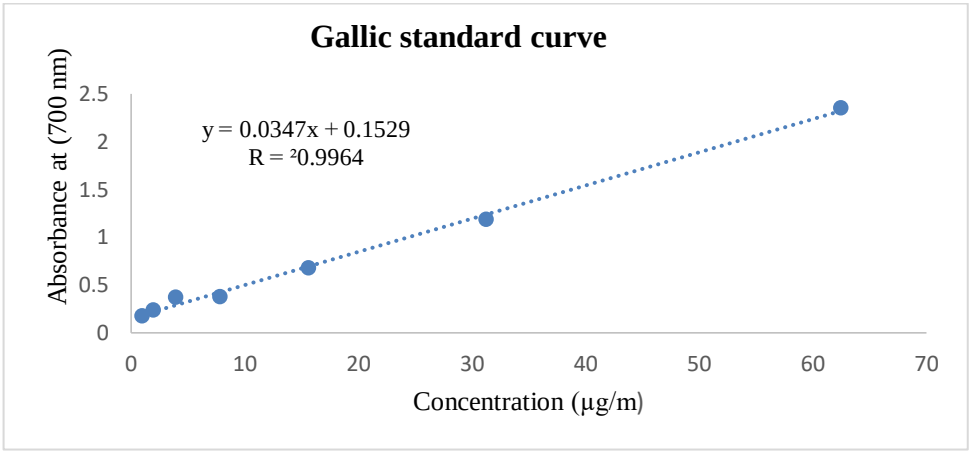


Figure. Standard curve of gallic acid for determination of total phenolic content in extracts

Annexe 03.

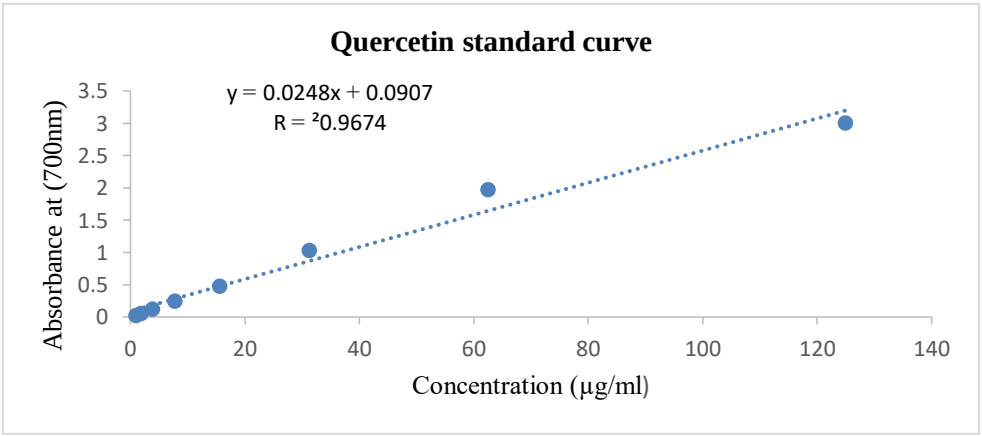
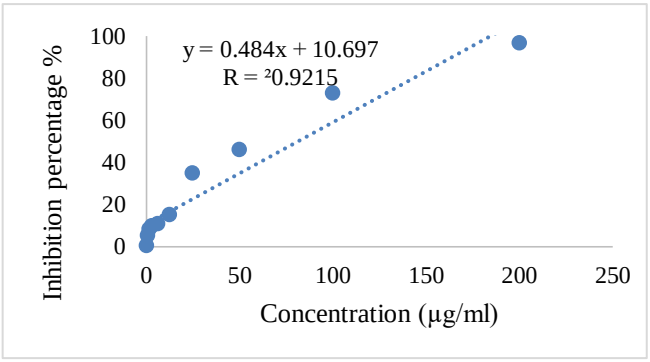
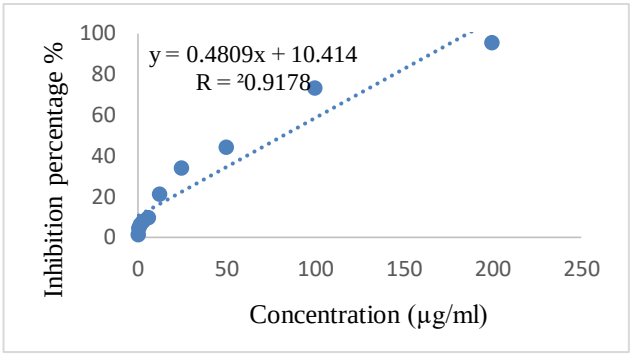
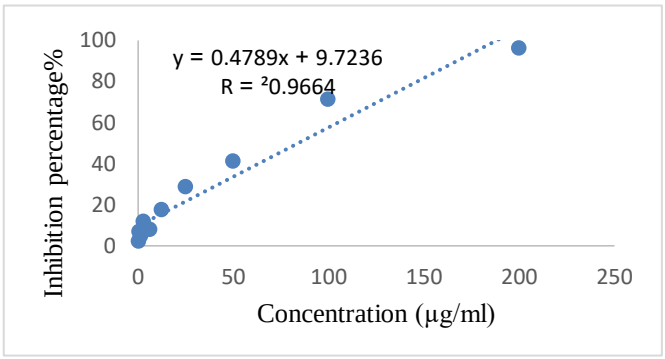


Figure. Standard curve of guercetin for determination of total flavonoid content in estracts

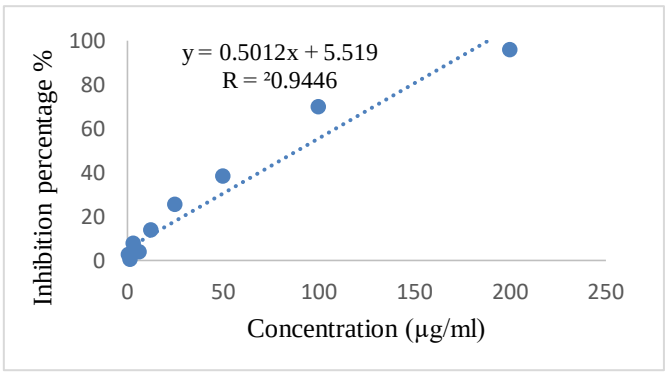
Annexe 04.

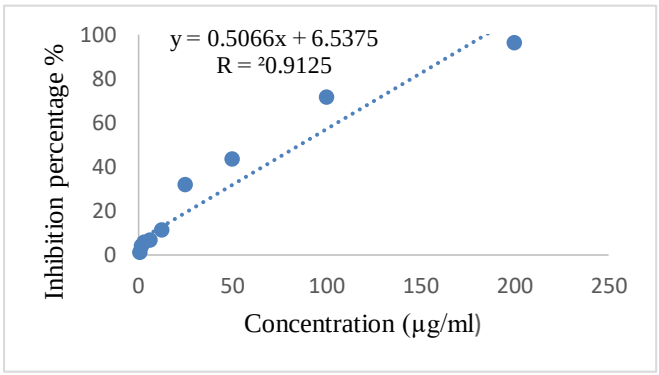


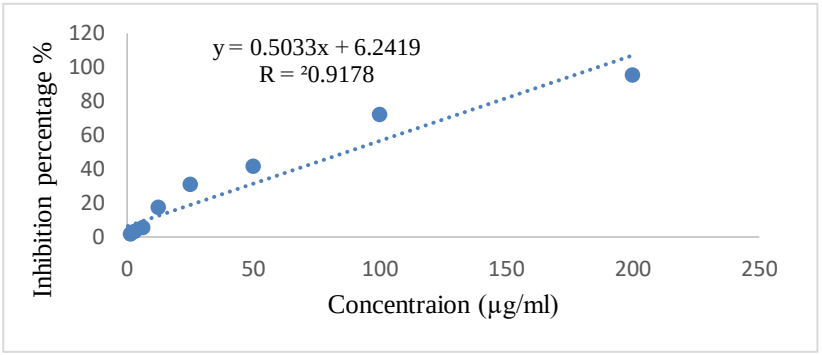




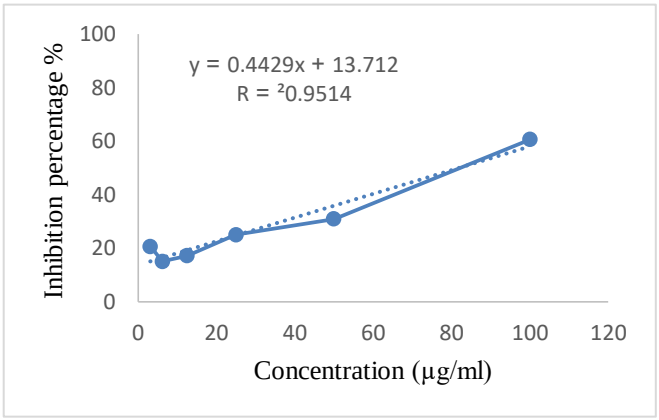
A. DPPH• radical scavenging activity of the different concentration of *B.muricata* aqueous extract

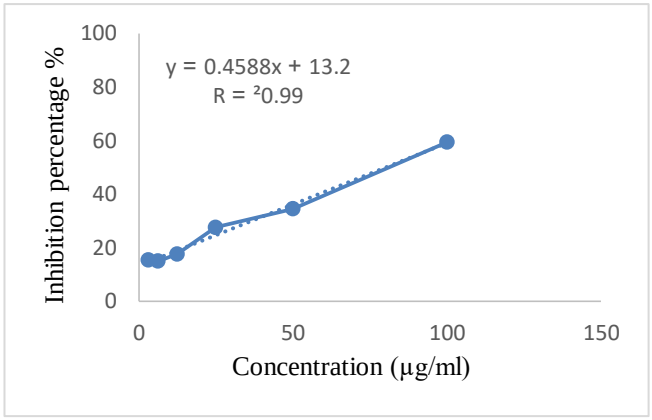


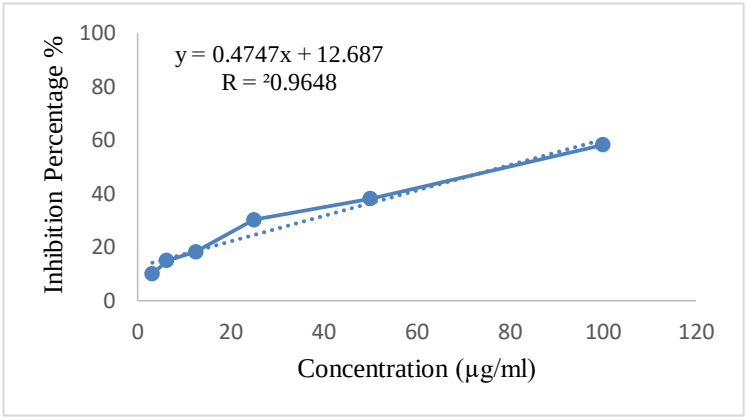




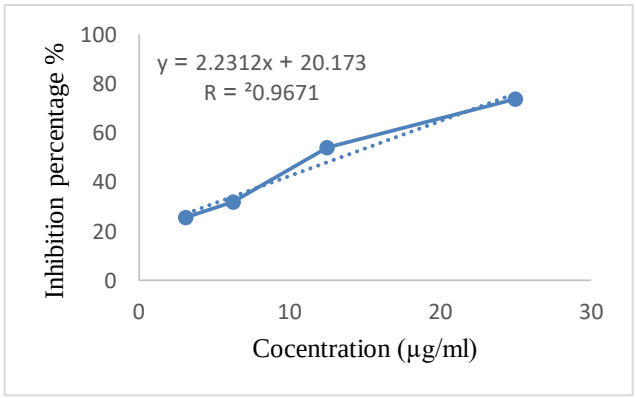
B. DPPH• radical scavenging activity of the different concentration of *S.mollis* aqueous extract

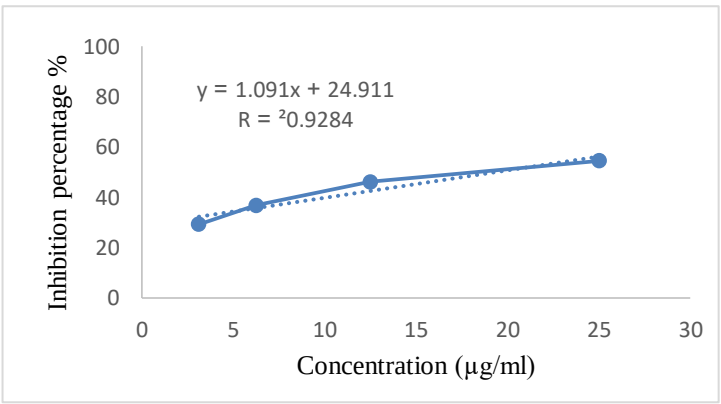


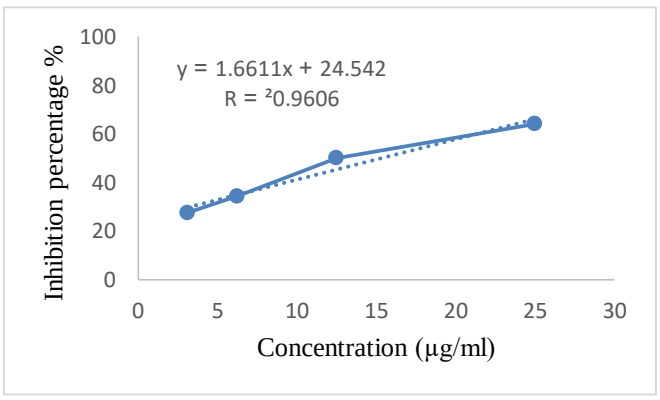




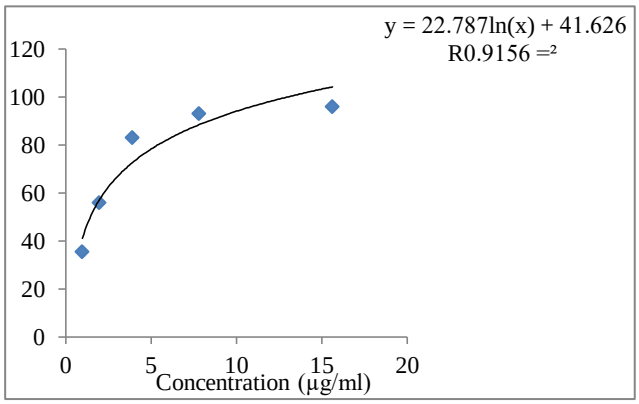
C. DPPH˙ radical scavenging activity of the different concentration of *B.muricata* alkaloid extract

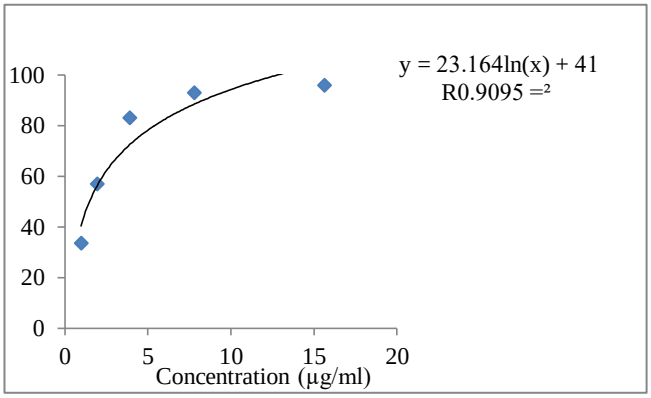


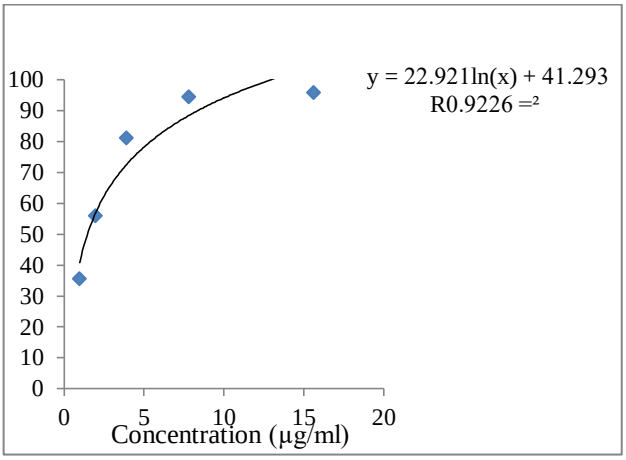




D. DPPH˙ radical scavenging activity of the different concentration of *S.mollis* alkaloid extract

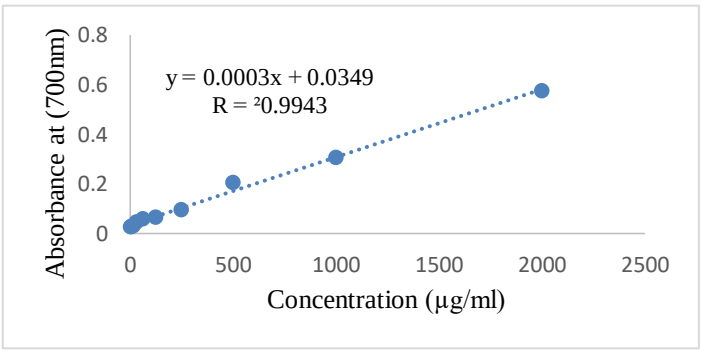


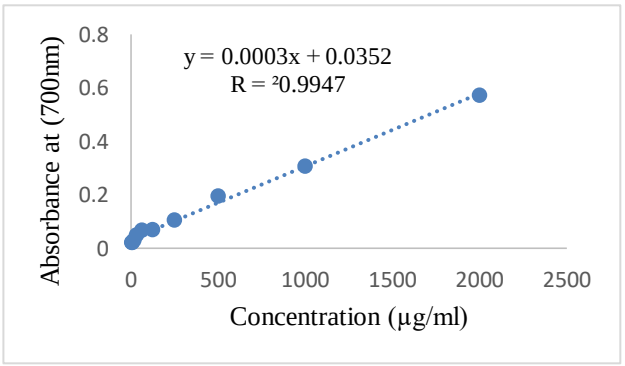


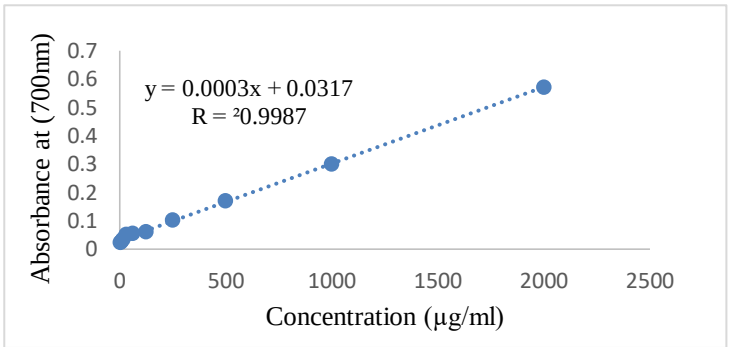


E. DPPH• radical scavenging activity of the different concentration of ascorbic acid

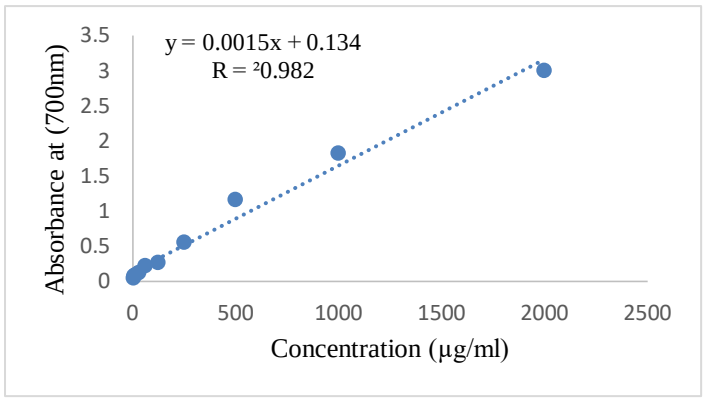
Annexe 05.

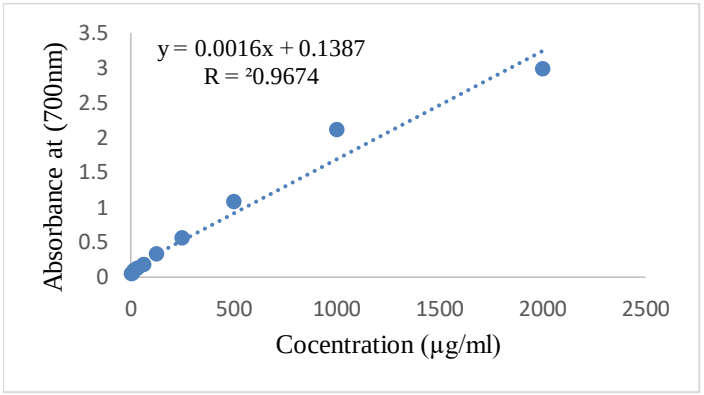


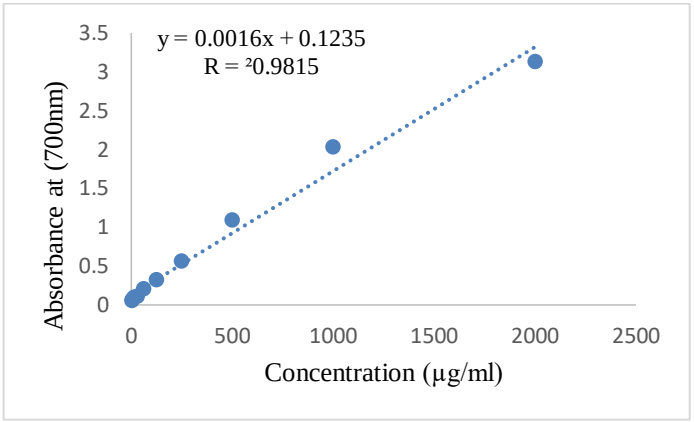




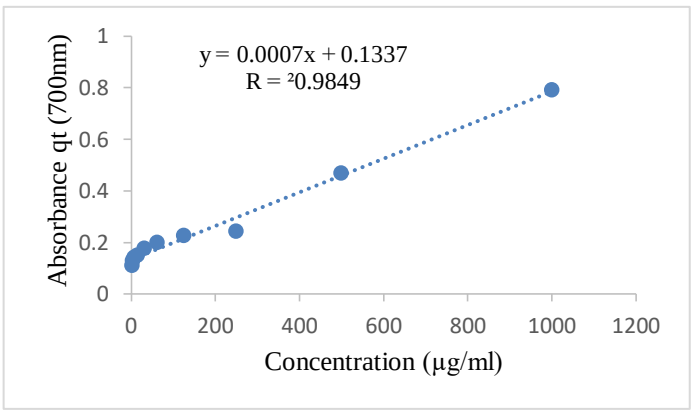
A. Reducing power assay of *B.muricata* aqueous extract

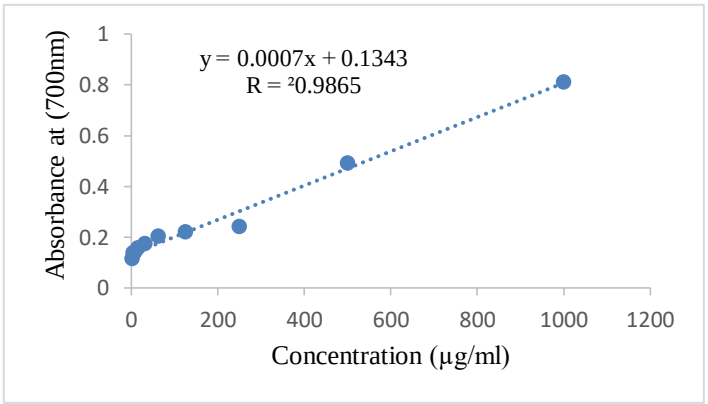


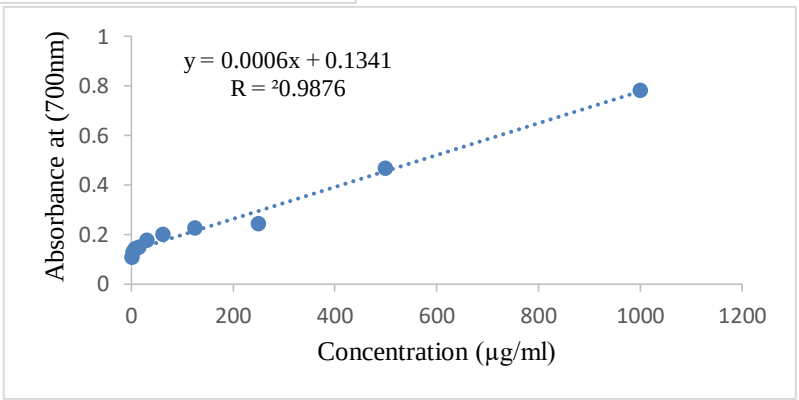




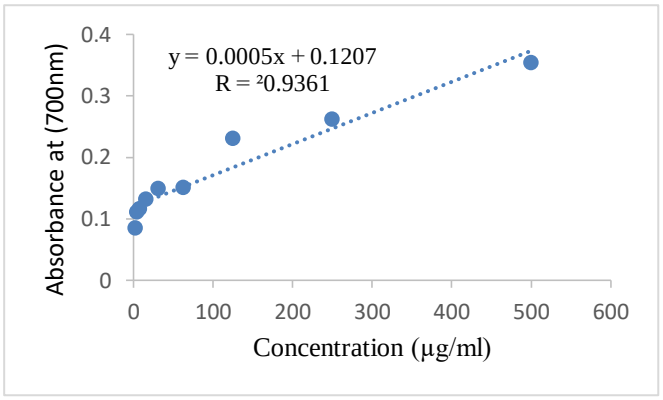
B. Reducing power assay of *S.mollis* aqueous extract

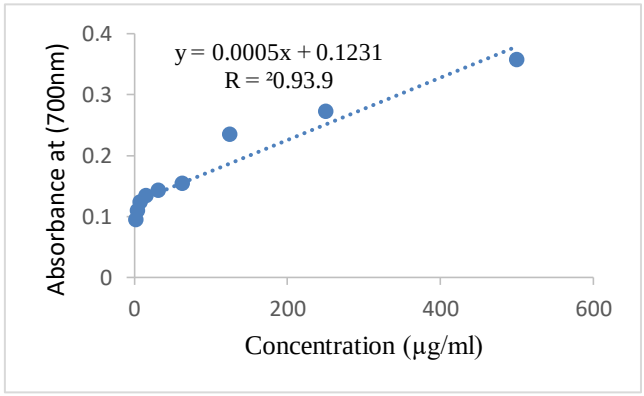


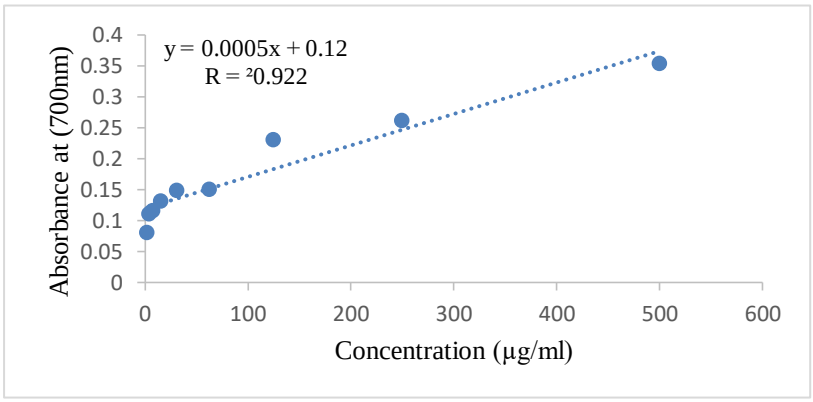




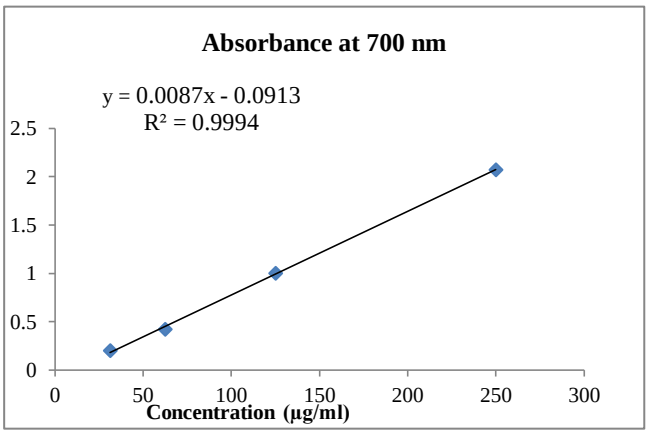
C. Reducing power assay of *B.muricata* alkaloid extract

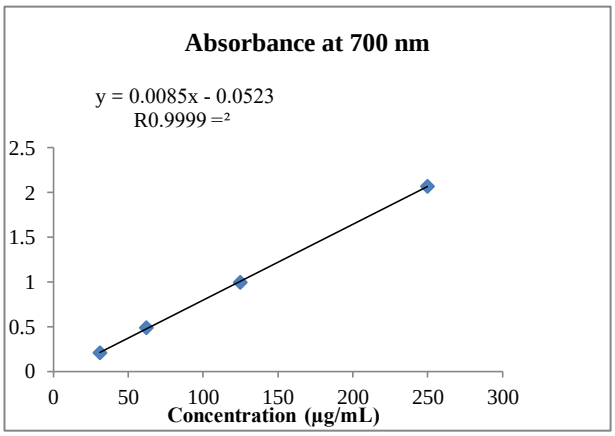


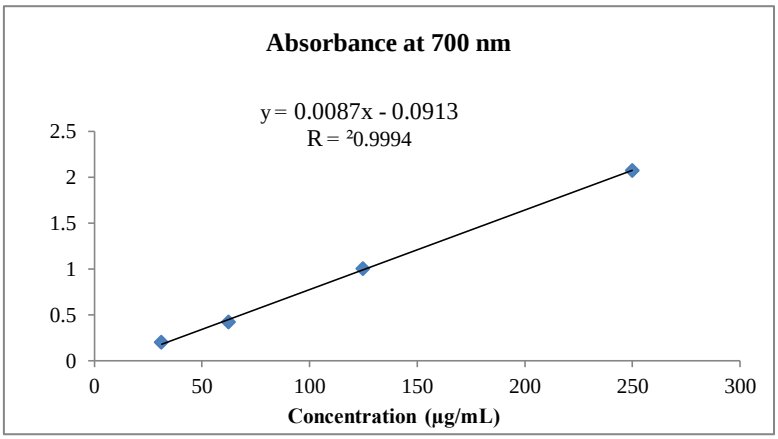




D. Reducing power assay of *S.mollis* alkaloid extract







E. Reducing power assay of ascorbic acid Axis X: concentration (µg/mL), Axis Y: absorbance (at 700 nm)

Annexe 06.

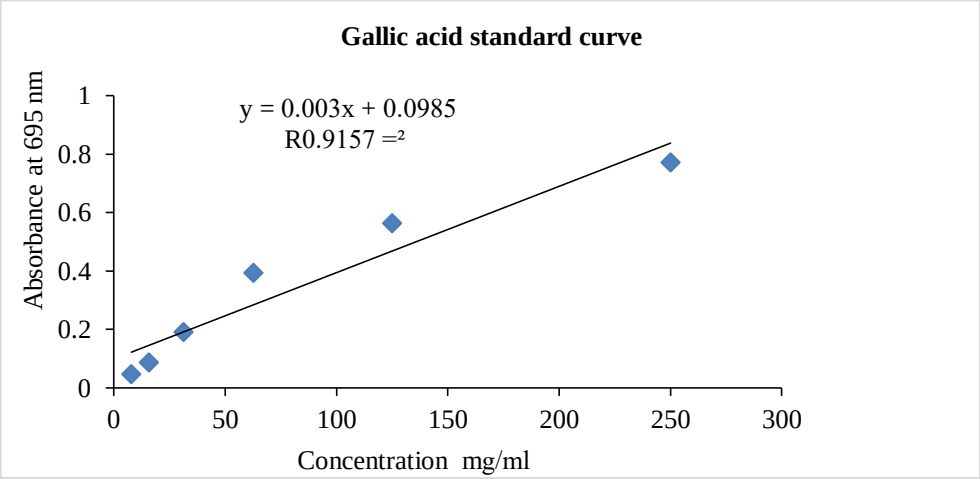
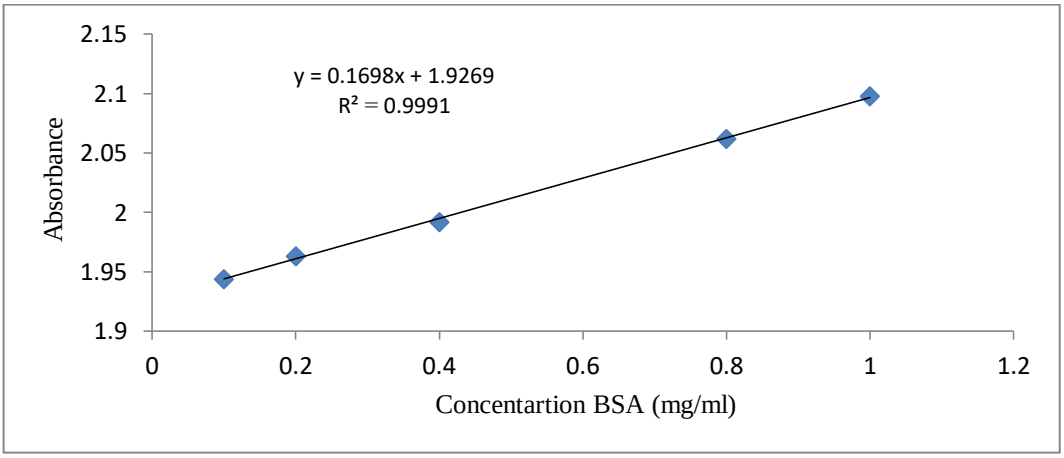


Figure. Standard curve of gallic acid for determination of the total antioxidant capacity of the plant extracts.

Annexe 07.



Calibration curve of protein assay **Figure.**

Annexe 08.

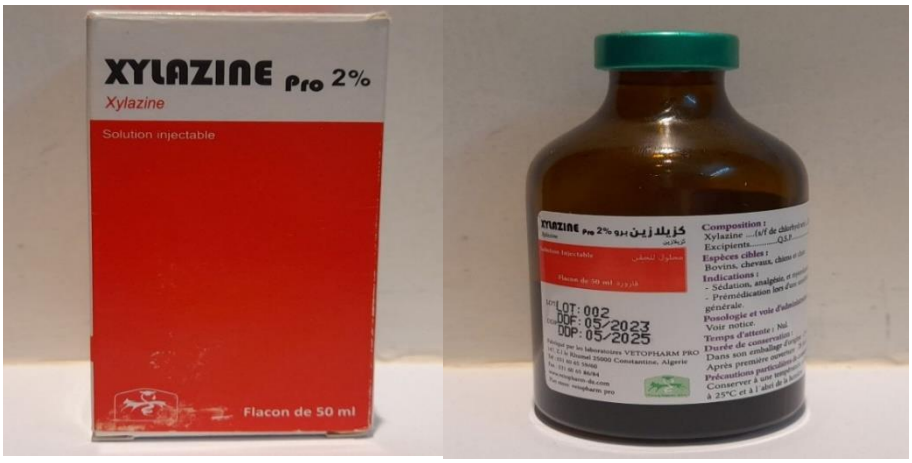


Figure. Xylazine anesthetic

Annexe 09.

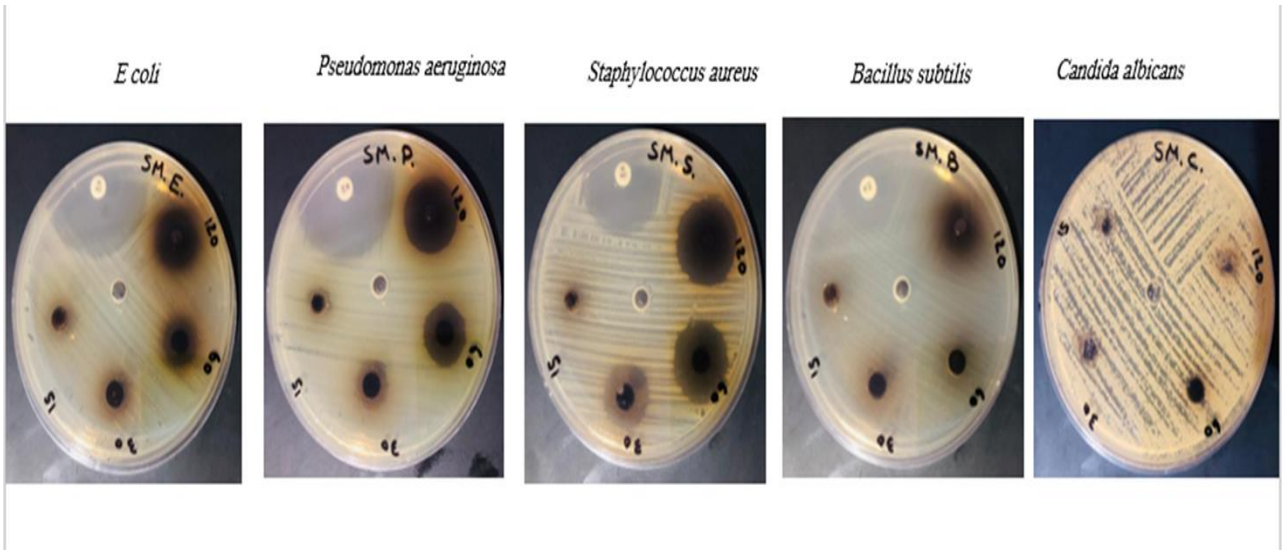


Figure. Antibacterial essay by the wells diffusion method for samples on agar plate *S.mollis*

Annexe 10.

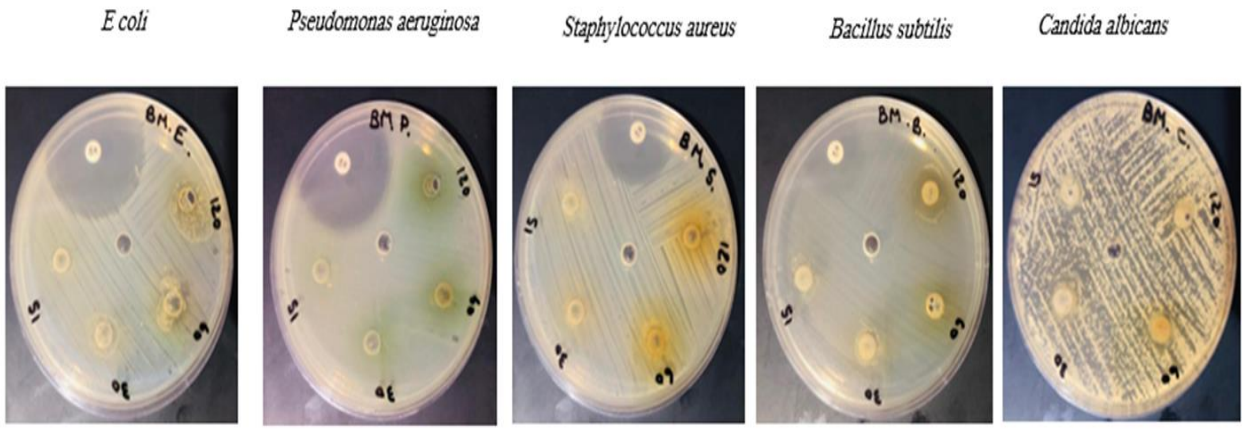


Figure. Antibacterial essay by the wells diffusion method for samples on agar plate *B.muricata*

Annexe 11.

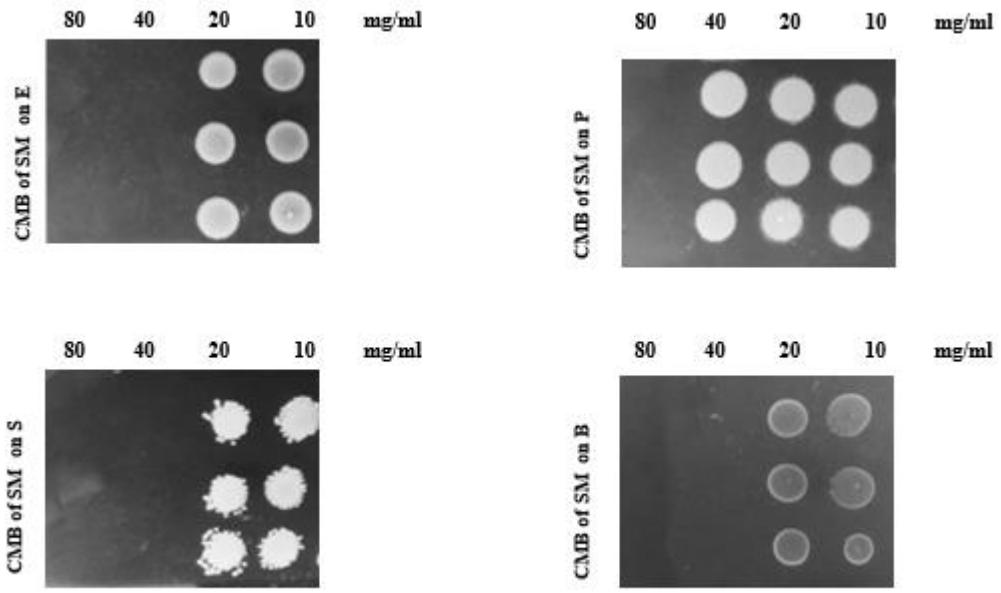


Figure. Broth microdilution method used for antimicrobial activity of S.mollis extract against Bacteria strains.

Annexe 12.

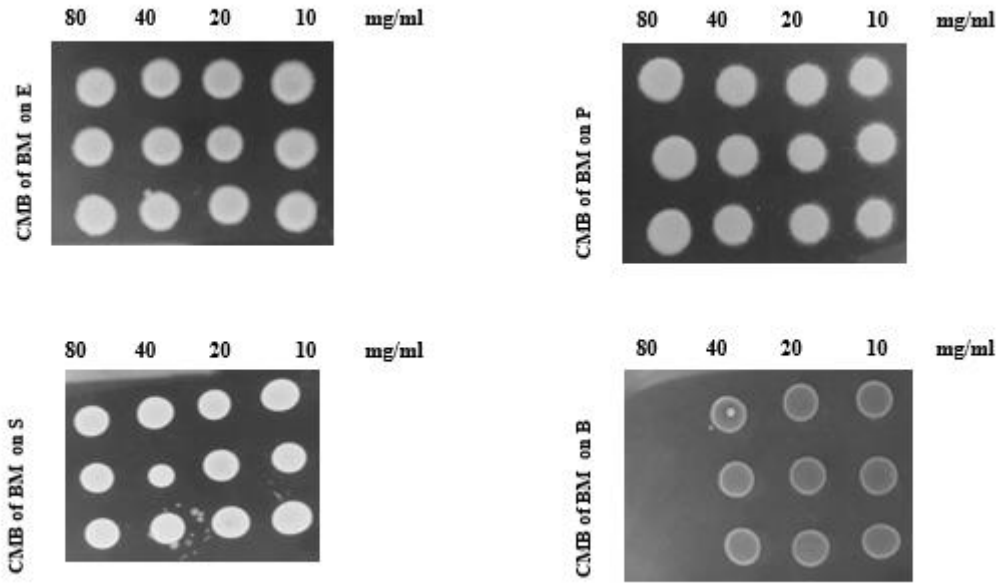


Figure. Broth microdilution method used for antimicrobial activity of *B.muricata* extract against Bacteria strains.

INSTITUT PASTEUR D'ALGERIE Petits Animaux de Laboratoire	Formulaire d'enregistrement	F PAL 0421/02
	Attestation d'acquisition d'animaux de laboratoire	Page : 1 / 3

Ce formulaire est rattaché à la procédure de vente des animaux de laboratoire P PAL 0121

N° de facture :

Date de l'enregistrement :

N° d'ordre de l'enregistrement :

Alger le 13 NOV. 2023

Le laboratoire des petits animaux de laboratoire de l'Institut Pasteur D'Algérie **(IPA)** atteste par la présente que Mme/Mr.....Chemsa....Ahmed....El Khalifa..... de l'université....El Oued..... s'est porté acquéreur d'animaux de laboratoire de type/souche ..Rats...Wistar....., au nombre de .....6o p..... et à statut **Holoxenique.** Ces animaux proviennent d'un élevage de **type conventionnel** et ne présentent aucun signe clinique de pathologies au moment de leur mise à disposition ; néanmoins, l'usage fait de ces animaux après avoir quitté l'enceinte des animaleries de l'IPA, leurs conditions de transport, d'hébergement, de manipulation (devant obéir à des règles d'hygiène et de sécurité et à une compétence dans ce domaine) et les possibles conséquences liées à cela relèvent de la responsabilité exclusive de l'acquéreur.

N.B : Ces animaux sont destinés à des activités scientifiques et ne peuvent être revendus, ni eux ni leur descendance.

Remarque :

Nom et prénom
(Si différent de l'acquéreur)

Boudaoud Khaled
EL HACHEMI

Laboratoire des animaux de laboratoire

Institut Pasteur d'Algérie
Laboratoire des Animaux
Dr Vétérinaire F. HACHEMI

* Suivie d'une note explicative relative aux bonnes pratiques en animalerie

R2-FO-03 E1DZ

الجمهورية الجزائرية الديمقراطية الشعبية
REPUBLIQUE ALGERIENNE DEMOCRATIQUE ET POPULAIRE Demande N°:1815

INSTITUT NATIONAL ALGERIEN DE LA PROPRIETE INDUSTRIELLE

المعهد الوطني الجزائري للملكية الصناعية

REQUETE EN DELIVREANCE D'UN BREVET D'INVENTION
طلب منح براءة الإختراع

1 Natrure de la demande de protection طبيعة الطلب

Brevet d'invention براءة الإختراع [x] | Demande divisionnaire طلب جزئي | Certificat d'addition شهادة الإضافة

Extension de la demande internationale PCT الإمتداد غير طلب دولي

2 INFORMATION SUR LE DEPOSANT معلومات حول مقدم الطلب — 71

Dénomination: إسم الشركة: Université d'El oued

Forme juridique: الطبيعة القانونية: EPCSCP

Secteur d'activité: قطاع النشاط التجاري: service

Adresse: العنوان: BP 789 EL-Oued, Algeria | Wilaya: الولاية: El Oued | Commune: البلدية: El-Oued

Téléphone: رقم الهاتف: +21332120740

3 CODE DU MANDATAIRE رمز الوكيل — 74

Nom du mandataire: إسم الوكيل: //////////

4 INFORMATIONS SUR 'INVENTEUR معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب: CHEMSA Ahmed Elkhalifa

Nationalité: الجنسية: DZ_Algeria

Adresse: العنوان: Cité 19 Mars , El Oued 39000, Algérie

Fonction المهنة: Employé

E-mail: البريد الإلكتروني: chemsakhalifa@gmail.com

5 DONNEES RELATIVES A LA PRIORITE بيانات الأولوية — 30

Date: تاريخ: ////////// Numéro: رقم الأولوية: //////////

Pays d'origine: ////////// البلد الأصلي

6 TITRE DE L'INVENTION عنوان الإختراع — 54

Un produit d'origine végétale pour soulager les symptômes du cancer de la peau

7 DOMAINE TECHNIQUE DE L'INVENTION المجال التقني للإختراع — 51

//////////

8 DONNEES RELATIVES AU DEPOT بيانات الإيداع

Date: تاريخ: 30 AVR. 2024 | Heure: الوقت:

Numéro: رقم الإيداع: 240340

9 DONNEES RELATIVES A LA DEMANDE INTERNATIONAL بيانات الطلب الدولي — 72

Date: تاريخ: | Heure: الوقت:

Numéro: رقم:

10 DECHEANCE إبطال

La déchéance d'un brevet d'invention intervient en cas de non-acquittement, à la date anniversaire du dépôt, des taxes de maintien en vigueur,

يسقط الحق على ملكية براءة الإختراع
في حالة عدم تسديد الرسوم السنوية المستحقة

CADRE RÉSERVÉ A L'INAPI إطار خاص بالمعهد

inapi مصلحة الإيداع Service Dépôt DZP

SIGNATURE (CACHET) ختم / توقيع

Adresse: 42, Rue Larbi BEN M'HIDI, Alger | E-mail: info-dpitt@inapi.org | Web : www.inapi.org العنوان : ٤٢ شارع العربي بن مهيدي، الجزائر

4 INFORMATIONS SUR L'INVENTEUR 2 معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب: GHERAISSA Noura

Nationalité: الجنسية: DZ

Adresse: العنوان: Cité Soummam, Debila, El Oued 39000, Algérie

Fonction المهنة: Chercheur

E-mail: البريد الإلكتروني: nouragherr@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 3 معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب: AZZI Manel

Nationalité: الجنسية: DZ

Adresse: العنوان: Cité EL Nadhour, El Oued 39000, Algérie

Fonction المهنة: Chercheur

E-mail: البريد الإلكتروني: manelaz@yahoo.fr

4 INFORMATIONS SUR L'INVENTEUR 4 معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب: MOUSSAOUI Ahlam

Nationalité: الجنسية: DZ

Adresse: العنوان: Cité El Salam ,Bayadha , El Oued 39000, Algérie

Fonction المهنة: Etudiant

E-mail: البريد الإلكتروني: aloma8276@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 5 معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب: KHELIFI Ikhlas

Nationalité: الجنسية: DZ

Adresse: العنوان: Cité 1er Novembre , Bayadha , El Oued 39000, Algérie

Fonction المهنة: Etudiant

E-mail: البريد الإلكتروني: ikhlas1487.kh@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 6 معلومات حول المخترع — 72

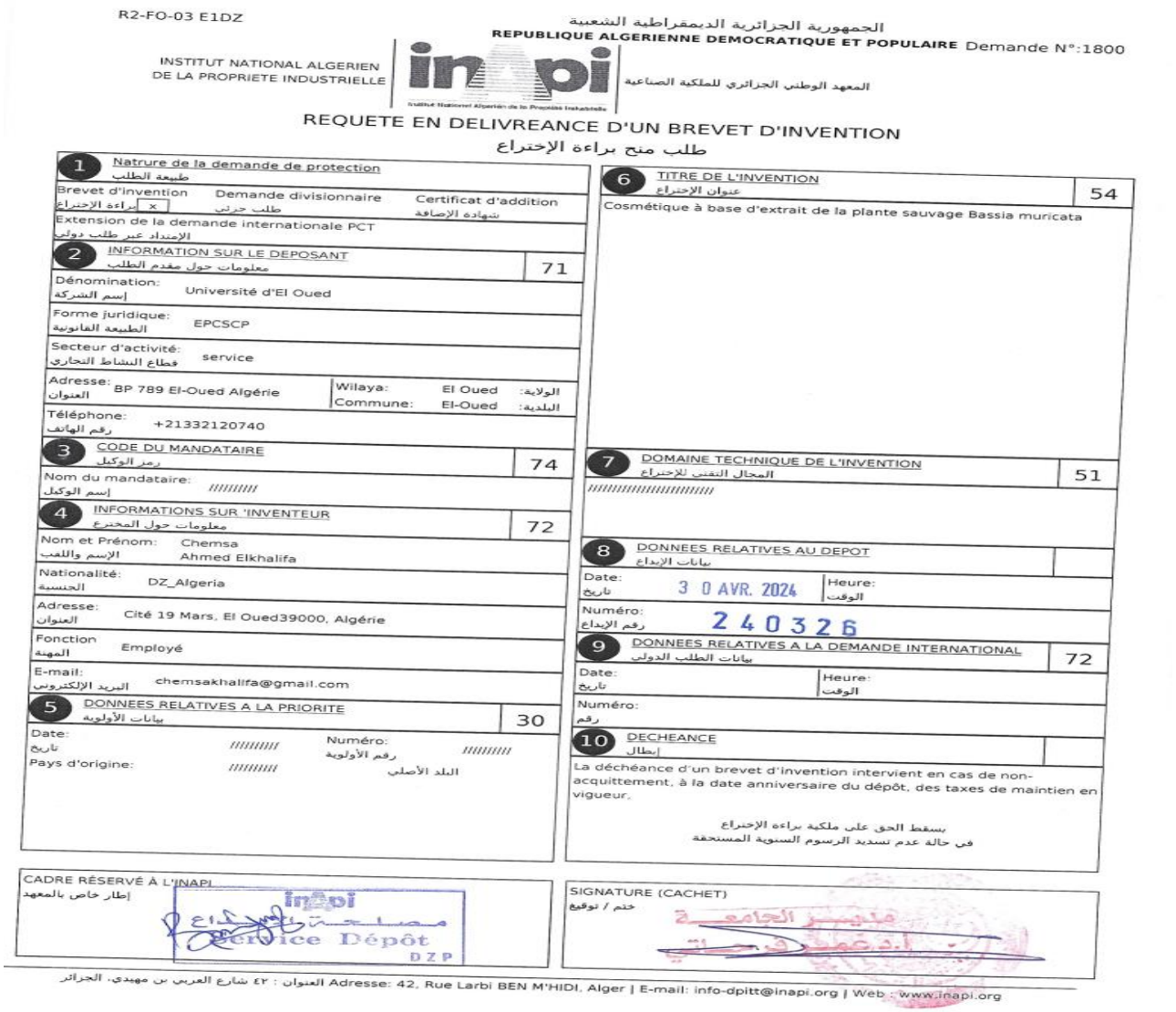
Nom et Prénom: الإسم واللقب: LACHEHEB Rania

Nationalité: الجنسية: DZ

Adresse: العنوان: Cité 1er Novembre ,Chott, El Oued 39000, Algérie

Fonction المهنة: Etudiant

E-mail: البريد الإلكتروني: ranialacheheb21@gmail.com



R2-FO-03 E1DZ

الجمهورية الجزائرية الديمقراطية الشعبية
REPUBLIQUE ALGERIENNE DEMOCRATIQUE ET POPULAIRE

Demande N°:1800

INSTITUT NATIONAL ALGERIEN DE LA PROPRIETE INDUSTRIELLE

المعهد الوطني الجزائري للملكية الصناعية

REQUETE EN DELIVREANCE D'UN BREVET D'INVENTION
طلب منح براءة الإختراع

1 Natrure de la demande de protection — طبيعة الطلب

Brevet d'invention براءة الإختراع [x] | Demande divisionnaire طلب جزئي | Certificat d'addition شهادة الإضافة

Extension de la demande internationale PCT — الإمتداد عبر طلب دولي

2 INFORMATION SUR LE DEPOSANT — معلومات حول مقدم الطلب — 71

Dénomination: إسم الشركة	Université d'El Oued
Forme juridique: الطبيعة القانونية	EPCSCP
Secteur d'activité: قطاع النشاط التجاري	service
Adresse: العنوان	BP 789 El-Oued Algérie — Wilaya: El Oued :الولاية — Commune: El-Oued :البلدية
Téléphone: رقم الهاتف	+21332120740

3 CODE DU MANDATAIRE — رمز الوكيل — 74

Nom du mandataire: إسم الوكيل ////////

4 INFORMATIONS SUR 'INVENTEUR — معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب	Chemsa Ahmed Elkhalifa
Nationalité: الجنسية	DZ_Algeria
Adresse: العنوان	Cité 19 Mars, El Oued39000, Algérie
Fonction المهنة	Employé
E-mail: البريد الإلكتروني	chemsakhalifa@gmail.com

5 DONNEES RELATIVES A LA PRIORITE — بيانات الأولوية — 30

Date: تاريخ //////// Numéro: رقم الأولوية ////////

Pays d'origine: //////// البلد الأصلي

6 TITRE DE L'INVENTION — عنوان الإختراع — 54

Cosmétique à base d'extrait de la plante sauvage Bassia muricata

7 DOMAINE TECHNIQUE DE L'INVENTION — المجال التقني للإختراع — 51

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8 DONNEES RELATIVES AU DEPOT — بيانات الإيداع

Date: تاريخ 3 0 AVR. 2024 Heure: الوقت

Numéro: رقم الإيداع 240326

9 DONNEES RELATIVES A LA DEMANDE INTERNATIONAL — بيانات الطلب الدولي — 72

Date: تاريخ Heure: الوقت

Numéro: رقم

10 DECHEANCE — إبطال

La déchéance d'un brevet d'invention intervient en cas de non-acquittement, à la date anniversaire du dépôt, des taxes de maintien en vigueur.

يسقط الحق على ملكية براءه الإختراع
في حالة عدم تسديد الرسوم السنوية المستحقة

CADRE RÉSERVÉ À L'INAPI — إطار خاص بالمعهد

inapi مصلحة الإيداع Service Dépôt DZP

SIGNATURE (CACHET) — ختم / توقيع

Adresse: 42, Rue Larbi BEN M'HIDI, Alger | E-mail: info-dpitt@inapi.org | Web : www.inapi.org العنوان : ٤٢ شارع العربي بن مهيدي، الجزائر

4 INFORMATIONS SUR L'INVENTEUR 2 — معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب	Gheraissa Noura
Nationalité: الجنسية	DZ
Adresse: العنوان	Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction المهنة	Chercheur
E-mail: البريد الإلكتروني	nouragherr@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 3 — معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب	Azzi Manel
Nationalité: الجنسية	DZ
Adresse: العنوان	Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction المهنة	Chercheur
E-mail: البريد الإلكتروني	manelaz@yahoo.fr

4 INFORMATIONS SUR L'INVENTEUR 4 — معلومات حول المخترع — 72

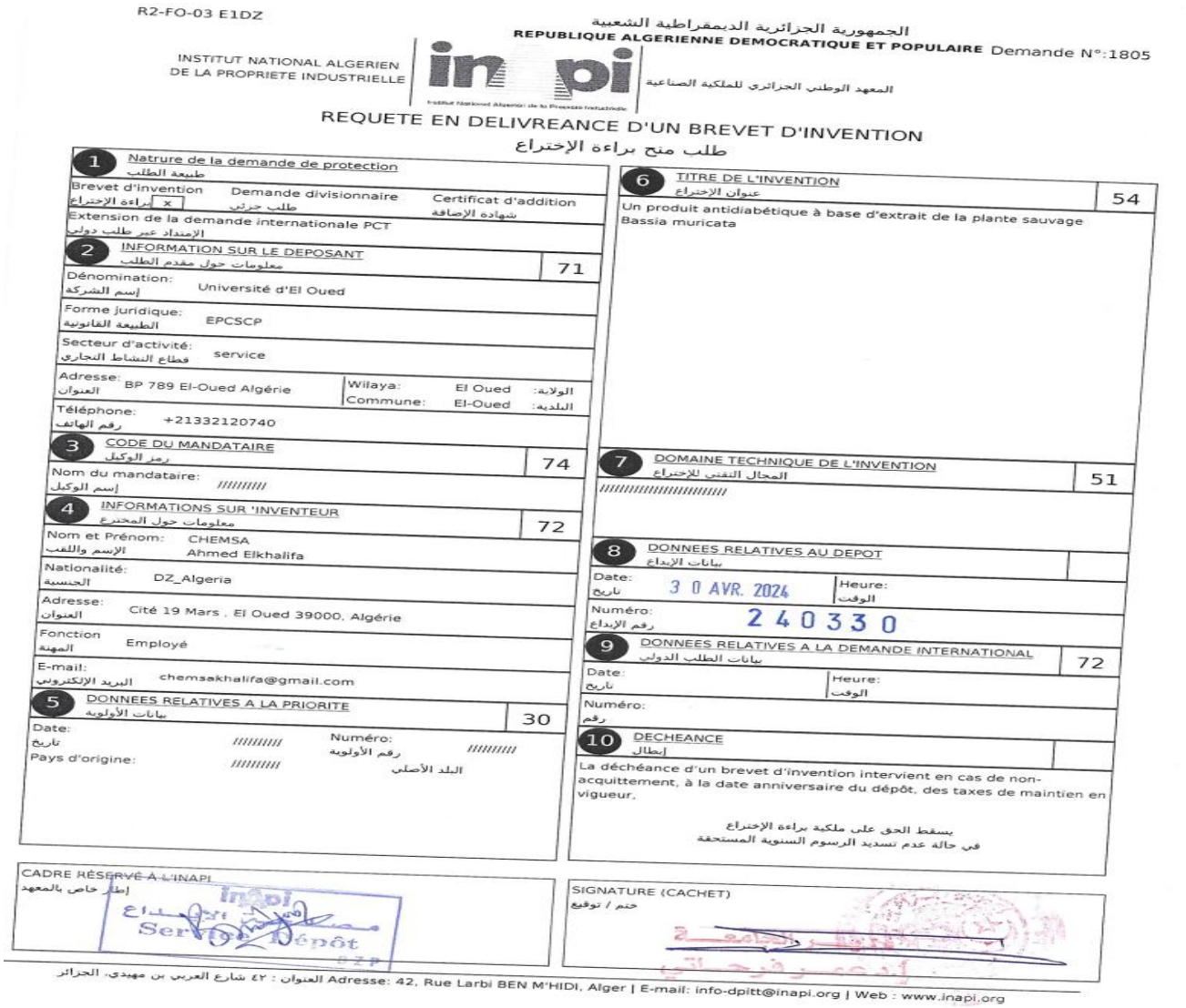
Nom et Prénom: الإسم واللقب	Lacheheb Rania
Nationalité: الجنسية	DZ
Adresse: العنوان	Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction المهنة	Etudiant
E-mail: البريد الإلكتروني	ranialacheheb21@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 5 — معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب	Khelifi Ikhlas
Nationalité: الجنسية	DZ
Adresse: العنوان	Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction المهنة	Etudiant
E-mail: البريد الإلكتروني	Ikhlas1487.kh@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 6 — معلومات حول المخترع — 72

Nom et Prénom: الإسم واللقب	Moussaoui Ahlam
Nationalité: الجنسية	DZ
Adresse: العنوان	Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction المهنة	Etudiant
E-mail: البريد الإلكتروني	Aloma8276@gmail.com



R2-FO-03 E1DZ

الجمهورية الجزائرية الديمقراطية الشعبية
REPUBLIQUE ALGERIENNE DEMOCRATIQUE ET POPULAIRE

INSTITUT NATIONAL ALGERIEN DE LA PROPRIETE INDUSTRIELLE

المعهد الوطني الجزائري للملكية الصناعية

Demande N°:1805

REQUETE EN DELIVREANCE D'UN BREVET D'INVENTION
طلب منح براءة الإختراع

1 Natrure de la demande de protection / طبيعة الطلب
Brevet d'invention براءة الإختراع [x] — Demande divisionnaire طلب جزئي — Certificat d'addition شهادة الإضافة
Extension de la demande internationale PCT الإمتداد غير طلب دولي

2 INFORMATION SUR LE DEPOSANT / معلومات حول مقدم الطلب — 71
Dénomination / إسم الشركة: Université d'El Oued
Forme juridique / الطبيعة القانونية: EPCSCP
Secteur d'activité / قطاع النشاط التجاري: service
Adresse / العنوان: BP 789 El-Oued Algérie — Wilaya / الولاية: El Oued — Commune / البلدية: El-Oued
Téléphone / رقم الهاتف: +21332120740

3 CODE DU MANDATAIRE / رمز الوكيل — 74
Nom du mandataire / إسم الوكيل: ////////

4 INFORMATIONS SUR 'INVENTEUR / معلومات حول المخترع — 72
Nom et Prénom / الإسم واللقب: CHEMSA Ahmed Elkhalifa
Nationalité / الجنسية: DZ_Algeria
Adresse / العنوان: Cité 19 Mars . El Oued 39000, Algérie
Fonction / المهنة: Employé
E-mail / البريد الإلكتروني: chemsakhalifa@gmail.com

5 DONNEES RELATIVES A LA PRIORITE / بيانات الأولوية — 30
Date / تاريخ: //////// — Numéro / رقم الأولوية: ////////
Pays d'origine / البلد الأصلي: ////////

6 TITRE DE L'INVENTION / عنوان الإختراع — 54
Un produit antidiabétique à base d'extrait de la plante sauvage Bassia muricata

7 DOMAINE TECHNIQUE DE L'INVENTION / المجال التقني للإختراع — 51
////////////////////

8 DONNEES RELATIVES AU DEPOT / بيانات الإيداع
Date / تاريخ: 3 0 AVR. 2024 — Heure / الوقت:
Numéro / رقم الإيداع: 2 4 0 3 3 0

9 DONNEES RELATIVES A LA DEMANDE INTERNATIONAL / بيانات الطلب الدولي — 72
Date / تاريخ: — Heure / الوقت:
Numéro / رقم:

10 DECHEANCE / إبطال
La déchéance d'un brevet d'invention intervient en cas de non-acquittement, à la date anniversaire du dépôt, des taxes de maintien en vigueur,
يسقط الحق على ملكية براءه الإختراع
في حالة عدم تسديد الرسوم السنوية المستحقة

CADRE RÉSERVÉ A L'INAPI / إطار خاص بالمعهد
Service Dépôt

SIGNATURE (CACHET) / ختم / توقيع

Adresse: 42, Rue Larbi BEN M'HIDI, Alger | E-mail: info-dpitt@inapi.org | Web : www.inapi.org — العنوان : ٤٢ شارع العربي بن مهيدي، الجزائر

4 INFORMATIONS SUR L'INVENTEUR 2 / معلومات حول المخترع — 72
Nom et Prénom / الإسم واللقب: GHERAISSA Noura
Nationalité / الجنسية: DZ
Adresse / العنوان: Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction / المهنة: Chercheur
E-mail / البريد الإلكتروني: nouragherr@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 3 / معلومات حول المخترع — 72
Nom et Prénom / الإسم واللقب: AZZI Manel
Nationalité / الجنسية: DZ
Adresse / العنوان: Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction / المهنة: Chercheur
E-mail / البريد الإلكتروني: manelaz@yahoo.fr

4 INFORMATIONS SUR L'INVENTEUR 4 / معلومات حول المخترع — 72
Nom et Prénom / الإسم واللقب: KHELIFI Ikhlas
Nationalité / الجنسية: DZ
Adresse / العنوان: Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction / المهنة: Etudiant
E-mail / البريد الإلكتروني: ikhlas1487.kh@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 5 / معلومات حول المخترع — 72
Nom et Prénom / الإسم واللقب: MOUSSAOUI Ahlam
Nationalité / الجنسية: DZ
Adresse / العنوان: Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction / المهنة: Etudiant
E-mail / البريد الإلكتروني: aloma8276@gmail.com

4 INFORMATIONS SUR L'INVENTEUR 6 / معلومات حول المخترع — 72
Nom et Prénom / الإسم واللقب: LACHEHEB Rania
Nationalité / الجنسية: DZ
Adresse / العنوان: Université Echahid Hamma Lakhder, El Oued 39000, Algérie.
Fonction / المهنة: Etudiant
E-mail / البريد الإلكتروني: ranialacheheb21@gmail.com