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TOPIC

Antidiabetic and antioxidant effects of single and combined extracts of two medicinal plants of the genus *Atriplex halimus* and *Suaeda mollis* on streptozotocin-induced diabetic rats

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Dedication

I dedicate this humble research work:

To my beloved Mother Saida,

For her unconditional love, the countless sacrifices, and her endless support.

You're the only reason of my determination; you're my Dunya & my Jannah.

To my dearest Father Ali,

Thank you for your endless love, encouragement and faith on me.

Every achievement I make carries a part of you, with all my gratitude and my love.

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To those who illuminated my journey, to those who will recognize themselves...

Abrazi Yamina

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Abstract

Diabetes mellitus is a major global health concern characterized by hyperglycemia, oxidative stress, and progressive damage to vital organs. Interest in halophytes as potential therapeutic agents has grown due to their richness in bioactive compounds and antioxidant properties. This study aimed to evaluate the phytochemical composition, antidiabetic and antioxidant potential of *Atriplex halimus* and *Suaeda mollis* extracts, individually and combined, in Streptozotocin (STZ)-induced diabetic rats.

The Fourier Transform Infrared Resonance analysis (FTIR) were used for the detection of functional groups present in the used extracts: aqueous and methanolic extracts of *A. halimus* (AEA, MEA), and of *S. mollis* (AES, MES). Total phenolic content (TPC), total flavonoid content (TFC), and antioxidant activity (DPPH, FRAP, and TAC) were quantified using spectrophotometric methods. Experimental diabetes was induced in male Wistar rats by a single intraperitoneal (IP) injection of STZ (60 mg/kg). Rats were divided into twelve groups (5 each), and treatment was administered orally for 15 days. This study assessed biochemical parameters: ASAT, ALAT, uric acid, creatinine, albumin, and total proteins. Moreover, hematological indices (WBC, LY, MO, GR, RBC, HGB, PLT, HCT) were counted by automated machines. Oxidative stress biomarkers (MDA, GSH, GPx, CAT, and SOD) were measured in the pancreas, liver, and kidneys, followed by their histopathological examination.

The results from the phytochemical characterization revealed higher ratio of the extraction yields for the aqueous fractions compared to the methanolic ones in both plants. Whereas, methanolic extracts displayed a greater diversity of functional group peaks, as confirmed by FTIR analysis. The TPC and TFC were highest in MES. Moreover, AES and MES exhibited superior antioxidant potential in DPPH and FRAP assays, whereas TAC was higher in the AEA and MEA than in those of AES and MES. The administration of STZ induced persistent hyperglycemia, weight loss, elevated transaminases, impaired renal biomarkers, and altered protein and hematological profiles. It also led to oxidative stress, and severe histopathological damage in pancreas, liver, and kidneys. Treatment with MES and the combined aqueous extracts of both plants (COMB) produced the strongest hypoglycemic activity, restoring near-normal glucose levels, attenuating body weight loss, and normalizing creatinine, uric acid, and albumin levels. These treatments also maintained hematological balance, reduced hepatic transaminases, enhanced antioxidant defenses, and conferred marked hepato- and nephroprotective effects, as confirmed by histopathological observations. The AES also showed notable hypoglycemic and protective effects against weight loss with partial tissue recovery, while *A. halimus* extracts particularly AEA exhibited weaker hypoglycemic activity and marked perturbation in hepatic and renal function.

In conclusion, *S. mollis* extracts and COMB demonstrated significant antidiabetic and antioxidant effects in STZ-induced diabetic rats. Conversely, *A. halimus* showed limited efficacy under the tested conditions. These findings highlight *S. mollis* as a promising candidate for developing plant-based therapies against diabetes and its complications, and underscore the need for prolonged study with advanced analyses to identify the major phytochemicals responsible of the observed effects.

Keywords: *Atriplex halimus*; diabetes; oxidative stress; phytotherapy; *Suaeda mollis*.

Résumé

Le diabète sucré est une préoccupation majeure de santé mondiale caractérisé par l'hyperglycémie, le stress oxydatif et des dommages progressifs des organes vitaux. Les halophytes sont riches en composés bioactifs ayant des propriétés antioxydantes et possèdent un intérêt thérapeutiques potentiels. Cette étude visait à évaluer la composition phytochimique, le potentiel antidiabétique et antioxydant des extraits d'*Atriplex halimus* et de *Suaeda mollis*, individuels et combinés, chez des rats diabétiques induits par la streptozotocine (STZ).

La spectroscopie infrarouge à transformée de Fourier (FTIR) a été utilisée pour identifier les groupes fonctionnels présents dans les extraits aqueux et méthanoliques d'*A. halimus* (AEA, MEA) et de *S. mollis* (AES, MES). Le contenu total en composés phénoliques (TPC), le contenu total en flavonoïdes (TFC) ainsi que les activités antioxydantes (DPPH, FRAP et TAC) ont été déterminés par des méthodes spectrophotométriques. Le diabète expérimental a été induit chez des rats mâles Wistar par une injection intrapéritonéale unique de STZ (60 mg/kg). Les animaux ont été répartis en douze groupes (n = 5) et traités par voie orale pendant 15 jours. Les paramètres biochimiques (ASAT, ALAT, acide urique, créatinine, albumine et protéines totales), les indices hématologiques (WBC, LY, MO, GR, RBC, HGB, PLT et HCT), ainsi que les biomarqueurs du stress oxydatif (MDA, GSH, GPx, CAT et SOD) dans le pancréas, le foie et les reins ont été évalués, puis complétés par une étude histopathologique de ces organes.

La caractérisation phytochimique a révélé que les rendements d'extraction étaient plus élevés pour les extraits aqueux que pour les extraits méthanoliques dans les deux plantes. Cependant, les extraits méthanoliques ont présenté une plus grande diversité de groupes fonctionnels correspondant aux pics identifiés par FTIR. Le TPC et le TFC étaient les plus élevés dans le MES. De plus, AES et MES ont présenté un potentiel antioxydant supérieur dans les tests DPPH et FRAP, tandis que le TAC était plus élevé dans l'AEA et le MEA. L'induction du diabète a entraîné une hyperglycémie persistante, une perte de poids, une élévation des transaminases et une altération des biomarqueurs rénaux. Elle a également perturbé les profils hématologiques et protéiques, tout en provoquant un stress oxydatif et des lésions histopathologiques sévères au niveau du pancréas, du foie et des reins. Le traitement avec le MES et la combinaison des extraits aqueux des deux plantes (COMB) a provoqué une baisse de la glycémie, ce qui a atténué la perte de poids corporel et normalisé les taux de créatinine, d'acide urique et d'albumine. Ces traitements ont également rétabli l'équilibre hématologique et ont réduit les transaminases hépatiques, et renforcé les défenses antioxydantes. Les observations histopathologiques ont confirmé des effets hépato- et néphroprotecteurs notables. L'AES a également exercé des effets hypoglycémiants et protecteurs marqués. En revanche, les extraits d'*A. halimus*, notamment l'AEA, ont montré une activité hypoglycémique plus faible et une perturbation des fonctions hépatiques et rénales.

En conclusion, Les extraits de *S. mollis* et COMB, ont démontré des effets antidiabétiques et antioxydants marqués chez les rats diabétiques, tandis que *A. halimus* a présenté une efficacité plus limitée dans les conditions testées. Cette étude mérite d'être approfondie et complétée par des analyses ciblées visant à caractériser les composés phytochimiques susceptibles d'être responsables des effets observés.

Mots-clés: *Atriplex halimus*; diabète; phytothérapie; stress oxidant; *Suaeda mollis*.

الملخص

يُعد مرض السكري مصدر قلق صحي عالمي رئيسي يتميز بارتفاع السكر في الدم، والإجهاد التأكسدي، والتلف التدريجي للأعضاء الحيوية. لقد تزايد الاهتمام بالنباتات الملحية كعوامل علاجية محتملة بسبب غناها بالمركبات النشطة بيولوجيًا وخصائصها المضادة للأكسدة. هدفت هذه الدراسة إلى تقييم التركيب الكيميائي النباتي والإمكانيات المضادة للسكري والمضادة للأكسدة لمستخلصات نباتي القطف والسويدة، بشكل فردي وممزوجة معًا، في فئران السكري المستحدث بالستربتوزوتوسين (STZ) .

تم استخدام تحليل التحويل الفوري بالأشعة تحت الحمراء (FTIR) للكشف عن المجموعات الوظيفية الموجودة في المستخلصات المستخدمة: المستخلصات المائية والميثانولية لنبات القطف (MEA, AEA)، والسويدة (MES, AES). تم تقدير الكمية الكلية من المركبات الفينولية (TPC)، والمركبات الفلافونويدية (TFC)، والنشاط المضاد للأكسدة (DPPH ، FRAP، TAC) باستخدام طرق الطيف الضوئي. وتم إحداث مرض السكري التجريبي في ذكور فئران ويستار عن طريق حقنة واحدة داخل الصفاق (IP) من STZ (60 ملغ/كغ). كما تم تقسيم الفئران إلى اثني عشرة مجموعة (5 في كل منها)، وقمنا بإعطاء العلاج عن طريق الفم لمدة 15 يومًا .قامت هذه الدراسة بتقييم التحليلات الكيميائية الحيوية (ASAT، ALAT، حمض اليوريك، الكرياتينين، الألبومين، البروتينات الكلية) ، والمؤشرات الدموية (WBC، LY، MO، GR، RBC، HGB، PLT، HCT). كما تم قياس مؤشرات الإجهاد التأكسدي (MDA، GSH، GPx، CAT، وSOD) في البنكرياس والكبد والكلى، تليها فحوصات النسيج المرضي.

كشفت النتائج عن نسب عائد استخلاص أعلى للمستخلصات المائية مقارنة بالمستخلصات الميثانولية في كلا النباتين. في المقابل، أظهرت المستخلصات الميثانولية تنوعًا أكبر في قمم المجموعات الوظيفية، كما أكده تحليل FTIR. كان الـ TPC والـ TFC أعلى في الـ MES. علاوة على ذلك، أظهرت الـ AES والـ MES إمكانات مضادة للأكسدة متفوقة في اختبارات DPPH وFRAP، بينما كان الـ TAC أعلى في الـ AEA والـ MEA. أدى حقن STZ إلى ارتفاع مستمر في السكر في الدم، وفقدان الوزن، وارتفاع إنزيمات ناقلة للأمين، وضعف المؤشرات الحيوية الكلوية، وتغير في البروتينات والملامح الدموية، وإجهاد تأكسدي، وتلف نسيجي مرضي شديد في البنكرياس والكبد والكلى .أظهر العلاج بالـ MES والمستخلص المائي المشترك لكلا النباتين (COMB) أقوى نشاط مضاد لارتفاع السكر في الدم، حيث أعاد مستويات الجلوكوز إلى ما يقرب من المعدل الطبيعي، وخفف من فقدان الوزن، وطبّع مستويات الكرياتينين وحمض اليوريك والألبومين. كما حافظت هذه العلاجات على التوازن الدموي، وخفضت إنزيمات ناقلة للأمين الكبدية، وعززت الدفاعات المضادة للأكسدة، ومنحت تأثيرات واقية ملحوظة للكبد والكلى، كما أكدتها الملاحظات النسيجية المرضية. كما أظهر المستخلص المائي (AES) تأثيرات خافضة للسكر بشكل ملحوظ، إضافةً إلى دوره في الحدّ من فقدان الوزن وتحقيق تعافٍ جزئي للأنسجة. في المقابل، كشفت مستخلصات نبات القطف، وخاصة المستخلص المائي (AEA)، عن نشاط خافض للسكر ضعيف، إلى جانب اضطرابات واضحة في وظائف الكبد والكلى.

الخلاصة: أظهر مستخلصات نبات السويدة والمستخلص المائي المشترك (COMB) تأثيرات مهمة مضادة للسكري، ومضادة للأكسدة، وواقية لمضاعفاته في فئران السكري المستحدث بالSTZ . على العكس من ذلك، أظهر نبات القطف فعالية محدودة في ظل الظروف المختبرة. تسلط هذه النتائج الضوء على نبات السويدة كمرشح واعد لتطوير علاجات نباتية ضد مرض السكري و، وتؤكد على الحاجة إلى تحليلات متقدمة لتحديد المركبات الكيميائية النباتية الرئيسية المسؤولة عن الآثار الملحوظة.

الكلمات المفتاحية :إجهاد تأكسدي؛ السويدة؛ القطف؛ سكري؛ علاج نباتي.

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Abbreviations	Full Terms
AGEs	Advanced Glycation End-products
AEA	Aqueous Extract of *Atriplex halimus*
AES	Aqueous Extract of *Suaeda mollis*
ALAT	Alanine Aminotransferase
ARE	Antioxidant Response Element
ASAT	Aspartate Aminotransferase
CAT	Catalase
COMB	Combination of aqueous Extracts
DM	Diabetes mellitus
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DTNB	5,5′-Dithiobis-(2-nitrobenzoic acid)
EC_{50}	The half-maximum Effective Concentration
EDTA	Ethylenediaminetetraacetic acid
FRAP	Ferric Reducing Antioxidant Power
GAD	Glutamic Acid Decarboxylase
GDM	Gestational Diabetes Mellitus
GLUT2	Glucose transporter 2
GR	Granulocytes
GSH-Px	Glutathione Peroxidase
GSH	Reduced Glutathione
HbA1c	Glycosylated Hemoglobin
H&E	Hematoxylin and Eosin
HCT	Hematocrit
HGB	Hemoglobin
HLA	Human Leukocyte Antigen
H_2O_2	Hydrogen Peroxide
•HO	Hydroxyl Radical
IC_{50}	Inhibitory concentration for 50% activity
ICA	Islet Cell Antigens
IDF	International Diabetes Federation
IP	Intraperitoneal
IRS	Insulin Receptor Substrate

KRW	Kidneys Relative Weight
LPO	Lipid Peroxidation
LRW	Liver Relative Weight
LY	Lymphocytes
MAPK	Mitogen-Activated Protein Kinases
MDA	Malondialdehyde
MEA	Methanolic Extract of *Atriplex halimus*
MES	Methanolic Extract of *Suaeda mollis*
MODY	Maturity-Onset Diabetes of the Young
MO	Monocytes
NADPH	Nicotinamide Adenine Dinucleotide Phosphate (Reduced)
NF-κB	Nuclear Factor Kappa B
NO^{-}	Nitric Oxide
Nrf2	Nuclear Related Factor 2
O_2^{-}	Superoxide Anion
$ONOO^{-}$	Peroxynitrite
OS	Oxidative Stress
PKB	Protein Kinase B
PLT	Platelets
PRW	Pancreas Relative Weight
RBC	Red Blood Cells
ROS	Reactive Oxygen Species
SGLT2	Sodium-Glucose Co-Transporter 2
SOD	Superoxide Dismutase
STZ	Streptozotocin
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TAC	Total Antioxidant Capacity
TFC	Total Flavonoids Content
TGF-β	Transforming Growth Factor-Beta
TPC	Total Phenolic Content
TNF-α	Tumor Necrosis Factor α
WBC	White Blood Cells

"Be less curious about people and

more curious about ideas"

-Marie Curie

INTRODUCTION

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by long-term hyperglycemia caused by either defective insulin secretion, defective insulin action, or a combination of both (Reddy, 2018). According to the International Diabetes Federation 11th edition (IDF), an estimated 589 million adults (20–79 years) were living with diabetes worldwide in 2025, representing approximately 11.1% (1 in 9) of the adult population. This number is projected to increase to 852.5 million by 2050 if current trends continue (Fig. 1) (IDF, 2025). Diabetes kills one person every six seconds, its fatality rate exceeds the combined yearly deaths caused by HIV (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million) (Tran et al., 2020). This rising rate has a severe economic and social burden worldwide.

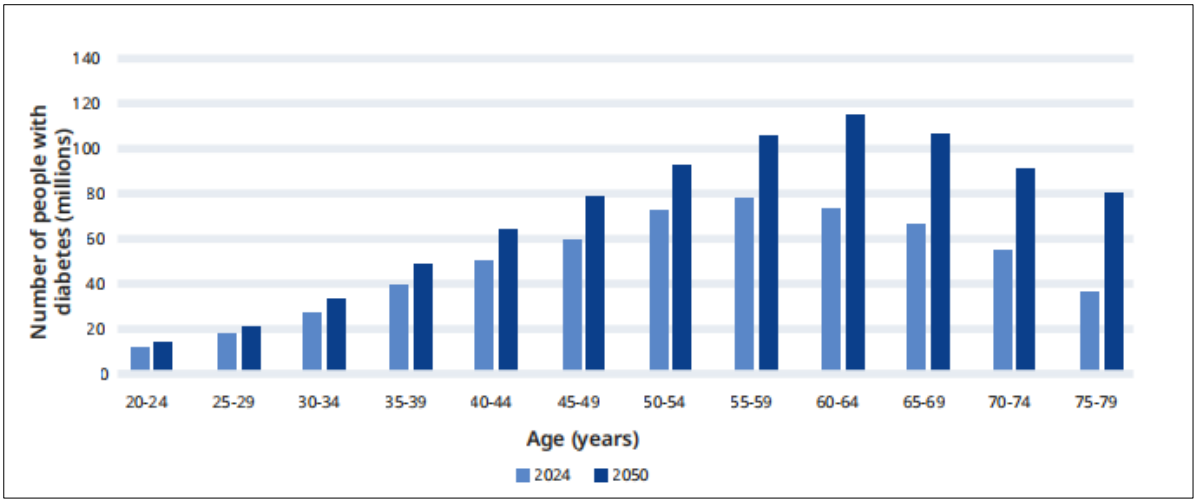


Figure 1. Number of adults (20–79 years) living with diabetes by age group in 2025 and projected prevalence by 2050 (IDF, 2025).

The pathophysiology of diabetes involves complex interactions between genetic susceptibility, environmental factors, and social lifestyles that lead to insulin resistance and β-cell dysfunction. Persistent hyperglycemia in diabetes contributes to progressive damage, dysfunction, and eventual failure of multiple organs, particularly the eyes, kidneys, nerves, heart, and blood vessels (Guo et al., 2023). Oxidative stress (OS) plays a central role in the

initiation and progression of diabetes and its associated complications. It arises from an imbalance between Reactive Oxygen Species (ROS) generation and the body's antioxidant defense systems (Chandimali et al., 2025). Excessive ROS levels disrupt insulin signaling pathways, fostering insulin resistance and damaging pancreatic β-cells, reducing insulin secretion (Gerber and Rutter, 2017). Moreover, OS is a key contributor to the onset of both microvascular and macrovascular complications in diabetic individuals. Given the complexity of diabetes and the involvement of OS, there is growing interest in natural therapies, many of which have roots in traditional medicine (Bhatti et al., 2022). The use of medicinal plants dates back over 5,000 years, with early documentation found in a Sumerian clay tablet describing more than 250 species used for healing (Hassan et al., 2015). This accumulated traditional knowledge has been preserved across cultures and continues to support modern phytotherapeutic practices (Mutombo et al., 2023; Gedlu et al., 2024).

Antioxidant therapy has been explored as a potential strategy to mitigate OS in diabetes. Studies have shown that antioxidants can improve insulin sensitivity and reduce the risk of complications (Hasanuzzaman et al., 2020; Dedvisitsakul and Watla-iad, 2022). However, the efficacy of synthetic antioxidants has been limited, prompting interest in natural antioxidants derived from plants. The management of diabetes primarily involves lifestyle modifications and pharmacological interventions aimed at controlling blood glucose level; commonly used antidiabetic drugs include metformin, sulfonylureas, and insulin therapy. While these treatments are effective in glycemic control, they have several limitations, including side effects, high costs, and limited accessibility, especially in low-resource settings. Moreover, these therapies often do not address the underlying OS associated with diabetes, highlighting the need for adjunct treatments that can provide both glycemic control and antioxidant benefits (Alam et al., 2022; Krawczyk et al., 2023). Phytotherapy refers to the use of medicinal plants and their bioactive compounds in the prevention and treatment of various diseases. It is rooted

in traditional medical practices and has gained scientific validation through numerous studies confirming the therapeutic efficacy of plant-derived compounds (Kasote et al., 2015). In the context of diabetes, phytotherapy offers a promising approach by utilizing natural substances such as polyphenols, flavonoids, and alkaloids, which have demonstrated significant hypoglycemic and antioxidant effects (Governa et al., 2018). This natural treatment strategy is especially valuable due to its accessibility, minimal side effects, and potential to target both hyperglycemia and accompanying OS (Mukherjee et al., 2024). The bioactive compounds that plants synthesize to protect themselves from oxidative damage caused by environmental stressors, not only support plant survival but also confer therapeutic benefits when consumed by humans (Alam et al., 2022). The interplay between environmental pressures and the production of these compounds highlights the intricate relationship between plants and their habitats, underscores the importance of preserving biodiversity for the continued discovery and use of medicinal plants (Heimler et al., 2017; Yeshi et al., 2022).

Halophytes are plant species that thrive in saline environments, exhibiting unique adaptations that enable them to survive under high salt concentrations. These adaptations often involve the synthesis of specialized metabolites with potential pharmacological properties (Ksouri et al., 2012). Recent studies have highlighted the medicinal virtues of halophytes, including antioxidant, anti-inflammatory, and antimicrobial activities (Hymery et al., 2021; Oueslati et al., 2023).

Among the Algerian halophytes, *Atriplex halimus* and *Suaeda mollis* have garnered attention for their potential therapeutic applications. *Atriplex halimus*, commonly known as saltbush, has a longstanding history in traditional medicine (Walker et al., 2014). Phytochemical analyses have revealed that it contains phenolic acids, flavonoids, and alkaloids, compounds known for their pharmacological activities (Roubi et al., 2024). Notably, *A.*

halimus has demonstrated antioxidant, antibacterial, and antidiabetic properties (Chikhi et al., 2014; Ounaissia et al., 2020).

Suaeda mollis has been less extensively studied. However, related species within the Suaeda genus have exhibited significant antimicrobial and anti-inflammatory activities, suggesting potential therapeutic applications (Oueslati et al., 2023). While *S. mollis* remains less studied pharmacologically, its ecological exposure to high salinity suggests a strong capacity for producing antioxidant defense compounds, making it a relevant candidate for antidiabetic evaluation.

Despite increasing interest in plant-based therapies for diabetes, the pharmacological potential of halophytic species remains underexplored. Although *A. halimus* has demonstrated antidiabetic and antioxidant activity, research on *S. mollis* is still limited and largely based on evidence from related species. Furthermore, no previous study has directly compared these two halophytes under identical experimental conditions or investigated the therapeutic potential of their combined administration. Therefore, we hypothesized that the extracts of *Atriplex halimus* and *Suaeda mollis*, administered individually, exert antidiabetic and antioxidant effects, and their combination, may produce enhanced therapeutic benefits by improving glycemic control, reducing oxidative stress, and protecting diabetes-induced damage in the pancreas, liver, and kidneys.

To test this hypothesis, the general objective of this study was to evaluate the therapeutic efficacy of the aqueous and methanolic extracts of these two Algerian halophytic plants, administered individually and in combination in streptozotocin-induced diabetic rats. The specific objectives were as follows:

- **Phytochemical characterization**

→ To identify the main functional groups of chemical compounds, present in the plant extracts using Fourier Transform Infrared (FTIR) spectroscopy.

→ To determine the total polyphenol and flavonoids contents of the aqueous and methanolic extracts of *A. halimus* and *S. mollis*, and to assess the antioxidant activity of the extracts using the Ferric Reducing Antioxidant Power (FRAP) assay, DPPH and the Total Antioxidant Capacity (TAC).

- ***In-vivo* evaluation in STZ-induced diabetic rats**

→ To induce experimental diabetes in adult Wistar rats using STZ and validate the model based on fasting blood glucose levels.

→ To monitor the hypoglycemic effect of the plant extracts, both individually and in combination, by measuring blood glucose levels at regular intervals (Days 1, 3, 5, 10, and 15).

→ To assess changes in body weight as an indirect indicator of metabolic alterations and treatment efficacy.

- **Assessment of oxidative stress markers**

→ To investigate the impact of diabetes and treatment on OS parameters, including: Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GSH-Px), Reduced glutathione (GSH), Malondialdehyde (MDA) in the pancreas, liver and kidneys homogenates using colorimetric techniques.

- **Biochemical and hematological analysis**

→ To evaluate hepatic function markers, including serum levels of: Aspartate aminotransferase (ASAT), Alanine aminotransferase (ALAT), Total proteins, Albumin.

→ To assess renal function markers, namely: Serum creatinine, uric acid

→ To analyze hematological parameters, including: White Blood Cells (WBC), Lymphocytes (LY), Monocytes (MO), Granulocytes (GR), Red Blood Cells (RBC), Hematocrit (HCT), Hemoglobin (HGB), Platelets (PLT)

- **Histopathological examination**

→ To examine histological alterations in the pancreas, liver and kidneys of diabetic and treated rats to assess tissue damage and the protective effects of the plant extracts.

- **Comparative and synergistic analysis**

→ To compare the effects of *A. halimus* and *S. mollis* when administered alone versus in combination.

→ To determine whether the combined treatment exerts a synergistic, additive, or antagonistic effect on the studied parameters, with a particular focus on glycemic control and liver and kidneys function.

LITERATURE REVIEW

I. OVERVIEW OF DIABETES MELLITUS

Diabetes mellitus is a heterogeneous group of chronic metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is classified into Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), Gestational Diabetes Mellitus (GDM), and other specific types. Diabetes is a significant public health concern due to its increasing prevalence and the risk of severe complications, including cardiovascular diseases, neuropathy, nephropathy, and retinopathy (WHO, 2020).

1. Historical background

Diabetes has been recognized since ancient times, the earliest signs of the disease date back to Ancient Egypt around 1500 BC. The term "diabetes" was first used in ancient Greece by the physician Aretaeus of Cappadocia, who described it as a condition characterized by excessive urination. The word itself is derived from the Greek "diabaíno", meaning “to pass through”, reflecting the frequent urination observed in patients. Additionally, the term “mellitus”, meaning “honey-sweet”, was added in the 19th century when scientists noted the sweet taste of diabetic urine, which was later attributed to high glucose (Eknoyan and Nagy, 2005).

Even before the Christian era, ancient Hindu physicians recognized this condition, observing that people who urinated frequently had sweet-smelling urinate and developed a fatal disease. The famous Muslim physician Avicenna (Ibn Sina, 980–1037) was among the first to provide a classification that closely resembled the modern distinction between T1D and T2D (Eknoyan and Nagy, 2005).

In the 18th century, physicians observed improvements in symptoms when patients reduced sugar consumption. Toward the end of that century, it was discovered that the pancreas plays a critical role in controlling blood sugar, and experiments on a dog in 1889 by Oskar Minkowski and Joseph von Mering revealed that pancreatectomy induced a fatal diabetes (Karamanou et al., 2016). The discovery of insulin in 1921 by Canadian scientists Frederick

Banting and Charles Herbert Best marked a turning point in diabetes treatment, transforming it from a fatal disease to one that could be managed with proper therapy. The first insulin injection was given in 1922 to Leonard Thompson, a 14-year-old boy suffering the end stages of DM, and which effectively saved his life. Since then, insulin therapy has become central to diabetes management (March et al., 2022).

2. Type 1 Diabetes

Type 1 diabetes is an autoimmune disease that most often appears suddenly before the age of 20, typically without any family history. It is caused by the presence of anti-pancreatic antibodies (anti-IA2, anti-ICA, anti-GAD, anti-insulin) that attack and destroy the β-cells of the islets of Langerhans. As a result, the body becomes unable to produce insulin, leading to a complete dependence on external insulin (insulin dependence) to regulate blood glucose levels (Popoviciu et al., 2023).

2.1. Risk Factors

The onset of the disease is linked to genetic predispositions as well as environmental factors:

- Genetic predisposition: Polymorphisms in immune-related genes, particularly Human Leukocyte Antigen (HLA) class II genes such as DR3, DR4, and DR3/DR4 located on chromosome 6, have been strongly associated with the development of T1D (Noble and Valdes, 2011).
- Environmental factors: Certain viruses from the enterovirus family, especially Coxsackie viruses, have been implicated as potential triggers for T1D (Zorena et al., 2022). Other viruses such as rotavirus and rubella virus have also been associated with the disease (Alves Abrantes et al., 2024). Nutritional factors may contribute as well, including vitamin D deficiency and the early introduction of cow's milk proteins during infancy.

3. Type 2 Diabetes

Type 2 diabetes is a slowly progressing disease, most commonly observed in overweight or obese individuals over the age of 45. It is frequently associated with hypertension and dyslipidemia. Unlike T1D, T2D does not initially require insulin therapy, but is instead characterized by a resistance of peripheral tissues to insulin (insulin resistance). Over time, this insulin resistance leads to progressive pancreatic exhaustion, resulting in a decline in insulin secretion due to the gradual destruction of β-cells in the islets of Langerhans. This progression eventually causes the patient to become insulin-requiring (insulin-requiring state), (Lu et al., 2024).

3.1. Risk factors

T2D is influenced by both genetic and environmental risk factors:

- Genetic risk factors: There is a hereditary predisposition, with an increased likelihood of developing T2D if at least one parent is affected, 30% risk if one parent, and up to 50% if both parents have T2D.
- Environmental risk factors: Overweight, obesity, lack of physical activity, and a sedentary lifestyle are major contributors to the development of insulin resistance and T2D.
- Other risk factors:

– Women who have had gestational diabetes are at increased risk of developing T2D later in life.

– Hypertension and dyslipidemia: Patients with arterial hypertension (HTN), whether or not associated with dyslipidemia, also face a higher risk of developing T2D.

– Aging: Advancing age is a significant risk factor for T2D.

– Signs of metabolic syndrome: Individuals presenting with features of metabolic syndrome are at greater risk of developing T2D, especially when three or more of the following criteria are present: Abdominal obesity (waist circumference: >88 cm in women, >102 cm

in men), hypertriglyceridemia (>1.50 g/L), low HDL cholesterol (<0.40 g/L in men, <0.50 g/L in women), high blood pressure (>130/80 mmHg or treated hypertension), and hyperglycemia (>1.10 g/L) (Murea et al., 2012).

4. Other specific types of diabetes

The other specific forms of diabetes are summarized in (Table I), based on the updated etiological classification of DM established by the American Diabetes Association (ADA) in its position statement "Diagnosis and Classification of Diabetes Mellitus" (ADA, 2014).

Table I. Etiologic classification of DM (ADA, 2014).

Type of Diabetes	Subtypes / Etiology	Examples / Details
I. Type 1 Diabetes (Destruction of β-cells, usually leading to absolute insulin deficiency)	A. Autoimmune origin B. Idiopathic	Autoimmune diabetes (with autoantibodies) Rare forms with unknown cause
II. Type 2 Diabetes (A variable spectrum...)	—	Peripheral insulin resistance with relative insulin deficiency Predominant insulin secretory defect with associated resistance
III. Other specific types of diabetes	A. Genetic defects of β-cell function	1. Chromosome 12, HNF-1 (formerly MODY3) 2. Chromosome 7, glucokinase (formerly MODY2) 3. Chromosome 20, HNF-4 (formerly MODY1) 4. Mitochondrial DNA mutation.
	B. Genetic defects in insulin action	1. Type A insulin resistance 2. Leprechaunism 3. Rabson-Mendenhall syndrome 4. Lipoatrophic diabetes
	C. Diseases of the exocrine pancreas	1. Pancreatitis 2. Trauma / pancreatectomy 3. Pancreatic cancer 4. Cystic fibrosis 5. Hemochromatosis 6. Fibrocalculous pancreatitis
	D. Endocrinopathies	1. Acromegaly 2. Cushing's syndrome 3. Glucagonoma 4. Pheochromocytoma 5. Hyperthyroidism

		6. Somatostatinoma 7. Primary hyperaldosteronism.
	E. Drug- or chemical-induced diabetes	1. Vacor (rodenticide) 2. Pentamidine 3. Nicotinic acid 4. Glucocorticoids 5. Thyroid hormones 6. Diazoxide 7. β-adrenergic agonists 8. Thiazide diuretics 9. Diphenylhydantoin 10. Interferon α.
	F. Infections	1. Congenital rubella 2. Cytomegalovirus, coxsackievirus B, adenovirus, and mumps.
	G. Uncommon forms of autoimmune diabetes	1. Stiff-man syndrome 2. Anti-insulin receptor antibodies
	H. Genetic syndromes sometimes associated with diabetes	1. Down syndrome 2. Klinefelter syndrome 3. Turner syndrome 4. Wolfram syndrome 5. Friedreich's ataxia 6. Huntington's chorea 7. Porphyria 8. Myotonic dystrophy 9. Prader–Willi syndrome
IV. Gestational Diabetes (Glucose intolerance first recognized during pregnancy)	—	May resolve after delivery or persist. Risk factor for developing T2D later in life.

5. Target organs in diabetes

5.1. Pancreas

The pancreas is a retroperitoneal organ located in the upper of human abdomen, situated posterior to the stomach. It weighs approximately 100 grams and measures between 15 to 25 cm in length. Anatomically, it is divided into the head (adjacent to the duodenum), the body, and the tail (near the spleen), based on its relationships with surrounding organs (Mihoc et al., 2024), (Fig. 2).

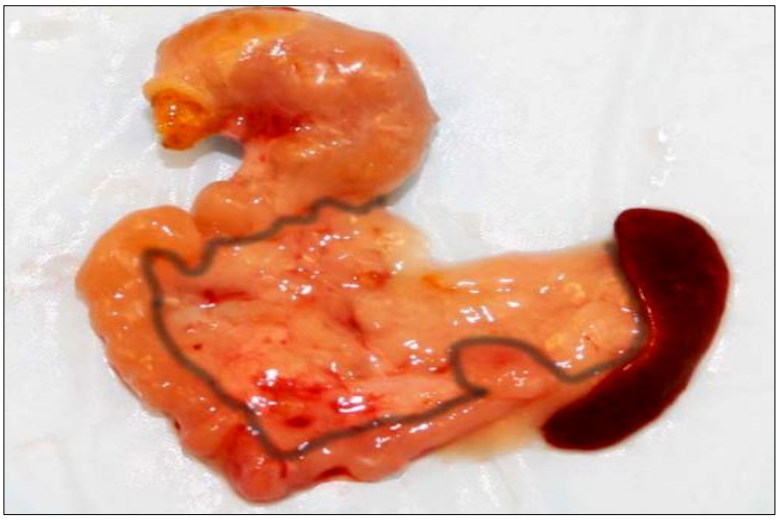


Figure 2. Mouse pancreas anatomy.

This is an adult mouse pancreas, which appears soft and diffuse compared to the human pancreas, is situated between several abdominal organs. It is surrounded by the stomach (superiorly), the duodenum and proximal jejunum (left and bottom), and the spleen (right). The duodenum encircles the head of the pancreas, as marked by the separation line (Longnecker, 2014).

Functionally, the pancreas is an amphicrine gland, meaning it possesses both exocrine and endocrine components:

- **Exocrine Portion:** Comprising roughly 95% of the pancreatic mass, the exocrine pancreas is responsible for secreting digestive enzymes such as amylase, lipase, and trypsin, which play essential roles in the breakdown of proteins, lipids, carbohydrates, nucleic acids, and dietary fibers. These enzymes are produced by acinar cells, which are closely packed and organized into lobules (acini). The enzymes are released in a bicarbonate-rich fluid that flows through a network of ducts starting with intralobular ducts, then interlobular ducts, and finally draining into the main pancreatic duct (Wirsung's duct) (Longnecker, 2014).
- **Endocrine Portion:** Representing about 1–2% of the total pancreatic mass, the endocrine component is primarily responsible for the secretion of hormones such as insulin, glucagon, somatostatin, pancreatic polypeptide, and minor regulatory hormones. These are produced by the islets of Langerhans, which are spherical clusters of cells typically ranging from 100 to 150 microns in diameter, although their size can vary considerably. A two-dimensional cross-section of an islet may show as few as a handful of cells. In humans, the total number

of islets is estimated to range from 500,000 to 1 million, unevenly scattered throughout the exocrine tissue (Fig. 3). Each islet comprises several specialized cell types:

→ Beta (β) cells, which produce insulin and typically make up around 75% of the islet cell population (though in some individuals, they may account for less than 50%),

→ Alpha (α) cells, which secrete glucagon,

→ Delta (δ) cells, which release somatostatin,

→ PP cells, which produce pancreatic polypeptide,

→ Epsilon (ε) cells, which are responsible for ghrelin secretion.

Each cell type contributes to the regulation of glucose homeostasis and digestive physiology through its hormone production (Longnecker, 2014).

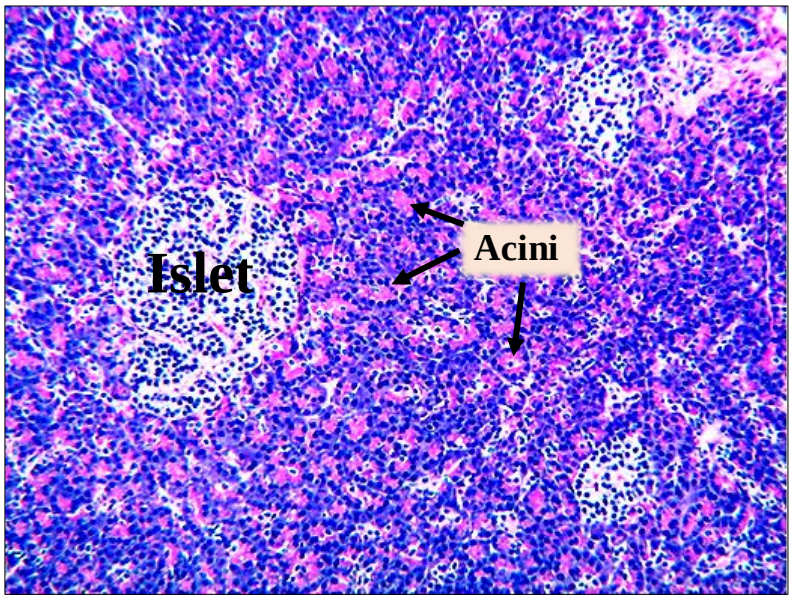


Figure 3. Histological section of human pancreas stained with Hematoxylin and Eosin (H&E) (Longnecker, 2014).

5.2. Liver

The liver is a central metabolic organ involved in glucose, lipid, and protein metabolism. It regulates blood glucose levels through three main processes: glycogenesis (storage of glucose as glycogen), glycogenolysis (breakdown of glycogen to glucose), and gluconeogenesis

(synthesis of glucose from non-carbohydrate precursors). These processes are tightly regulated by insulin and glucagon signaling (Lema-Pérez, 2021). In diabetes, hepatic insulin resistance disrupts this regulation, leading to excessive glucose production and reduced glycogen synthesis. As a result, the liver becomes a significant contributor to fasting and postprandial hyperglycemia. Additionally, the diabetic liver often undergoes steatosis due to altered lipid metabolism, a condition commonly referred to as non-alcoholic fatty liver disease. Over time, hepatic steatosis can progress to non-alcoholic steatohepatitis, fibrosis, and cirrhosis. The pathophysiological changes are closely linked to OS, mitochondrial dysfunction, and the activation of inflammatory pathways. Elevated serum levels of liver enzymes such as ALAT and ASAT frequently reflect hepatic injury in diabetic individuals (Jiang et al., 2020).

5.3. Kidneys

Beyond their role in glucose reabsorption, the kidneys are target organs affected by diabetic complications, they are essential in regulating glucose balance through glomerular filtration, tubular reabsorption, and renal gluconeogenesis. Normally, glucose filtered by the glomeruli is reabsorbed in the proximal tubules, mainly through the Sodium-Glucose Co-Transporter 2 (SGLT2), (Lema-Pérez, 2021).

In diabetic condition, chronic high blood sugar levels increase both the filtration and reabsorption of glucose, largely due to the upregulation of SGLT2, which paradoxically contributes to sustained hyperglycemia and worsens insulin resistance.

In addition to altered glucose handling, the kidneys are affected by chronic hyperglycemia, leading to diabetic nephropathy, one of the most prevalent microvascular complications of DM. This condition typically begins with glomerular hyperfiltration and microalbuminuria, progressing over time to overt proteinuria, a decline in glomerular filtration rate, and eventually end-stage renal disease. Histopathological changes in diabetic kidneys include thickening of

the glomerular basement membrane, mesangial matrix expansion, glomerulosclerosis, and podocyte depletion (Hesp et al., 2020).

The pathophysiological mechanisms of diabetic nephropathy are multifactorial, involving OS, inflammation, and fibrotic signaling pathways. Chronic hyperglycemia promotes the excessive ROS production, activation of Transforming Growth Factor-Beta (TGF-β) and Nuclear Factor Kappa B (NF-κB), and accumulation of Advanced Glycation End-products (AGEs). These factors drive inflammation, fibrosis, and progressive loss of renal function (Jin et al., 2023).

6. Pathophysiology of diabetes mellitus

The pathophysiology of diabetes involves disturbances in carbohydrate, fat, and protein metabolism. T1D is an autoimmune disease characterized by T-cell-mediated destruction of pancreatic β-cells, leading to insulin deficiency and hyperglycemia, with its onset influenced by both genetic and environmental factors. The diagnosis of T1D often relies on the detection of specific autoantibodies, such as those against Glutamic Acid Decarboxylase (GAD 65), Insulinoma-Associated Protein 2 (IA-2), Islet Cell Antigens (ICA), Insulin Autoantibodies (IAA), and Zinc Transporter 8 (ZnT8). The prevalence of these autoantibodies varies across age groups and helps distinguish T1D from other autoimmune forms of diabetes, such as Latent Autoimmune Diabetes in Adults (LADA). Type 1 diabetes is strongly associated with certain HLA haplotypes, particularly HLA-DR3 and HLA-DR4, as well as non-HLA genes. The autoimmune destruction of pancreatic β-cells is primarily mediated by $CD4^+$ and $CD8^+$ T lymphocyte infiltration, which is accompanied by the production of autoantibodies such as ICA, anti-GAD, anti-insulin, and anti-IA2, that serve as reliable biomarkers of the autoimmune response. T1D is also frequently associated with other autoimmune disorders, further supporting its immunological basis (Banday et al., 2020). In T2D, insulin resistance is the central defect, with peripheral tissues becoming less responsive to insulin, while the pancreas

is unable to compensate with sufficient insulin production. This results in increased hepatic glucose production and decreased glucose uptake by peripheral tissues. Additionally, elevated levels of free fatty acids due to impaired insulin action promote insulin resistance and hepatic steatosis, exacerbating the metabolic dysfunction. Long-term hyperglycemia can lead to serious complications (Banday et al., 2020).

7. Complications of diabetes mellitus

Diabetes leads to a wide range of complications on both microvascular and macrovascular levels. Microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy, occur due to long-term hyperglycemia, which damages the small blood vessels that supply organs like the eyes, kidneys, and nerves (Yapislar and Gurler, 2024). These complications are driven by endothelial dysfunction, the accumulation of AGEs, and increased OS (Barakat et al., 2020).

Macrovascular complications, including coronary artery disease, stroke, and peripheral arterial disease, result from the accelerated process of atherosclerosis in individuals with diabetes. Hyperglycemia leads to dyslipidemia and altered endothelial function, promoting to arterial wall thickness and plaque formation. These macrovascular complications, when combined with microvascular damage, significantly elevate the risk of diabetes-related morbidity and mortality (Cade, 2008).In addition to vascular complications, diabetes also impairs immune function, making the organism more susceptible to infections. Hyperglycemia disrupts innate immunity by altering neutrophil chemotaxis, phagocytosis, and microbial killing. It also affects adaptive immunity by impairing lymphocyte proliferation and cytokine production. The glycation of immunoglobulins and complement proteins further compromises immune defense mechanisms. Moreover, hyperglycemia promotes a pro-inflammatory environment, characterized by elevated levels of cytokines such as IL-6 and Tumor Necrosis Factor α (TNF-α), which contribute to chronic low-grade inflammation. This persistent

inflammatory state not only weakens the immune response but also delays wound healing and increases the risk of severe infections, such as urinary tract infections, respiratory tract infections, and diabetic foot infections (Vaibhav et al., 2024), (Fig. 4).

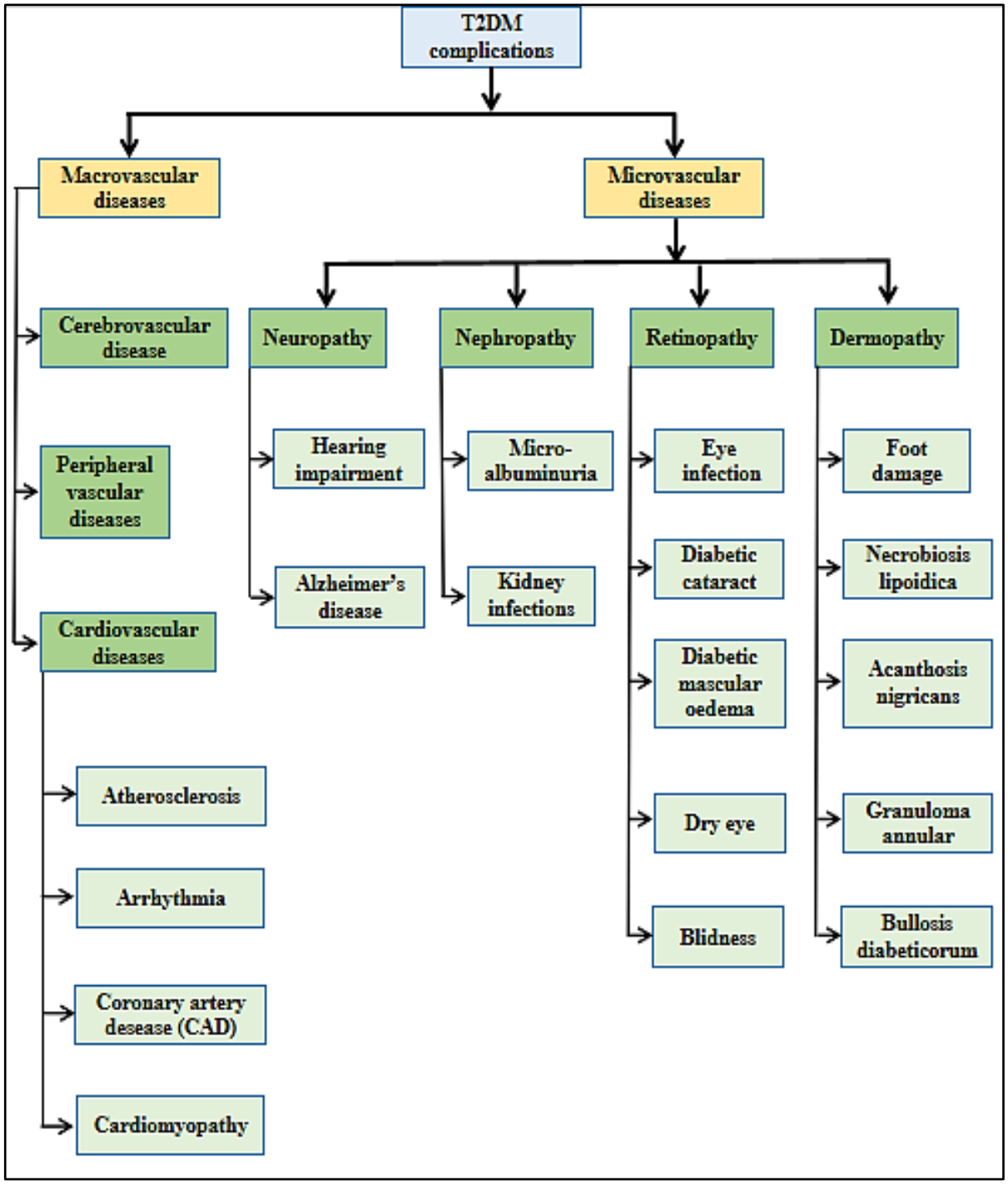


Figure 4. Flow chart of T2D associated vascular complications (Ansari et al., 2024).

II. OXIDATIVE STRESS AND ITS ROLE IN DIABETES PATHOGENESIS

Oxidative stress is a phenomenon that occurs as a result of exposure to xenobiotics, inappropriate diet or pathological situations. Under normal conditions, ROS are important in cells to destroy bacteria and viruses. Yet, when there is an imbalance between its production and elimination, severe damage can occur due to the oxidation of critical cellular components. ROS are highly reactive oxygen-containing molecules, including free radicals such as Superoxide Anion (O_2^-), Hydrogen Peroxide (H_2O_2), Hydroxyl Radical (•OH), and Reactive Nitrogen Species (RNS) like Nitric Oxide (NO^-) and peroxynitrite ($ONOO^-$). While they play essential roles in physiological signaling and immune responses, their overproduction can damage lipids, proteins, and nucleic acids, thereby contributing to chronic diseases such as cancer, neurodegenerative disorders, cardiovascular diseases, and metabolic conditions like DM (Liguori et al., 2018; Sies et al., 2022).

In both T1D and T2D, elevated blood glucose levels lead to increased production of ROS, primarily through mitochondrial dysfunction, the polyol pathway, glucose autoxidation and the formation of AGEs. These ROS are highly reactive and can damage cellular components, including proteins, lipids, and DNA, contributing to the progression of diabetic complications. In addition, ROS production is exacerbated by hyperglycemia, leading to endothelial dysfunction, β-cell apoptosis, and impaired insulin signaling. This oxidative damage plays a significant role in the development of diabetic complications. Furthermore, ROS-induced inflammation promotes the recruitment of immune cells and the release of pro-inflammatory cytokines, further perpetuating tissue damage (Caturano et al., 2023).

The body has a complex antioxidant defense system designed to neutralize ROS and prevent oxidative damage. Antioxidant enzymes, such as SOD, CAT, and GSH-Px, play a crucial role in maintaining the redox balance (Ighodaro and Akinloye, 2018). However, in diabetic individuals, the efficiency of this antioxidant system is often compromised, particularly in

organs that are most affected by diabetes, such as the kidneys, liver, and pancreas (Jomova et al., 2024). The antioxidant defense system can be bolstered by external sources, such as dietary antioxidants found in fruits, vegetables, and medicinal plants. Plant-derived compounds such as polyphenols and flavonoids exhibit ROS-scavenging properties and have been reported to support glycemic control and reduce OS in diabetic individuals (Mukherjee et al., 2024), (Fig. 5).

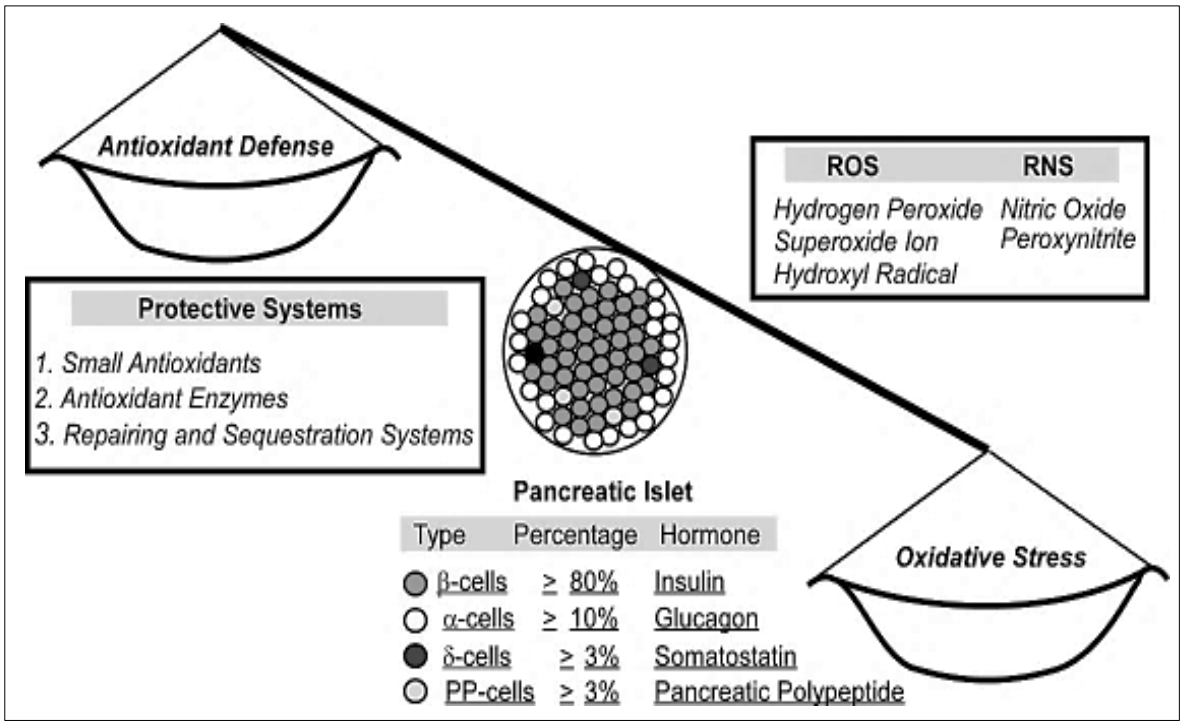


Figure 5. Overview of endocrine cell types and functions, main forms of ROS and RNS, and antioxidant defense systems in pancreatic islets (Lei and Vatamaniuk, 2011).

1. Molecular pathways linking hyperglycemia and ROS

In diabetes mellitus, OS is both a cause and a consequence of chronic hyperglycemia. Elevated glucose levels activate several ROS-generating pathways. Glucose autoxidation, a non-enzymatic oxidation process, generates free radicals. The polyol pathway converts glucose to sorbitol via aldose reductase, consuming NADPH and depleting cellular GSH (Galicia-Garcia et al., 2020). The hexosamine pathway alters protein function through abnormal glycosylation, disturbing cellular signaling (Stefano et al., 2016) (Fig. 6). The accumulation of

AGEs, formed through non-enzymatic glycation of proteins and lipids, engage their receptors (RAGE), thereby initiating oxidative and pro-inflammatory cascades (Zawada et al., 2022). Mitochondria are also a major source of ROS during hyperglycemia. High intracellular glucose levels overwhelm the mitochondrial electron transport chain, particularly complexes I and III, leading to electron leakage and excessive ROS overproduction (Zhang et al., 2023). This damages mitochondrial DNA and proteins, impairs adenosine triphosphate (ATP) synthesis and initiates apoptotic signaling in insulin-secreting β-cells (Sivitz and Yorek, 2010). β-cells are especially vulnerable due to their low antioxidant enzymes expression (Lei and Vatamaniuk, 2011).

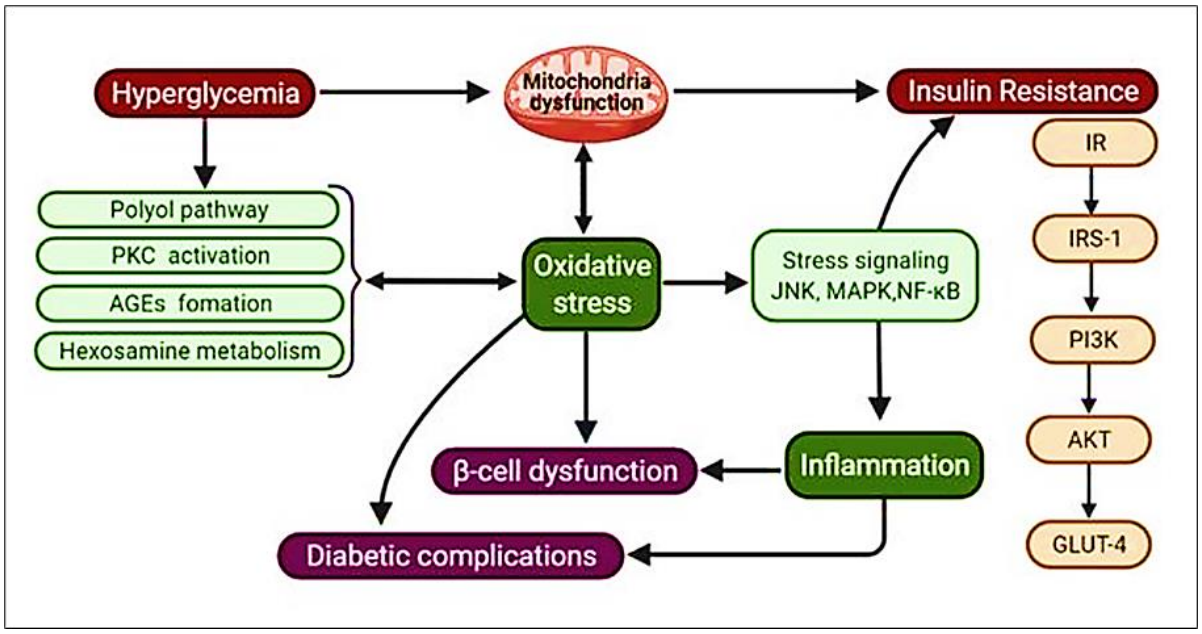


Figure 6. Oxidative stress pathways in DM (Xu et al., 2021).

2. Differential impact of oxidative stress in T1D vs T2D

Oxidative stress plays a crucial role in both T1D and T2D, though distinct mechanisms. In T1D, autoimmune destruction of β-cells is exacerbated by oxidative and nitrosative stress. Pro-inflammatory cytokines released from immune cells increase ROS and RNS production, which

overwhelms the antioxidant defense systems of β-cells, causing mitochondrial dysfunction, DNA fragmentation, and apoptosis (Kaneto et al., 2007).

In T2D, OS impairs insulin secretion and contributes to peripheral insulin resistance. β-cells with low antioxidant capacity are particularly susceptible to ROS-induced damage, reducing insulin gene transcription and secretion (Dludla et al., 2023). In insulin-sensitive tissues (liver, muscle, and adipose tissue), ROS interfere with the insulin signaling cascade by preventing the tyrosine phosphorylation of Insulin Receptor Substrate (IRS), a critical step for activating Phosphoinositide 3-Kinase (PI3K) and Protein Kinase B (PKB/Akt). This hinders Glucose Transporter Type 4 (GLUT4) translocation to the cell membrane and reduces glucose uptake (Boucher et al., 2014). Under normal conditions, insulin binding to its receptor initiates tyrosine phosphorylation of IRS, which activates phosphoinositide 3-kinase (PI3K) and downstream signaling molecules such as PKB. This cascade facilitates the translocation of GLUT4 to the plasma membrane, enabling glucose uptake. However, oxidative stress promotes serine/threonine phosphorylation of IRS, inhibiting its function and impairing downstream signaling. ROS also reduce PKB activation and trigger the activation of stress-related kinases, including c-Jun N-terminal kinase (JNK) and IκB kinase β (IKKβ), which aggravate insulin resistance (Swiderska et al., 2018; Lee et al., 2021).

3. Chronic oxidative stress and diabetes-related complications

Prolonged OS plays a pivotal role in the development of diabetes-related complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease. It activates intracellular signaling pathways such as NF-κB and Mitogen-Activated Protein Kinases (MAPKs), which promote the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adhesion molecules. These changes drive vascular inflammation, endothelial dysfunction, and progressive tissue damage (Chen et al., 2017). In the vasculature, ROS-induced endothelial damage impairs vasodilation and accelerates atherosclerosis. In the kidneys, OS intensifies

glomerular injury and leads to proteinuria, hallmark signs of diabetic nephropathy. In the retina, it causes capillary degeneration, contributing to visual impairment seen in diabetic retinopathy (Li et al., 2023; Yang et al., 2024).

4. The role of phytochemicals in enhancing antioxidant defense

To counteract OS, the body relies on a sophisticated antioxidant defense system comprising both enzymatic and non-enzymatic components. Major enzymatic antioxidants include SOD, CAT, and GSH-Px, while non-enzymatic antioxidants consist of GSH, ascorbic acid (vitamin C), tocopherols (vitamin E), carotenoids, flavonoids, and polyphenols (Fig. 7). Together, these systems maintain cellular homeostasis by regulating the balance between ROS production and elimination (Jomova et al., 2024).

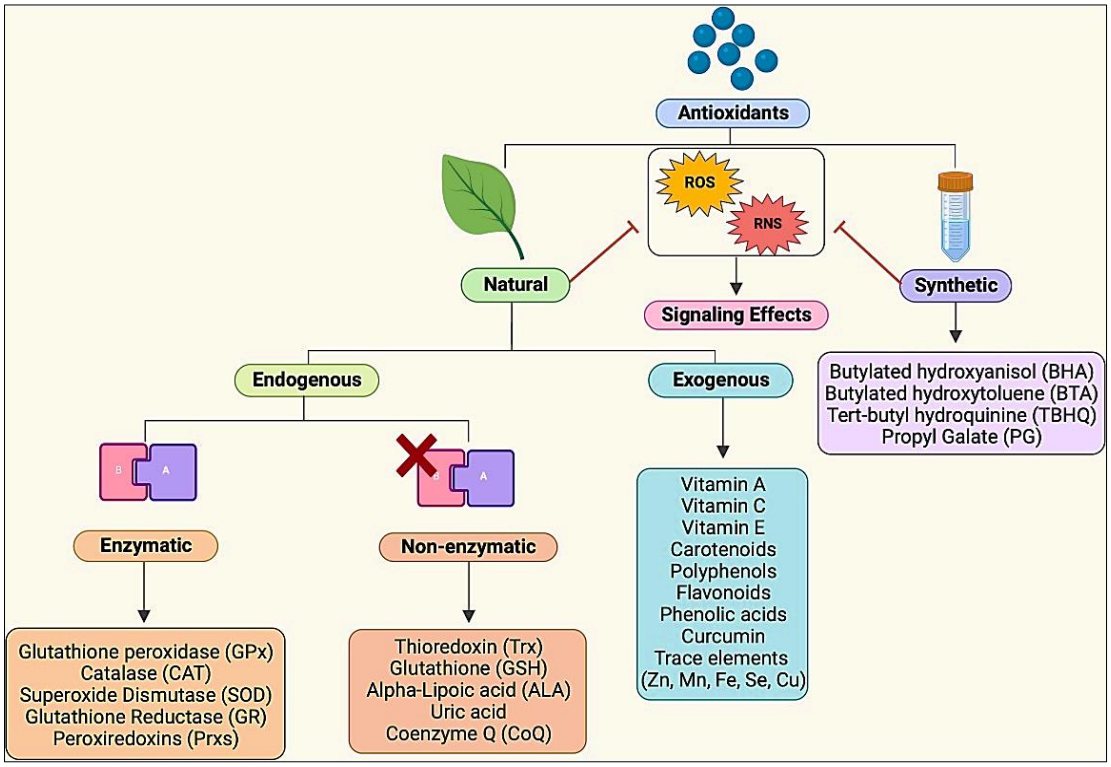


Figure 7. Classification of antioxidants based on their origin (Fatima et al., 2023).

The antioxidant mechanisms of phytochemicals are diverse and include:

- Scavenging of free radicals: Many bioactive compounds donate electrons or hydrogen atoms to neutralize ROS directly.

- Chelation of metal ions: Certain antioxidants bind transition metals like iron and copper, preventing them from catalyzing ROS formation.
- Upregulation of endogenous antioxidants: Some phytochemicals activate the pathway of Nrf2 (Nuclear Related Factor 2) /ARE (Antioxidant Response Element), enhancing the expression of antioxidant enzymes.
- Inhibition of oxidative enzymes: Compounds such as quercetin and curcumin inhibit enzymes like NADPH oxidase and xanthine oxidase, reducing ROS generation.
- β-cell survival: By stabilizing mitochondrial membranes and preventing cytochrome C release, antioxidants reduce apoptotic signaling (Jena et al., 2023).

However, in the context of diabetes, this redox balance is frequently disrupted due to impaired antioxidant defenses, resulting in elevated OS. This leads to an accumulation of oxidative damage markers such as MDA, protein carbonyls, and 8-hydroxydeoxyguanosine (8-OHdG), indicators of lipid, protein, and DNA oxidation, respectively (Maciejczyk et al., 2018). Persistent OS contributes to cellular dysfunction and apoptosis, further aggravating diabetic complications.

5. The therapeutic potential of natural antioxidants

Given the pivotal role of OS in the pathogenesis of diabetes, antioxidant therapies have gained increasing attention as promising therapeutic strategies. Although synthetic antioxidants may be effective in certain contexts, their use is progressively discouraged due to potential harmful and carcinogenic effects, raising serious concerns about their long-term safety (Tumilaar et al., 2024). Consequently, there is a growing preference for natural antioxidants derived from medicinal plants, which have demonstrated notable efficacy in scavenging free radicals, restoring redox balance, and protecting pancreatic β-cells (Fatima et al., 2023; Ferreira et al., 2024).

III. PHYTOTHERAPY

Phytotherapy, derived from the Greek words phyton (plant) and therapeia (treatment), refers to the therapeutic use of medicinal plants and their extracts for both the prevention and treatment of various diseases. Historically, it has been a cornerstone of traditional medical systems such as Ayurveda, widely practiced across India and Nepal, as well as traditional Chinese medicine and Greco-Arab medicine. These ancient practices, which predate modern pharmacology by centuries, relied extensively on the healing properties of plant-based remedies to address a broad spectrum of health conditions (Patwardhan et al., 2005; Saad, 2014).

1. From tradition to evidence: Phytotherapy in the post-pandemic era

In recent years, plant-based therapies have gained increasing global importance, a notable shift that was particularly evident during the COVID-19 pandemic. The urgent search for effective treatments led to renewed interest in natural remedies, with phytotherapy attracting attention for its potential antiviral and immunomodulatory properties (Coopoosamy et al., 2023) . Several plant-derived constituents such as alkaloids, flavonoids, and phenolic acids, have demonstrated the ability to modulate immune responses, inhibit viral replication, and block the viral entry mechanisms (Lim et al., 2021; Sohail et al., 2021). According to the World Health Organization, more than 80% of the global population relies on traditional medicine, including herbal remedies, for primary healthcare. This widespread reliance has fueled a growing body of research aimed at identifying, standardizing, and validating plant-based therapies that meet contemporary clinical and pharmacological standards (WHO, 2020). With advances in phytochemical and pharmacological studies, the therapeutic efficacy and underlying mechanisms of numerous plant-derived compounds have now been scientifically substantiated, strengthening the credibility of phytotherapy and its integration into evidence-based medical practice (Balkrishna et al., 2024).

2. Phytotherapy in diabetes mellitus

In DM, phytotherapy has attracted significant scientific interest due to its potential to complement or even substitute synthetic antidiabetic agents. Numerous medicinal plants contain bioactive compound such as alkaloids, flavonoids, polyphenols, terpenoids, and saponins, that exert hypoglycemic effects through diverse mechanisms. These include stimulation of insulin secretion, enhancement of glucose uptake by peripheral tissues, modulation of hepatic glucose metabolism, inhibition of hepatic glycogen hydrolysis, and suppression of carbohydrate-digesting enzyme activity. Moreover, plant-based therapies are often associated with fewer side effects compared to synthetic drugs, making them attractive candidates for long-term diabetes management (Tran et al., 2020).

3. Role of antioxidants in diabetes

Oxidative stress plays a central role in the pathophysiology of diabetes and its complications. Chronic hyperglycemia leads to overproduction of ROS, which in turn damages cellular components and impairs insulin signaling. In this context, phytotherapy offers a dual advantage: in addition to glycemic control, many plant-derived compounds possess strong antioxidant properties that can counteract OS. These compounds act through multiple pathways, including free radical scavenging, enhancement of endogenous antioxidant enzyme systems, and suppression of pro-inflammatory mediators (El Allaoui et al., 2025).

In diabetes management, flavonoids such as quercetin, kaempferol, catechins, and rutin have been reported to improve insulin sensitivity, reduce blood glucose levels, and protect pancreatic β-cells from oxidative damage (Al-Ishaq et al., 2019). Polyphenols also modulate enzymes involved in glucose metabolism, including α-amylase and α-glucosidase, thereby reducing postprandial glucose spikes (Shahidi and Danielski, 2024). In addition, they activate the Nrf2 pathway, which upregulates antioxidant enzymes such as SOD, CAT, and hemeoxygenase-1.

This contributes to maintaining redox homeostasis and protecting against diabetes-induced OS and inflammation (Ebrahimi et al., 2025).

Several phytochemicals have been identified for their potent antidiabetic and antioxidant effects, including:

- Curcumin: [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a phytonutrient obtained from the dried rhizomes of *Curcuma longa L*. It possesses a variety of pharmacological qualities including anti-inflammatory, antioxidant, anti-angiogenic and apoptogenic activities. In addition, it could delay the development of T2D, improve β-cell functions, prevent β-cell death, and reduces insulin resistance so decreasing AGEs in DM. (Marton et al., 2021).

- Hydroxytyrosol: Among phenols, hydroxytyrosol (3, 4-dihydroxyphenylethanol) stands out as a compound of high added value. It has various biological activities, such as downregulation of the immunological response, preventing human erythrocytes from oxidative damage induced by H_2O_2, anti-inflammatory, antithrombotic, and hypocholesterolemic effects. Besides, it protects pancreatic cells from damage and death leading to the increase of insulin secretion (Ahangarpour et al., 2019).

- Geniposide (*Gardenia jasminoides*): Modulates hepatic glucose metabolism and activates the PI3K/Nrf2 signaling axis, leading to reduced OS (Gao and Feng, 2022).

- Resveratrol (present in grapes and berries): Enhances insulin sensitivity and mitochondrial function via activation of SIRT1 and related signaling pathways. Treatment with resveratrol significantly decreases the level of glycosylated hemoglobin (HbA1c) (Lagouge et al., 2006).

- Ellagic acid: (2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde] chromene-5,10 dione) is a phytochemical known to have anti oxidative, anti-mutagen, anti-inflammatory, and also has anticarcinogenic properties. The mechanism of glucose lowering action may be through

potentiation of insulin secretion from β-cells or due to enhanced transport of blood glucose to the peripheral tissue (Ahangarpour et al., 2019).

The multifaceted mechanisms by which plant-derived compounds exert antidiabetic effects include the modulation of glucose homeostasis, inhibition of OS, and attenuation of inflammatory responses. A central mechanism is the activation of the Nrf2/ARE pathway, which orchestrates the transcriptional activation of genes responsible for antioxidant defense. Recent studies have highlighted the antidiabetic and antioxidant potential of polyphenol-rich extracts, particularly those obtained from halophyte species, which are naturally adapted to survive in oxidative environments (Ferreira et al., 2024). By mitigating oxidative damage and supporting endogenous detoxification systems, these phytochemicals help preserve pancreatic β-cell function and reduce the risk of diabetes complications (Baumel-Alterzon et al., 2021).

IV. HALOPHYTIC PLANTS

1. Overview

Halophytes are salt-tolerant plant species that have naturally adapted to thrive in high-salinity environments, often completing their life cycles in conditions containing at least 200 mM NaCl (Flowers and Colmer, 2008). Although they constitute only about 1–2% of the world's flora, halophytes exhibit remarkable ecological diversity and occupy a wide range of saline habitats, from coastal salt marshes and dunes to arid inland deserts and salt-affected agricultural lands (Mann et al., 2023). These species play a significant ecological role by contributing to soil desalination, enhancing nutrient availability, and supporting biodiversity in challenging environments. Due to their unique physiological adaptations, halophytes are gaining attention not only for their ecological value but also for their potential use in agriculture and industry (Lombardi et al., 2025). Many species have shown promise as alternative crops for fodder, food, fuel, pharmaceuticals, and environmental restoration. Families such as *Amaranthaceae*, *Poaceae*, *Fabaceae*, and *Asteraceae* are particularly rich in halophyte species, making them valuable resources for future research and sustainable development in saline-prone regions (Marinoni et al., 2019).

2. Classification of halophytes

Halophytes, found in both coastal and inland saline habitats across all continents except Antarctica, are classified based on diverse criteria such as habitat salinity, physiological responses, salt absorption/exclusion mechanisms, and anatomical adaptations (Hameed et al., 2024). Classifications range from ecological types like euhalophytes and pseudohalophytes to morphological categories such as succulents and non-succulents. Over time, various researchers including Hedenberg, Chapman, Waisel, Yensen, and Grigore, have proposed different systems to reflect the complexity and diversity of halophyte adaptations to saline

environments (Fig. 8). These classifications provide more information about their ecological roles and adaptive strategies (Hameed et al., 2024).

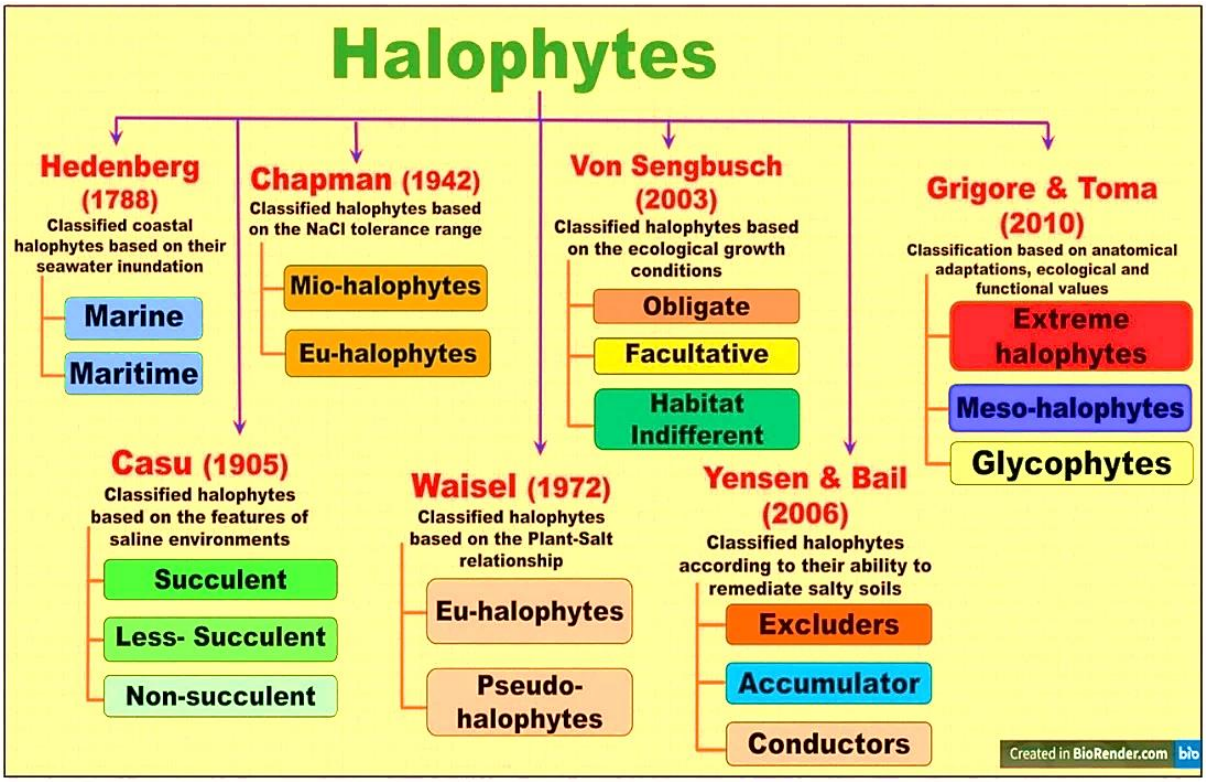


Figure 8. Some common classifications of halophytes (Hameed et al., 2024).

3. Distribution of halophytes

The global distribution of halophytes reflects their ability to colonize and dominate environments characterized by natural or anthropogenic salinity. These include coastal ecosystems (e.g., tidal marshes, mangroves), saline inland basins, estuaries, saline deserts, and degraded farmlands affected by secondary salinization (Flowers and Colmer, 2008). Halophytes are particularly abundant in arid and semi-arid regions where evapotranspiration rates exceed precipitation, leading to salt accumulation in soils. Major halophytic zones are found across the Mediterranean basin, the Middle East, Central Asia, sub-Saharan Africa, Australia, and the western coasts of the Americas. Countries like Iran, India, China, and Australia possess vast saline ecosystems that host diverse halophyte species adapted to varying degrees of salinity and environmental stress (Flowers and Colmer, 2015).

In Algeria, halophytes are predominantly found in the steppe and Saharan zones, occupying saline depressions (Sebkhas), salt lakes (Chotts), and degraded rangelands. These regions include:

- Steppe and Sahara zones: Halophytic vegetation is indeed present in Algeria's steppe and Saharan regions, particularly in areas characterized by saline depressions such as Chotts and Sebkhas. For instance, the Chott el Hodna and Chott Melrhir are notable for their halophytic plants, including species like *Salicornia*, *Salsola*, and *Atriplex*. These regions are part of the broader Saharan halophytic ecoregion, which encompasses various low-lying evaporite depressions and wetlands across North Africa (Rabah et al., 2012; Boucherit et al., 2017).

- High Plains (e.g., Khenchela, M'Sila): It is a high plateau area consisting of undulating, steppe-like alluvial plains lying between the Tell and Saharan Atlas ranges (Boucherit et al., 2017). These regions are characterized by semi-arid climates and steppe vegetation. While these areas do experience salinization issues, the presence of halophytes is more localized and often associated with specific saline habitats within the broader steppe landscape (Abdessamad and Belkaid, 2018).

- Southern Basins (e.g., Ouargla, El Oued): In the southern Sahara regions, particularly around Ouargla and El Oued, halophytes are more prevalent. Studies have documented diverse plant communities in these areas, including halophytic species such as *Halocnemum strobilaceum*, *Suaeda fruticosa*, *Atriplex halimus*, and *Seidlitzia rosmarinus*, which are adapted to saline and arid environments.

- Northern Wetlands (the case of Macta): Among Algeria's diverse wetlands, the Macta Wetland in the north-west region serves as an important halophytic zone. It is a rich ecological site formed by the confluence of the Sig and Habra rivers near the Gulf of Arzew. This wetland supports a wide variety of salt-tolerant flora (Megharbi and Kechairi, 2021). An ethnobotanical survey conducted in this region identified 32 halophytic species traditionally used for medicinal

purposes, including treatments for inflammatory disorders and diabetes (Megharbi and Kechairi, 2021; Miara et al., 2021). This highlights the cultural and pharmacological value of halophytes in wetland ecosystems and their potential in phytotherapeutic applications, particularly in arid and saline environments (Ziane et al., 2023; Hanafi et al., 2024).

The distribution correlates strongly with natural salinization processes and poor drainage conditions, which lead to the formation of alkaline and saline soils. The Algerian halophytic flora is primarily represented by species from families such as *Amaranthaceae*, *Asteraceae*, *Poaceae*, and *Brassicaceae*, which display remarkable adaptability to high salinity and harsh environmental conditions (Haddad et al., 2024). Their importance lies in their roles in soil stabilization, salinity reduction, and as potential resources for bio-saline agriculture, and forage (Navarro-Torre et al., 2023). Besides their ecological functions, Algerian halophytes hold increasing significance for sustainable agriculture and traditional medicine. Their resilience to abiotic stress positions them as potential candidates for cultivation in marginal lands under conditions of water scarcity and salinity (Nedjimi, 2020). Furthermore, several native species are under investigation for their phytochemical richness and pharmacological potential, aligning with the global trend toward biosaline agriculture and the valorization of halophytes in phytotherapy and environmental management (Hameed et al., 2024).

4. Phytochemical composition of halophytes

The phytochemical diversity and richness of halophytes are largely driven by their adaptation to salinity-induced oxidative stress and extreme abiotic conditions including (drought, salinity, cold, heat, UV radiation, etc.). These stressors trigger the production of various secondary metabolites based on a series of physiological, metabolic and molecular mechanisms, which can vary depending on the plant species, its genetic background, developmental stage, and the specific type and intensity of the stress encountered. Aside from

their ecological value, these plants do possess high medicinal properties and have been extensively used for centuries in traditional medicine (Hasanuzzaman et al., 2020).

The phytochemical arsenal of halophytes comprises diverse classes of secondary metabolites including phenolic compounds, flavonoids, alkaloids, terpenoids, saponins, glycosides, tannins, and essential oils (Stevanovic et al., 2019), (Fig. 9). Among these, phenolic acids and flavonoids are particularly abundant and have been strongly correlated with antioxidant and anti-inflammatory effects. The richness and diversity of these compounds are largely attributable to the environmental pressures exerted by saline soils, which activate phenylpropanoid and terpenoid biosynthetic pathways (Sharma et al., 2019).

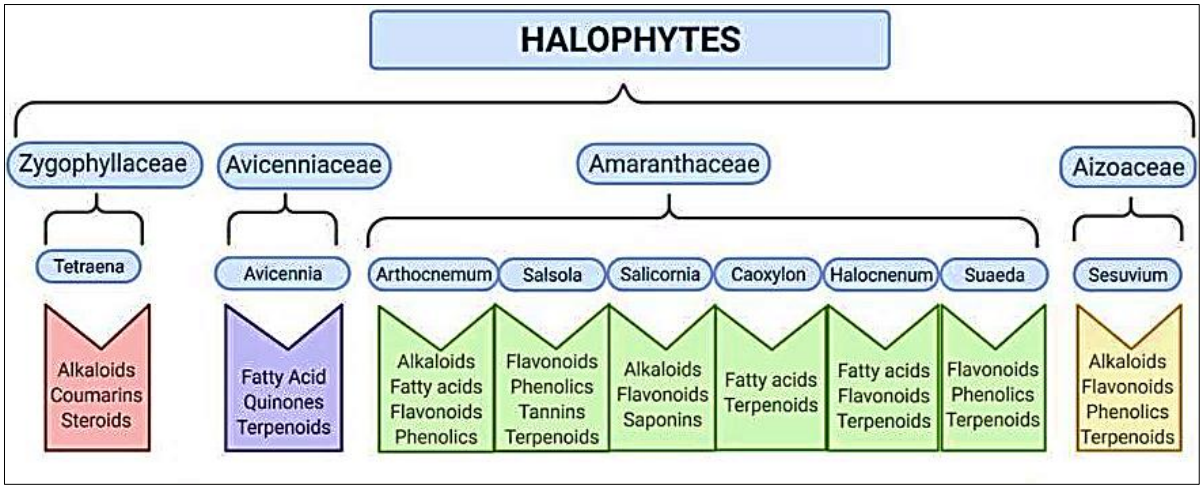


Figure 9. Phytochemical composition of some common coastal halophytes (Giordano et al., 2021).

In addition, halophytes are exceptionally rich in essential macro and microelements, which play pivotal roles in human and animal nutrition as well as in the therapeutic efficacy of plant-based remedies. These plants often accumulate high concentrations of potassium (K^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), iron (Fe^{2+}/Fe^{3+}), zinc (Zn^{2+}), selenium (Se), and sodium (Na^+), depending on species and soil conditions (Matinzadeh et al., 2013; Xu et al., 2016). For example, *Salicornia europaea* and *Atriplex halimus* have been shown to contain significant

levels of potassium and magnesium, contributing not only to cardiovascular support but also to the modulation of OS and inflammatory processes (Nedjimi et al., 2013; Kim et al., 2021).

5. Therapeutic applications

Halophytes represent a largely underexplored reservoir of bioactive compounds with promising potential in the treatment of various human diseases. Their rich and diverse phytochemical profiles, developed as an adaptive response to extreme environmental conditions, make them valuable sources for a wide range of biomedical applications. Recent research has highlighted several notable properties, including:

- Antioxidant Activity: Halophytes are rich in antioxidant compounds, particularly polyphenols and flavonoids, which contribute to their strong antioxidant properties by scavenging ROS, inhibiting Lipid Peroxidation (LPO), enhancing antioxidant enzyme activity, and chelating metal ions. Numerous studies have highlighted the significant antioxidant potential of various halophyte species, demonstrating their capacity to protect against OS-related diseases (Nazir et al., 2018; Pungin et al., 2022).
- Antidiabetic Effects: Certain halophytes are now recognized for their potential antidiabetic effects, owing to their rich phytochemical profiles that appear to act through multiple complementary mechanisms (Pungin et al., 2022). Halophyte extracts have been shown to inhibit key carbohydrate-digesting enzymes (e.g., α-amylase and α-glucosidase), thereby slowing starch breakdown and limiting postprandial glucose absorption (Al-Omar et al., 2020). Simultaneously, bioactive compounds from halophytes can directly enhance insulin action: for example, certain cyclitols and flavonoids stimulate glucose-stimulated insulin secretion by pancreatic β-cells and upregulate insulin signaling pathways (PI3K/Akt, etc) (Lee et al., 2025). These agents also improve peripheral insulin sensitivity and glucose uptake, in part by promoting translocation of GLUT4 transporters into muscle and adipose membranes (Al-Ishaq et al., 2019). Some halophyte constituents even suppress endogenous

glucose production: for instance, extracts of *Salicornia spp*. downregulate hepatic gluconeogenic enzymes (PEPCK and glucose-6-phosphatase) and lipogenesis genes, thus lowering basal glucose output (Park et al., 2006).

- Anti-inflammatory properties: Halophyte-derived flavonoids and triterpenoids inhibit key mediators of inflammation. Flavonoids are known to inhibit the NF-κB signaling pathway, thereby suppressing transcription of key pro-inflammatory cytokines (e.g. TNF-α, IL-1β, IL-6) (Choy et al., 2019; Al-Khayri et al., 2022). Similarly, many triterpenes commonly found in halophytes (e.g. ursolic, oleanolic and boswellic acids) block NF-κB and STAT3 activation, thereby diminishing the expression of IL-1β, TNF-α and other cytokines (Mohammed et al., 2023). Through this combined action, rebalancing cytokine profiles (limiting pro-inflammatory signals while sparing or enhancing anti-inflammatory ones) and inhibiting leukocyte activation, halophyte phytochemicals can effectively dampen chronic inflammatory responses (Giordano et al., 2021).
- Antimicrobial Potential: Halophytes produce unique antimicrobial peptides and secondary metabolites capable of disrupting bacterial cell membranes and inhibiting microbial growth. They insert into lipid bilayers and form pores or cause lipid phase segregation, leading to increased permeability and leakage of cellular contents (Benfield & Henriques, 2020; Ferreira et al., 2022). For example, some crude extracts produced significant inhibition of Gram-negative strains such as *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Acinetobacter baumannii*, as well as vancomycin-resistant *Enterococcus* (Chekroun-Bechlaghem et al., 2021; Sanchez-Hernandez et al., 2021).
- Hepatoprotective and Gastroprotective properties: The antioxidant-rich extracts from halophytes can reduce hepatic LPO and enhance liver enzyme function, supporting their use in managing liver disorders (Ben Hsouna et al., 2022). Furthermore, they protect the gastrointestinal tract. In an ethanol-induced ulcer model, pretreatment with *Suaeda*

fruticosa extract markedly reduced gastric mucosal lesions and bleeding; this gastroprotective effect was attributed to antioxidant, antisecretory and cytoprotective actions of its constituents (Ayaz et al., 2022).

- Anticancer and cytotoxic activity: Some halophytes contain polyphenolic compounds that exhibit selective cytotoxicity against cancer cell lines. In vitro studies have shown that halophyte extracts can trigger apoptosis in tumor cell lines while sparing normal cells. Mechanistically, many of these compounds induce mitochondrial (intrinsic) apoptosis, they generate excessive ROS in cancer cells, disrupt mitochondrial membrane potential, activate caspases, and ultimately fragment nuclear DNA (Custodio et al., 2022).
- Improvements in renal function and histology: Findings from animal models of nephrotoxicity demonstrated that halophyte-derived bioactive products mitigate renal OS and inflammation, thereby preserving kidney function (Tienda-Vázquez et al., 2022). By scavenging free radicals and upregulating endogenous antioxidants, halophyte extracts prevent the cascade of damage (LPO, protein oxidation, apoptosis) that drives nephrotoxic injury. The resulting anti-inflammatory milieu may also suppress profibrotic signaling (Grabowska et al., 2023). Multiple in vitro and *in-vivo* studies confirm that halophytic plant extracts can lower serum creatinine and urea, reduce renal oxidative biomarkers, and improve histopathological results (Patel, 2016; Tienda-Vázquez et al., 2022).

V. SELECTED PLANT SPECIES

Halophytes have drawn increasing attention as potential sources of bioactive compounds in the ongoing search for natural therapies for many diseases. This work focuses on two Algerian halophytes, *A. halimus* and *S. mollis*. These plants with four other species are consumed by *Psammomys obesus*, a desert rodent known for its metabolic sensitivity (Daly and Daly, 1973). Interestingly, when *P. obesus* is removed from its natural habitat (where its diet consists mainly of halophytes) and fed standard laboratory chow rich in carbohydrates, it rapidly develops obesity and hyperglycemia (Schmidt-Nielsen et al., 1964; Kaiser et al., 2012). This phenomenon suggests that the phytochemical composition of these halophytes may play a role in glucose homeostasis and metabolic regulation. The following sections provide an overview about the two species, their phytochemical profiles, biological activities, as well as their recognized therapeutic applications.

1. *Atriplex halimus* L.

1.1. Botanical description

Atriplex halimus L., has a frequently used names as Mediterranean saltbush, sea orache, shrubby orache, or silvery orache, and known in Arabic as Raghl (رغل ملحي) or G'atef (القطف). This perennial, woody plant is characterized by a dense, semi-evergreen shrub, typically reaching heights of up to 2 meters and spreading approximately 2.5 meters wide (Cherrada et al., 2024). The plant is identified by its alternate, leathery leaves that are ovate or diamond-shaped, measuring up to 6 cm in length and often displaying slightly toothed margins (Fig. 10). During late spring and summer months, *A. halimus* bears small greenish-white flowers that are grouped in terminal panicles, which can grow up to 30 cm long (Megharbi and Kechairi, 2021). This species is well-adapted to extreme environmental circumstances, showing a high capacity for enduring drought, saltiness, strong coastal winds, and alkaline soils, but it has a low tolerance for water-logging. Besides, it is very resistant to both pests and diseases. The Atriplex

genus encompasses about 250 species, including *Atriplex nummularia*, *Atriplex lentiformis*, *Atriplex amnicola*, and *Atriplex canescens*. Many of them are utilized as high-quality forage crops because of their high protein content, thus contributing to extensive plantations along the Mediterranean coast for soil restoration and feeding livestock (Zerdoner Calasan et al., 2022; Nouha et al., 2024). In this research, *A. halimus* was selected for its strong ecological resilience, its traditional medicinal use in most of Algeria's arid and semi-arid regions particularly in managing hyperglycemia and cysts showing a potential source of natural antioxidants (Soliman et al., 2015; Roubi et al., 2024).

Figure 10. The leaves of *Atriplex halimus*. (Source: Author's photograph).

1.2. Taxonomy

The taxonomic classification of *Atriplex halimus* is shown in (Table II) (Tela Botanica, 2023).

Table II. Taxonomy of *Atriplex halimus* L.

Classification	
Kingdom	Plantae
Division	Spermaphyta
Clade	Magnoliophyta (Angiospermae)
Class	Eudicotyledoneae
Order	Caryophyllales
Family	Amaranthaceae [Chenopodiaceae]
Genus	*Atriplex*
Species	*halimus* L.

1.3. Morphology

Atriplex halimus has a deep and extensive root system that allows for the uptake of water from deep soil layers, which is vital in dry environments. The stems are erect, branched, and woody with age, which provides structural strength to deal with environmental stresses. The leaves are fleshy and simple, and they are covered by a cuticle. Trichomes (fine hair-like structures) on the leaves are essential for reducing transpiration by blocking water vapor and preventing leaf overheating and for coping with intense sunlight and dryness to keep the plant from losing water. These trichomes also collect salt crystals, which burst and release excess salt when there is a harmful buildup on the plant tissue. For reproductive structures, there are small, greenish flowers that have no petals; male and female flowers may be found on one or separate plants. The fruits are small, dry, and enclosed within bracteoles, aiding in seed dispersal (Ortíz-Dorda et al., 2005; Walker et al., 2014; Ounaissia et al., 2019).

1.4. Traditional uses

Atriplex halimus L. has a rich history of traditional use across its native distribution (Mediterranean Basin, North Africa, and parts of the Middle East). Ethnobotanical records highlight its use in managing metabolic disorders, particularly diabetes and hypertension. It is also traditionally prescribed for digestive issues (stomach catarrh, constipation, diarrhea, gas, bloating), parasitic infections (e.g., hydatid cysts), and inflammatory conditions like rheumatism and arthritis. Topical applications for wound healing and skin infections are also common. In Algeria, where it is locally known as "G'taf," *A. halimus* holds also importance in traditional healthcare. It is commonly prepared as decoctions, infusions, or powders mixed with honey, oil, or local butter (Dhan) and used to treat hypertension, diabetes, kidney stones, gastrointestinal disorders, gynecological conditions (fibroids, infertility), and infections such as otitis and tonsillitis. Its antiseptic properties are valued for treating burns, wounds, and ulcers (Hadjadj et al., 2015; Soliman et al., 2015). The plant’s integration into Algerian ethnomedicine

reflects its therapeutic significance, especially in arid and semi-arid regions where it thrives. Today, scientific studies increasingly support its antioxidant properties, reinforcing its traditional use in managing inflammation and OS-related conditions (Walker et al., 2014; Roubi et al., 2024).

1.5. Chemical composition

The chemical composition of *A. halimus* has been the subject of several studies. The plant is rich in both organic and inorganic compounds, which contribute to its pharmacological effects.

- Organic composition: *A. halimus* contains various bioactive secondary metabolites. Studies have identified a variety of flavonoids such as flavanol, flavanone, and flavone glycosides, with specific compounds like quercetin derivatives, isorhamnetin, tricin, and isoorientin being reported (Clauser et al., 2013). Other notable organic constituents include tannins, saponins, and alkaloids. Terpenoids and steroids like stigmasterol and campesterol are also present. The plant contains both saturated and unsaturated fatty acids, as well as various free and protein amino acids, contributing to its nutritional value. Essential oils, with components like D-limonene, have also been identified and linked to biological activities such as antioxidant and antimitotic effects (Chaouche et al., 2021; Roubi et al., 2024).
- Mineral composition: The plant is also characterized by its accumulation of inorganic elements, a trait common to halophytic plants. Analysis of the mineral composition has revealed the presence of substantial levels of sodium, potassium, calcium, magnesium, phosphorus, copper, zinc, manganese, iron, and selenium. While the high sodium content is a physiological adaptation to saline environments, the presence of essential minerals contributes to the plant's overall nutritional profile and therapeutic value. Certain minerals, such as chromium, have been specifically implicated in the plant's potential antidiabetic effects through their influence on insulin activity (Dessena and Mulas, 2021).

2. *Suaeda mollis* (Desf.) Delile

2.1. Botanical description

Suaeda mollis (Desf.) Delile in Arabic referred to (السويدة), belonging to the Amaranthaceae family, is a perennial succulent halophyte adapted to saline and alkaline environments. It generally grows in salt marshes, coastal zones, and inland salt flats, where it plays a key ecological role due to its tolerance to harsh conditions such as high salinity and drought (Nedjimi, 2018). Flowering typically occurs in spring from (March–April) and again in autumn (November), although flowering from August to October has also been reported depending on climatic conditions (Nedjimi, 2022). The flowers are mostly bisexual, purplish-pink in color, and lack petals. They are grouped in small clusters (glomerulus) located in the leaf axils. The central flowers are bisexual, while the peripheral ones are functionally female (Quézel, 1962). The fruit is a small utricle, enclosed within a persistent calyx that remains open in bisexual flowers but closed in female ones. Seeds are small (about 1 mm), black, shiny, and kidney-shaped. These characteristics reflect the plant's high physiological adaptations, making it a potential candidate for ecological restoration in degraded saline areas (Maire et al., 1952).

2.2. Taxonomy

The classification of *S. mollis* (Desf.) Delile has been subject to considerable debate due to its morphological similarities with closely related taxa. A major point of contention lies in its synonymy with *S. monodiana* and *S. vermiculata*. Initially described by Maire (1937) based on sessile leaves, *S. monodiana* was later reassessed by the same author in 1962, who acknowledged that the leaves were actually inserted on small tubercles, characteristics consistent with *S. mollis* (Maire et al., 1952). Consequently, he suggested that *S. monodiana* may represent a western subspecies of *S. mollis*. Maire (1939) considered *S. mollis* distinct from *S. vermiculata* and retained it as a separate species. However, subsequent taxonomists such as Zohary (1966), Täckholm (1974), and Jafri & El-Gadi (1978) placed both *S. mollis* and

S. monodiana in synonymy with *S. vermiculata Forssk*. *S. mollis* was originally named *Salsola mollis* by Desfontaines, later renamed *S. mollis* by Delile (Attioui and Lemmel, 2020). Despite these debates, the most widely accepted classification in Algeria continues to recognize *Suaeda mollis* (Desf.) Delile as a valid species (Table III), particularly in regional floristic records and ecological studies, where it is distinguished from *S. vermiculata* based on subtle morphological and ecological traits.

Table III. Taxonomy of *Suaeda mollis* (Desf.) Delile (GBIF, 2023).

Classification	
Kingdom	Plantae
Division	Tracheophytes
Clade	Angiospermae
Class	Eudicots
Order	Caryophyllales
Family	Amaranthaceae
Genus	*Suaeda*
Species	*mollis* (Desf.)

2.3. Morphology

Suaeda mollis generally grows as an erect subshrub or small bush, reaching heights of 40 to 90 cm. It has a woody base and numerous smooth, slender, and highly branched stems emerging from the base. Young branches are green or slightly purplish, turning whitish and woody with age. Leaves are alternate, glabrous, and highly succulent, ranging from cylindrical to ovoid or sub globular in shape. They are usually convex or flattened on the upper surface and end in a rounded tip. Each leaf is attached by a very short petiole, appearing articulated at a small stem protrusion (Fig. 11). Internally, the leaf is structured to retain water, with a palisade chlorenchyma layer above a zone of amyliferous cells surrounding a large aquiferous parenchyma tissue, contains a large cell with a thin wall and a very large vacuole, where water is stored. The vascular network is arranged in a single plane. The flowers are small and

greenish, about 4 mm wide, with five sepals partially fused at the base. They contain five stamens and a conical ovary with three slender, free stigmas inserted at the top (Maire et al., 1952; Quézel, 1962).

Figure 11. *Suaeda mollis* (Desf.) Delile.

Real photo in the right (Source: Author's photograph), and image in the left extracted from (Flore de l'Afrique du Nord by Maire) showing: A: Flowering branch, B: Open and spread flower, C: Stamen, D: Seed, style, and staminal filaments, E: Cross-section of the ovary of a flower (Maire et al., 1952).

2.4. Traditional uses

Suaeda mollis holds significant traditional medicinal value rooted in local ethnobotanical practices. In Algerian folk medicine, it is primarily used for the treatment of liver disorders such as hepatitis, as well as for reducing fever and managing inflammatory conditions. These applications are typically prepared as decoctions or infusions of the aerial parts, especially leaves, and administered orally (Nedjimi, 2022). In southern Tunisia, *S. mollis* leaves were traditionally applied to wounds (with the burnt ash used in chewing tobacco) (Zaier et al., 2022). Although *S. mollis* is not among the most frequently cited species in ethnobotanical surveys, its practical uses, such as wool dyeing in certain regions, further reflect its integration

into traditional life. Recent pharmacological *in-vitro* studies have validated many of these conventional claims, confirming the plant's antioxidant, anti-inflammatory, and anticancer properties, thus reinforcing its relevance as a bioactive halophyte in ethnomedicine (Oueslati et al., 2023) .

3. Adverse effects of plants use

Medicinal plants have long been a longstanding practice attributed to their potential therapeutic benefits. Although, it is essential to recognize that "natural" does not always mean "safe". Despite offering organ-protective benefits, some plant species can be toxic and cause harmful effects. *A. halimus* and *S. mollis* offer therapeutic benefits, but their safety cannot be assumed based on their natural origin. *A. halimus* poses potential health risks due to its ability to accumulate salts, oxalates, nitrates, and tannins, which may contribute to hypertension, kidney damage, and OS (Nedjimi et al., 2013; Nedjimi, 2022). These risks are mainly indirect, linked to mineral content rather than inherent toxicity. *S. mollis* appears to have low acute toxicity, with no reported clinical side effects, but safety data are limited. *In-vitro* studies have shown that certain non-polar extracts of *S. mollis* exhibit cytotoxicity affecting both cancerous and normal human cells (Oueslati et al., 2023), and contamination from heavy metals remains a concern (Nedjimi, 2018). Therefore, toxicological evaluations and studies of their therapeutic potential are necessary to ensure both safety and efficacy.

MATERIALS & METHODS

Study aims and objectives

This research was conducted to investigate the antidiabetic and antioxidant potentials of the aqueous and methanolic extracts of *A. halimus* and *S. mollis*, individually and combined, through a series of *in-vitro* and *in-vivo* assessments. The study follows a structured approach that includes: Phytochemical analysis, evaluation of antioxidant activity, induction of experimental diabetes, investigation of biochemical, hematological and oxidative stress parameters, and histopathological examination of target organs (pancreas, liver, and kidneys). The following schematic representation summarizes the main stages of experimental design and study objectives (Fig. 12).

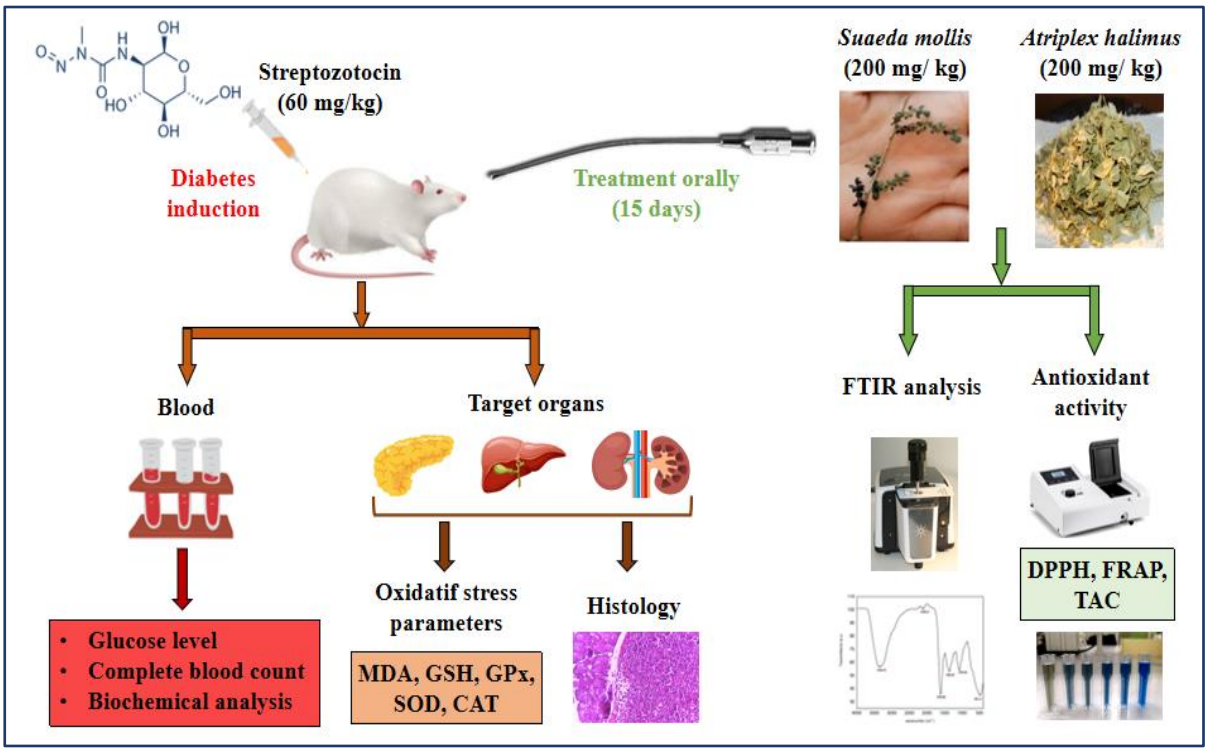


Figure 12. Experimental design and study workflow**.**

I. MATERIALS

1. Plant materials

Atriplex halimus L. (Ouled Bedira, M'Sila, Algeria; 35.74° N, 4.56° E) and *Suaeda mollis* (Desf.) Del. (Djellal, Khenchela, Algeria; 34.92° N, 6.89° E) were collected in June 2019 and March 2020 respectively. Professor BOUGHEDIRI Larbi (Badji Mokhtar University, Annaba) has identified the plant specimens according to the book of (Ozenda, 1991). The leaves from each plant were cleaned and air-dried in a shaded area to prevent degradation of bioactive compounds. Once fully dried, they were ground separately into a fine powder using an electric grinder. The prepared powder was stored in an airtight container at room temperature until further use.

2. Animals

Adult male Wistar rats, weighing 150 - 300g were purchased from Pasteur institute in Algiers- Algeria. They were selected and housed at the animal research unit of the sciences faculty in Badji Mokhtar- Annaba University under standard environmental conditions (24 ± 1°C), with 12 h light and 12-h dark cycles. The rats had a free access to standard food pellets and water *ad libitum*. The Ethical committee of the directorate general for scientific research and technological development at Algerian ministry PNR/SF 08/2012 approved all healthcare procedures.

3. Chemicals and reagents

All chemical products used in this study were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).

3.1. Streptozotocin

Streptozotocin (2-deoxy-2(([methyl (nitroso) amino] carbonyl) amino)- (α and β)-D glucopyranose) is a natural antibiotic produced by *Streptomyces achromogenes*. Its selective diabetogenic effect on pancreatic β-cells results from its dual structure (Fig. 13): A

glucopyranosyl group that enables uptake via Glucose Transporter 2 (GLUT2) and a nitrosourea moiety that induces DNA alkylation, leading to β-cell necrosis (Lenzen, 2008; Ghasemi and Jeddi, 2023). STZ has been widely used to induce T1D in experimental models. STZ is a highly hydrophilic compound, and its stability and toxicity are influenced by pH and solvent conditions. In acidic solutions, it may cause hemolysis of red blood cells and pain at the injection site in rats (Eleazu et al., 2013; Ghasemi and Jeddi, 2023).

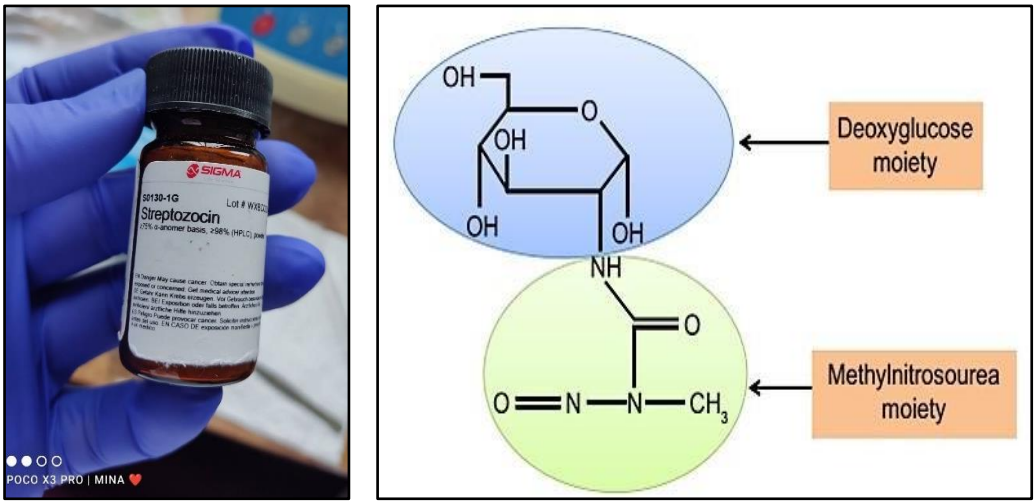


Figure 13. (A) commercial vial of STZ (Source: Author's photograph), (B) chemical structure of STZ (Abu Zeid, 2019).

II. METHODS

1. Preparation of the extracts

The extract was obtained as follows, 10 g of the plant powder are added to 100 mL of distilled water/methanol (1/10) in a container and putted in a magnetic stirring for 24 h. The micelle is separated from marc (the damp solid material) by filtration through Whatman cellulose filter papers (Sigma-Aldrich), subsequently, the filtrate is then evaporated in an oven to obtain the dried extract, which was stored at 4°C until use. The percentage yield was obtained using the dry weight, from the equation bellow:

$$\text{Yield (\%)} = \frac{\textit{The mass of extract after solvent evaporation } (g)}{\textit{The mass of the dried plant powder used for extraction } (g)} \times 100$$

The administered extracts were freshly prepared daily before oral administration to animals, with a concentration of 200 mg from the dried extract per 1kg of animal body weight (BW) in 2 mL of water.

2. Fourier transform infrared resonance analysis (FTIR)

Functional groups in AEA/MEA and AES/MES were detected using (FTIR; Agilent Cary 630, USA spectrometer). The measurements were performed between 25°C and 27°C and recorded from 400 to 4000 cm-1 with a spectral resolution of 4cm-1. This technique was used to determine the functional groups of the bioactive chemicals present in the extracts, which were separated via their peak's wavenumbers. FTIR transmittance spectrum was designed using Origin 2019b 64 Bit version, where it was reprocessed using a baseline correction and smoothing to reduce the noise.

3. Determination of the total phenolic content (TPC)

The polyphenols were determined using Folin-Ciocalteu reagent, according to the technique described by (Agbor et al., 2014). The absorbance is measured at 765 nm, and the total amounts of phenols are expressed in milligram of gallic acid equivalent per gram of extract's dry weight (mg GAE/g DW) based on a gallic acid standard curve (Fig. 14).

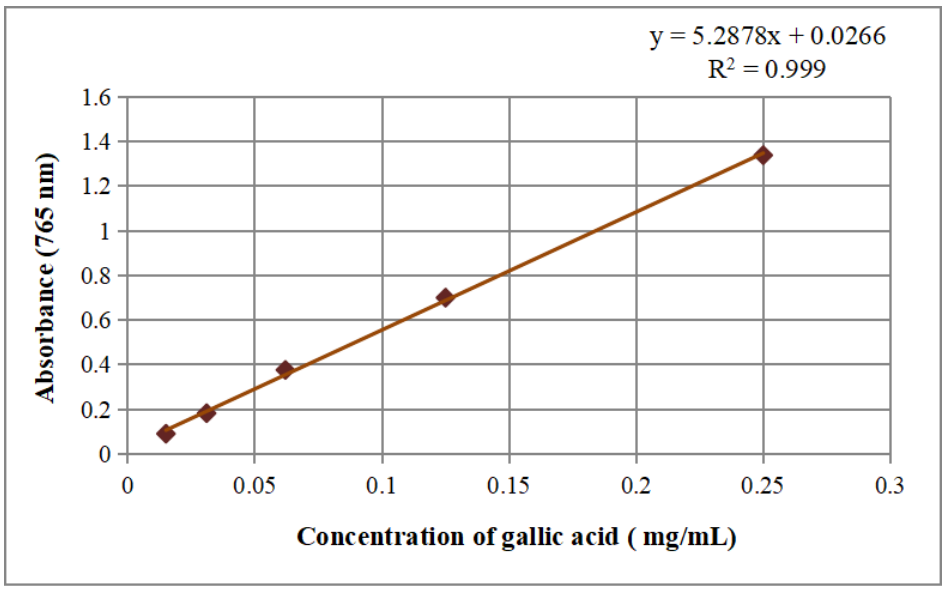


Figure 14. Gallic acid calibration curve (mg/mL).

4. Determination of the total flavonoids content (TFC)

Flavonoids were determined using the aluminium chloride colorimetric method (Pourmorad et al., 2006). The measurement of absorbance was carried out at 415 nm, and the flavonoids content is expressed in milligrams of quercetin equivalent per gram of extract's dry weight (mg QE/g DW) based on a quercetin standard curve (Fig. 15).

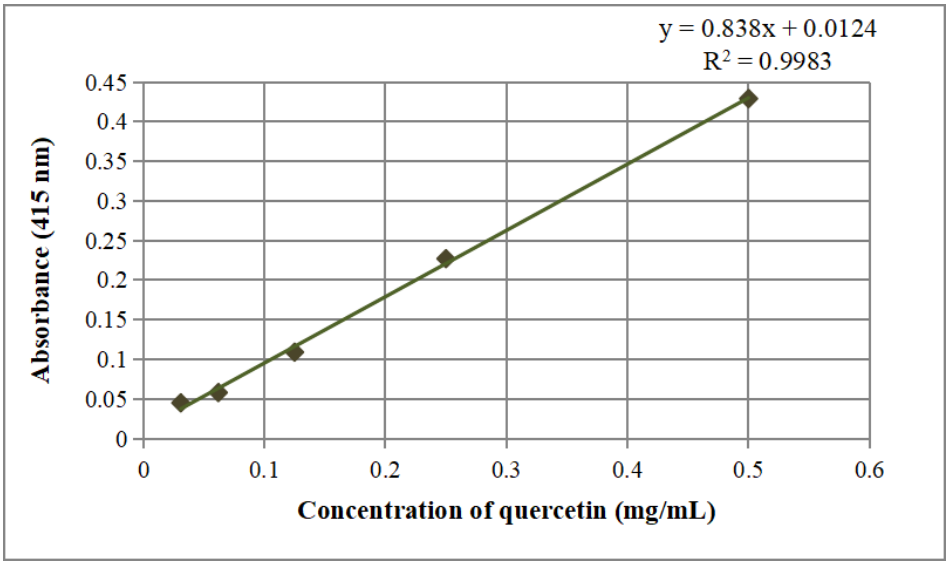


Figure 15. Quercetin calibration curve (mg/mL).

5. *In-vitro* antioxidant and antiradical activities of plants extracts

The antioxidant potential of the plant extracts was evaluated using the following spectrophotometric methods assessed at the research laboratory of biochemistry and environmental toxicology (LBTE):

5.1. The DPPH test

To evaluate the scavenging ability of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, the approach suggested by (Kabir et al., 2016) was adopted. Quercetin has been used as a standard, and absorbance was measured at 517 nm. The result was shown as the amount of extract required to capture 50% of the radicals (IC50 mg/mL).

5.2. The FRAP assay

The FRAP was measured using the technique described by (Yildirim et al., 2001). This method is based on the extract's ability to deliver an electron while converting ferric iron from ferric tripiridyl (Fe^{3+}) to a ferrous form (Fe^{2+}). When antioxidants are present in the extract, this reaction produces a detectible blue color at 700 nm. As a result, a high absorbance indicates that the extract possesses strong reducing potential. The result was presented as (EC50 µg/mL), which is the half-maximum effective concentration necessary to achieve a greater potency.

5.3. The total antioxidant capacity (TAC)

The phosphomolybdenum assay is based on the reduction of molybdenum Mo (VI) present in the form of molybdate ions MoO_4^{2-} to molybdenum Mo (V) MoO^{2+} in the presence of the extract or an antioxidant agent. At an acidic medium, this reduction results in the creation of a greenish complex (phosphate/Mo). The increase of this complex coloration in the presence of an antioxidant is detected at 695 nm (Prieto et al., 1999). Ascorbic acid is used as a standard and the results obtained are expressed in milligram of ascorbic acid equivalent per gram of the extract's dry weight (mg AAE/g DW), (Fig. 16).

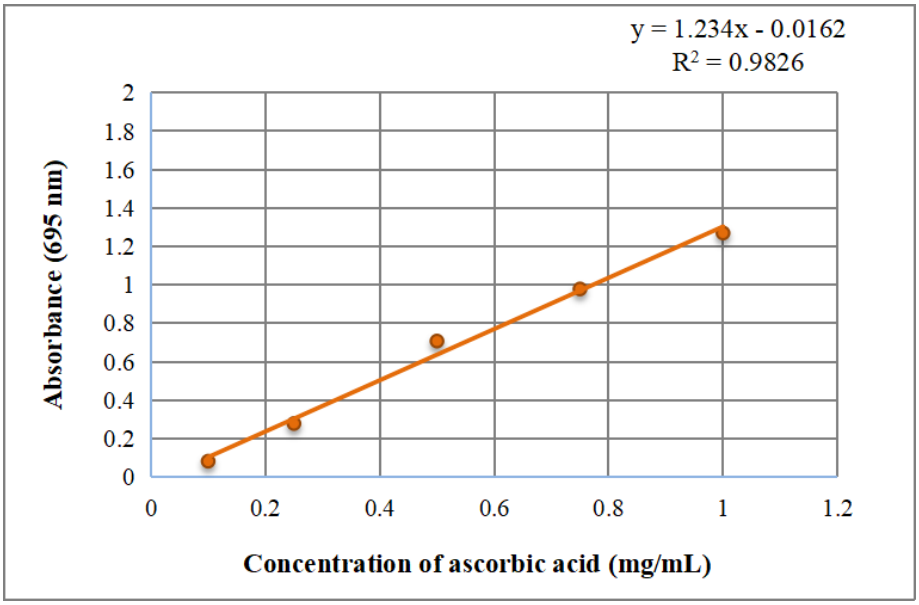


Figure 16. Ascorbic acid calibration curve (mg/mL).

6. The *in-vivo* acute toxicity test of the extracts of plants

Five doses of the aqueous/methanolic extracts of *A. halimus* and *S. mollis* were orally administered to five groups of male albino rats (four rats per group) following the guidelines No. 420 to assess acute toxicity (OECD, 2002). The administered doses were 100, 200, 500, 800, and 1000 (mg/kg BW, orally). After dosing, animals were closely monitored for 24 hours to detect any signs of toxicity, such as changes in locomotor activity, salivation, convulsions, coma, or mortality. Therefore, daily observations were conducted for 7 days to detect any delayed clinical signs of toxicity or mortality.

7. The *in-vivo* antidiabetic and antioxidant activity of plant extracts

7.1. Induction of experimental diabetes

Following a two-week acclimatization period, the animals were injected with streptozotocin intraperitoneally as a single dose of 60 mg/kg after an overnight fasting. For this purpose, distilled water was used to dissolve STZ, the solution was freshly prepared to reach final concentration of 20 mg/mL just before use (Al-Hariri, 2012). After 1h, all the injected rats

received glucose to avoid the hypoglycemic effect of STZ. Normal groups received IP injection of distilled water only. After 3 days, only rats with a fasting glucose level of 2.5 g/l were selected for the group of diabetics.

7.2. Groups design

The study was conducted using 60 adult rats, which were divided into 12 groups, each containing five rats (Fig. 17). The groups were formed based on the rats' body weight, ensuring that the animals in each group had similar weights. The experimental groups were organized as follows:

→ Group 1 (C): Normal control group; healthy rats without treatment.

→ Group 2 (STZ): Diabetic control group; rats received a single IP injection of STZ at a dose of 60 mg/kg to induce diabetes. No treatment was administered.

→ Group 3 (AEA): Non-diabetic rats treated orally with 200 mg/kg of AEA.

→ Group 4 (STZ+AEA): Diabetic rats treated orally with AEA (200 mg/kg).

→ Group 5 (MEA): Non-diabetic rats treated orally with MEA extract at (200 mg/kg).

→ Group 6 (STZ+MEA): Diabetic rats treated orally with MEA (200 mg/kg).

→ Group 7 (AES): Non-diabetic rats treated orally with AES at (200 mg/kg).

→ Group 8 (STZ+AES): Diabetic rats treated orally with AES (200 mg/kg).

→ Group 9 (MES): Non-diabetic rats treated orally with MES (200 mg/kg).

→ Group 10 (STZ+MES): Diabetic rats treated orally with MES (200 mg/kg).

→ Group 11 (COMB): Non-diabetic rats treated orally with a combination of AEA and AES (200 mg/kg each; total 400 mg/kg, 1:1 ratio).

→ Group 12 (STZ+COMB): Diabetic rats treated with the combined extracts (400 mg/kg).

The extract dose was determined based on preliminary acute toxicity tests. The treatments were initiated on the sixth day after the STZ exposure and this was the beginning of the first day of the treatments. Body weight was recorded and blood glucose levels were measured on

days (1st, 3rd, 5th, 10th and 15th) of the experiment using a reflective glucometer (Vital-Check MM1200).

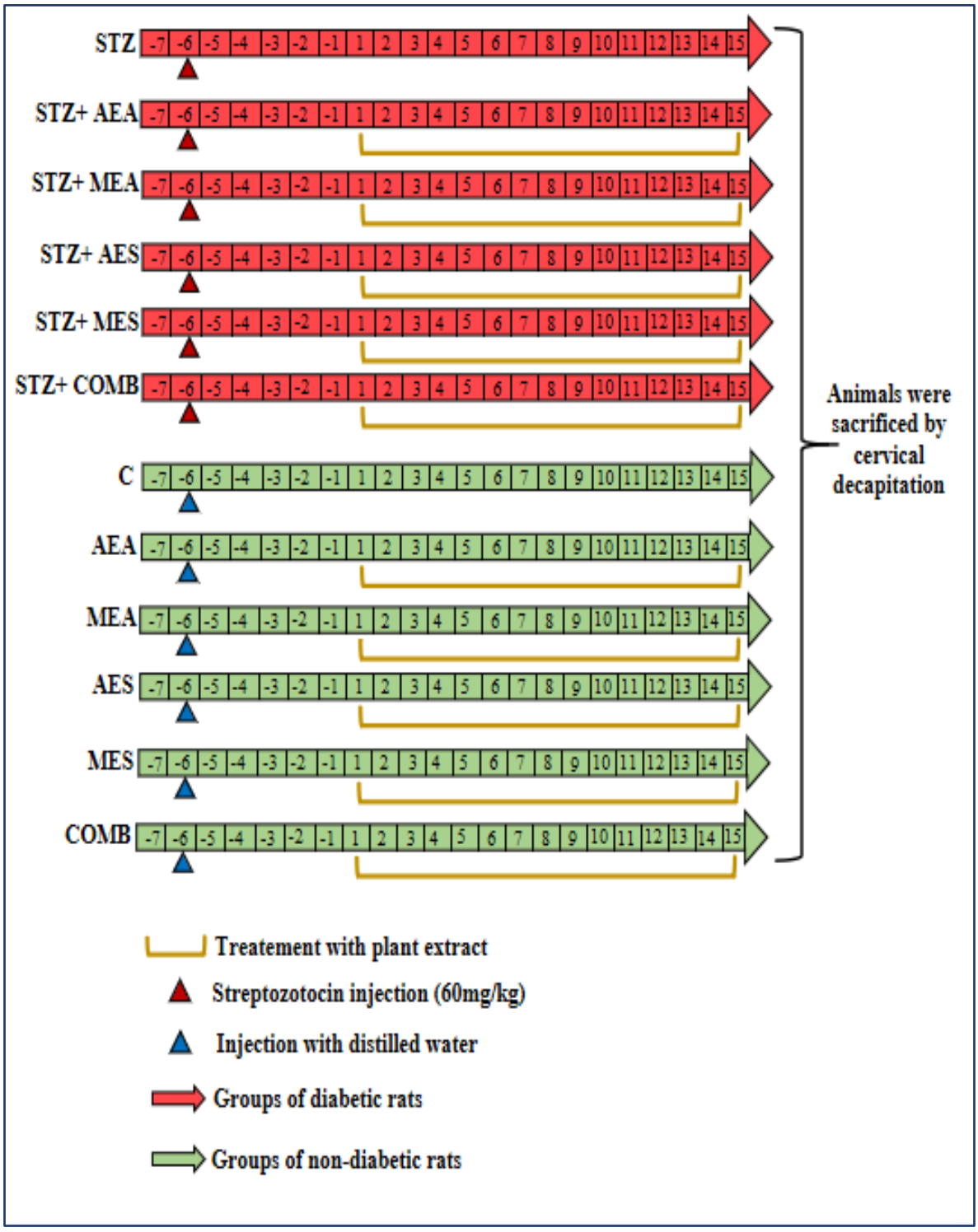


Figure 17. Schematic representation of experimental groups.

7.3. Blood sampling for biochemical and hematological analysis

After two-weeks of the experiment, rats were fasted an overnight before being sacrificed by cervical decapitation to avoid animal stress, and the total blood was separated into tubes containing Ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, and tubes without EDTA. The tubes with EDTA were utilized for hematological analysis (counts of WBC, LY, MO, GR, RBC, HCT, HGB, and PLT, which were measured using an automated blood cell counter (ERMA INC-PCE 210N; Japan) at the research laboratory of biochemistry and environmental toxicology (LBTE). The tubes without anticoagulant were centrifuged at 3000 rpm for 15 minutes at 4°C. The resulting serum was then stored in the Eppendorf tubes at -20 °C for biochemical analysis (the serum levels of creatinine, uric acid, albumin, total proteins, ALAT, ASAT). They were estimated using an automatic biochemical analyzer (VITROS® 5600 Integrated System, Quidel Ortho Corporation; USA) at the biochemical laboratory of anti-cancer CHU Ibn Roched-Annaba.

7.4. Determination of oxidative stress biomarkers

In order to prepare the organs homogenate, the pancreas/liver/kidney samples were homogenized at a rate of 1:2 w/v in a Tris-Buffered Saline (TBS): 50 mm Tris, 150 mm NaCl, pH 7.4, and centrifuged (9000xg/15 minutes/4°C). The obtained supernatant was conserved at -20°C for the assessment of OS markers.

- **The glutathione (GSH)** assay is performed following the method developed by (Weckbecker and Cory, 1988). This assay is based on measuring the optical absorbance at 412 nm of the 2-nitro-5-mercapturic acid resulting from the reduction of 5,5-dithio-bis-2-nitrobenzoic acid (DTNB) by the (-SH) groups of glutathione. The results are expressed as nanomoles of GSH per milligram of protein (nmol of GSH/mg of proteins).
- **The glutathione peroxidase (GSH-Px)** enzymatic activity was assessed using the (Flohé and Günzler, 1984) method, which relies on the reduction of H_2O_2 in the presence of GSH.

This reaction leads to the transformation of GSH into GSSG under the influence of GSH-Px. Optical densities were measured at 412 nm. The results are expressed as nanomoles of reduced GSH per milligram of protein (nmol GSH/mg of proteins).

- **The superoxide dismutase (SOD)** assay using the Nitro Blue Tetrazolium (NBT) method relies on the photo-reduction of the riboflavin/methionine complex, which generates superoxide anions (O^{2-}). The oxidation of NBT by O^{2-} is employed for detecting the presence of SOD. In an aerobic environment, the combination of riboflavin, methionine, and NBT results in a bluish coloration. The presence of SOD hinders the oxidation of NBT (Beyer and Fridovich, 1987). The absorbances of the samples are measured at 560 nm. The results are expressed as international unit per milligram of protein (U/mg protein).
- **The malondialdehyde (MDA)** assay is performed using the method of (Esterbauer et al., 1991). This assay is based on the condensation of MDA in an acidic and hot environment with thiobarbituric acid (TBA), resulting in the formation of a pink pigment. This chromogen can be measured at 530 nm. The results are expressed as (nmol/mg of proteins).
- **The catalase level (CAT)** was determined using the technique of (Aebi, 1984). Absorption was recorded at 240 nm every 15 seconds for 1 minute. The results are expressed as micromoles of H_2O_2 consumed on minute per milligram of protein (µM H_2O_2/min/mg protein).
- **The Bradford test** was used to determine the protein concentrations in samples. It is a spectrophotometric method based on a colorimetric interaction between the bleu of Coomassie (G-250) and the cationic groupments of proteins (He, 2011). Serum bovine albumin (BSA) was utilized as a standard to determine the concentration (Fig. 18).

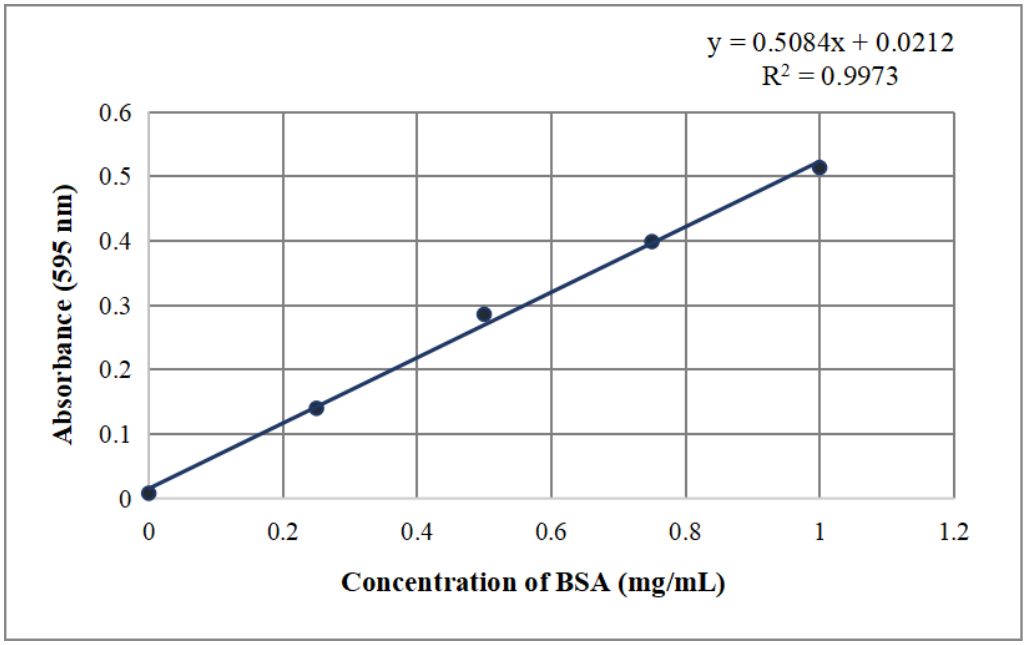


Figure 18. Calibration curve of BSA (mg/mL).

7.5. Histology

Animals were dissected, the pancreas, liver and kidneys were quickly removed, carefully cleaned from fat, and weighted before being preserved in 10% formaldehyde. The histological sections were prepared in the anatomic pathology department of the hospital center "Grine Ammar–El Hadjar, Annaba". The used technique is that described by (Hould, 1984). Samples were rinsed, dehydrated with an increasing concentration of ethanol (70%, 95%, and 100%), and cleared in xylene. After 12 h of paraffin impregnation in an incubator at 60C°, they were then embedded in paraffin blocks. Subsequently, the blocks were sliced using a (Leitz 1512) rotary microtome (Marshall Scientific, Hampton, NH 03842, USA). After dewaxing and rehydration, the sections were stained with H&E. The resulting slides were then observed under a light microscope (Leica Microsystems, DM 1000 LED) and the digital camera (Leica ICC50 HD) was used to take microphotographs for histopathology analysis.

8. Statistical analysis

All data are presented as mean ± standard error of the mean (mean ± SEM). Data normality was assessed using the Shapiro–Wilk test before conducting parametric analyses. Most datasets satisfied the assumption of normality; therefore, differences among groups were analyzed using one-way ANOVA followed by Sidak's multiple comparisons test or two-way ANOVA followed by Tukey's post hoc test, as appropriate. Statistical analyses were performed using GraphPad Prism version 8.0.2 (263) (GraphPad Software Inc., San Diego, CA, USA). A *p*-value < 0.05 was considered statistically significant.

RESULTS & DISCUSSION

Introduction to the chapter

Diabetes mellitus is one of the most prevalent metabolic and endocrine disorders worldwide, characterized by chronic hyperglycemia and its associated complications. In recent years, growing attention has been directed toward the use of traditional medicinal plants as alternative or complementary therapies for diabetes management. In this context, the present study investigated the hypoglycemic and antioxidant effects of *A. halimus* and *S. mollis* in both normal and STZ-induced diabetic rats. This chapter presents and discusses the results obtained from the preliminary phytochemical characterization and the *in-vivo* evaluation of the aqueous and methanolic extracts of both plants, administered individually and in combination. The findings are analyzed in relation to their antidiabetic and antioxidant potentials. Moreover, they are discussed with respect to their nephroprotective and hepatoprotective properties, supported by biochemical, hematological, and histopathological examinations. Comparisons among the different experimental groups provide insight into the therapeutic effect of these extracts, and the results are interpreted in the context of relevant scientific literature.

1. FTIR spectral analysis of plant extracts

Numerous phytochemicals produced by plants are a significant resource that may one day be employed as potent drugs to treat and prevent many of human illnesses (Kaushik et al., 2021). This potential inspired us to investigate their secondary metabolites, aiming to gain deeper insight into their chemical composition. FTIR spectroscopy was employed in this study to identify the major functional groups present in the aqueous and methanolic extracts of *A. halimus* (AEA, MEA) and *S. mollis* (AES, MES). This technique provides comprehensions into the composition of the extracts by detecting characteristic vibrational frequencies of functional groups, which indicate the presence of bioactive phytochemicals. The results from the FTIR analysis spectrum revealed the existence of nine peaks for various functional groups in MEA and MES, and six elongation bands in AEA and AES as shown in the (Figs. 19-22).

In all four extracts, broad and strong absorption bands around 3291–3371 cm^{-1} region were observed (AEA: 3291.7; MEA: 3316.2; AES: 3338.8; MES: 3371.4), which are attributed to the O–H stretching vibration of hydroxyl groups, indicating the presence of alcohols and phenolic compounds (Ogunkanmi et al., 2018). This functional group is known for contributing to antioxidant activity by donating hydrogen atoms to neutralize free radicals (Kostić et al., 2023). Similar findings were reported by Abdelfatah et al. in the FTIR spectrum of *A. halimus* leaves extract collected from Egypt, further supporting the consistency of our result (Abdelfatah et al., 2022). In the methanolic extracts (MEA and MES), medium to weak intensity bands observed in the 2929–2936 cm^{-1} region correspond to the stretching vibrations of aliphatic CH_2 and CH_3 groups, while C–H deformation vibrations between 1360 cm^{-1} and 1415 cm^{-1} support the presence of alkanes (Chandran, 2014; Portaccio et al., 2023). These bands are indicative of lipophilic constituents such as fatty acids, terpenoids, or steroidal saponins (Albuquerque et al., 2003).

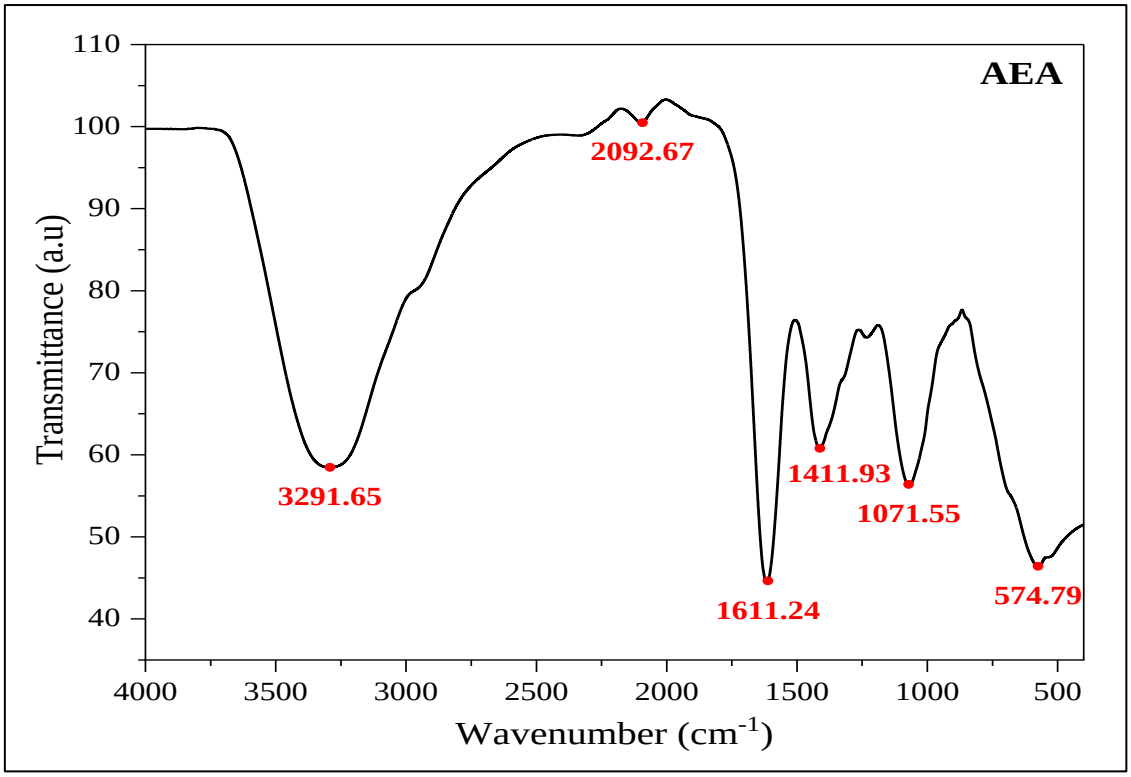


Figure 19. FTIR spectrum of the aqueous extract of *Atriplex halimus.*

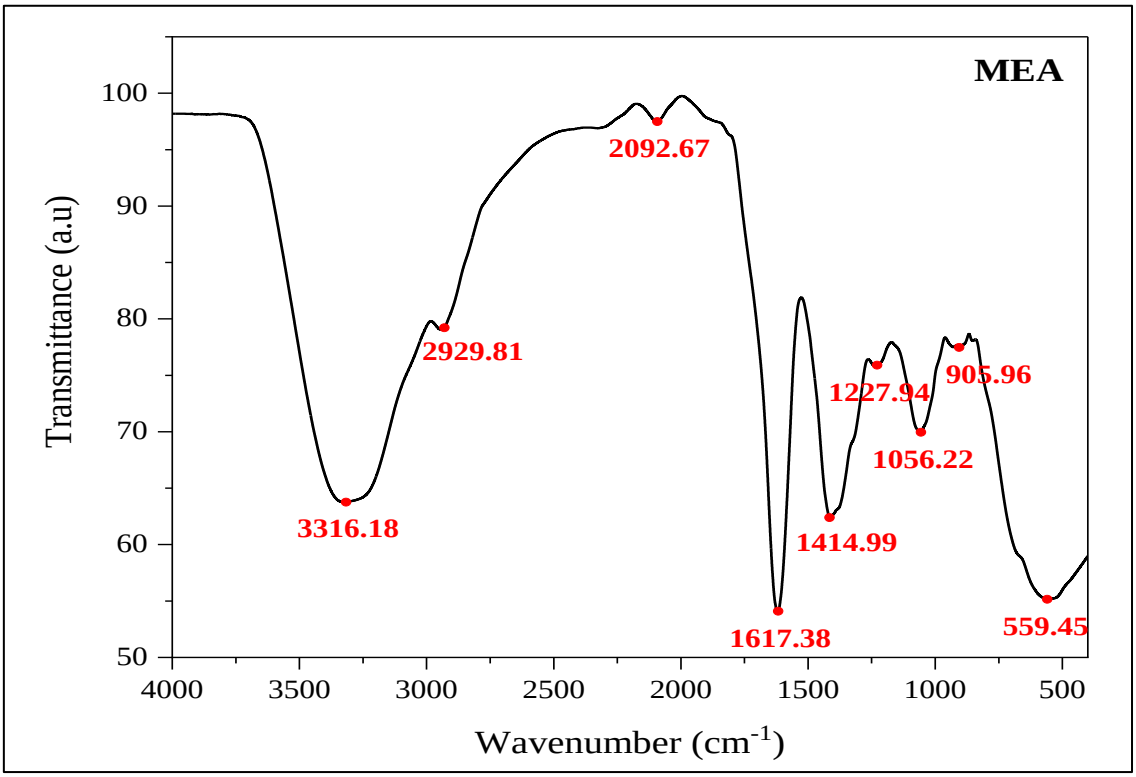


Figure 20. FTIR spectrum of the methanolic extract of *Atriplex halimus.*

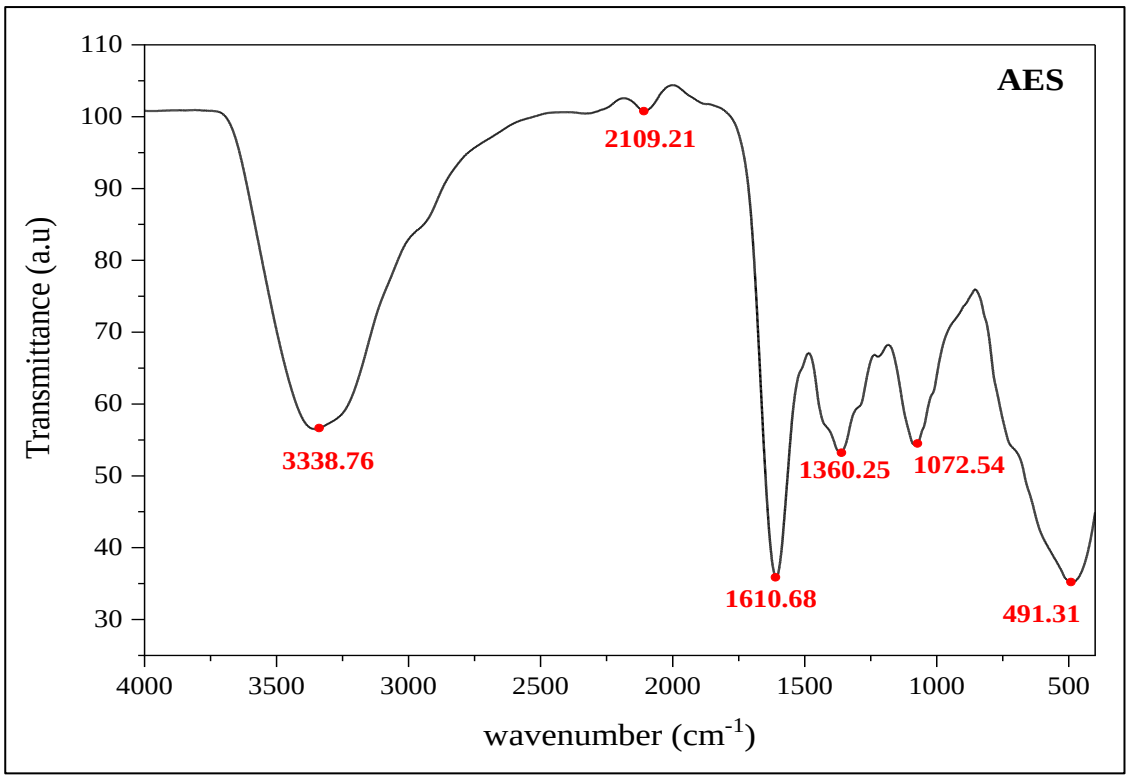


Figure 21. FTIR spectrum of the aqueous extract of *Suaeda mollis.*

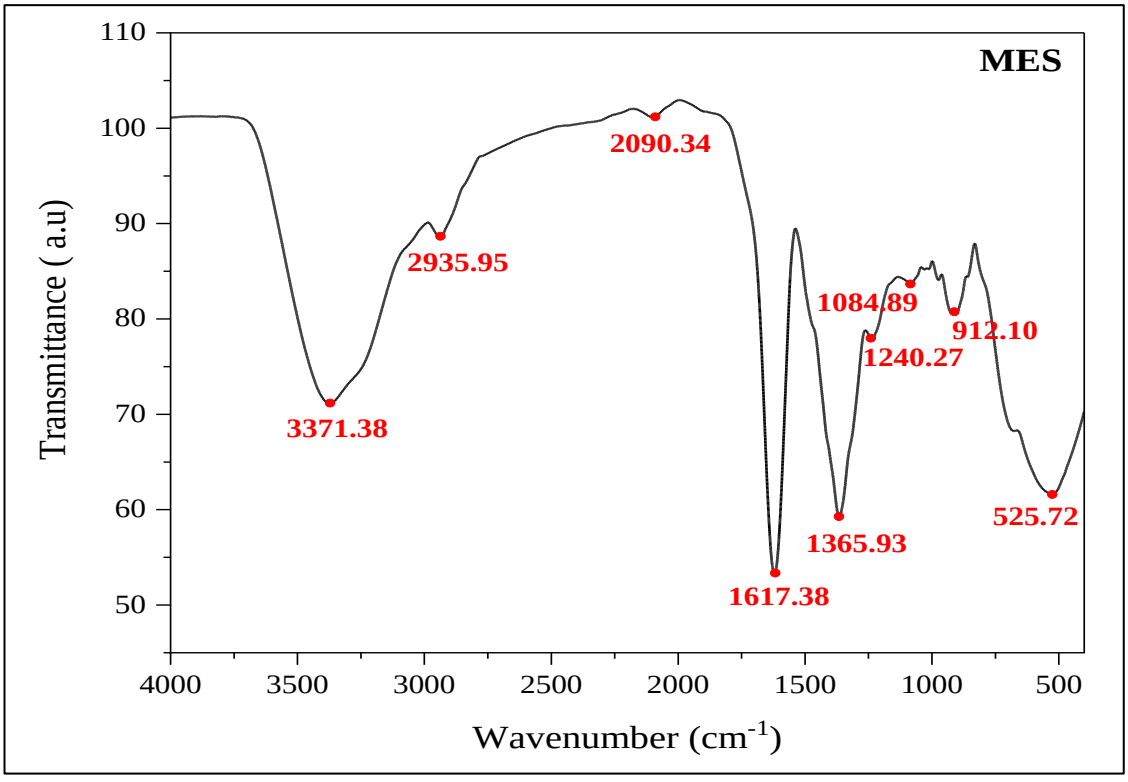


Figure 22. FTIR spectrum of the methanolic extract of *Suaeda mollis.*

In both *A. halimus* and *S. mollis*, the methanolic extracts (a medium-polarity solvent) exhibited more intense aliphatic C–H stretching bands. These bands were absent or weaker in the aqueous extracts, indicating that methanol is more effective in extracting lipophilic constituents such as fatty acids, terpenoids, or other non-polar compounds, findings that are consistent with those reported in other studies (Chandran, 2014; Sachin et al., 2018). Weak absorption bands observed in the 2090–2109 cm^{-1} region from all four extracts (AEA, MEA, AES, and MES) suggest the presence of triple bond-containing compounds, likely corresponding to unsaturated hydrocarbons with C≡C (alkyne) or C≡N (nitrile) functional groups. Although such compounds are less commonly reported in plant extracts, their presence may reflect minor constituents, biosynthetic intermediates, or specialized metabolites with potential ecological or physiological roles (Dixon and Dickinson, 2024). This feature may indicate a unique phytochemical trait of halophytic species such as *A. halimus* or *S. mollis*, which are known to accumulate diverse and uncommon metabolites as part of their adaptive responses to environmental stressors (Isah, 2019). Further structural elucidation techniques such as HPLC or LC-MS would be required to confirm the identity of these compounds. Strong sharp peaks near 1610–1617 cm^{-1} in all samples are characteristic of C=C stretching vibrations in aromatic rings or conjugated C=O stretch. These groups support the presence of flavonoids, phenolic acids, terpenoids, and polyphenolic structures, which are well known for their antioxidant and hypoglycemic properties (Oliveira et al., 2016). These are often associated with plant defense compounds that may enhance the therapeutic efficacy of the extracts. In the region of 1056–1084 cm^{-1}, strong peaks were present in AEA and AES while medium to weak peaks in MEA and MES point to C–O stretching of secondary alcohols, ethers, or carbohydrates, the strong frequence generally refers to high levels of polysaccharides or phenolic glycosides, compounds often involved in antioxidant and antidiabetic actions (Kaushik et al., 2021). These results align with previous reports on halophytes and mangrove,

showing similar wavenumbers characteristic of carbohydrate and glycosides accumulation, which are essential for structural and metabolic adjustments to saline environments, including cell wall polysaccharides, osmotic regulation, and salt stress adaptation (Mehta et al., 2024). MEA and MES exhibited additional peak at 1227 cm^{-1} and 1240 cm^{-1} respectively, which predict the presence of C–OOH stretch of carboxylic acids. These peaks combined with the broad 2500–3300 cm^{-1} bands of O-H previously reported, are highly consistent with C–O stretching of C-OOH groups in phenol-carboxylic acids and free fatty acids (Sachin et al., 2018). Peaks at 905.96 cm^{-1} in MEA and 912.10 cm^{-1} in MES correspond to C–C skeletal vibrations characteristic of alkane structures, which suggest the presence of saturated hydrocarbons, potentially derived from lipid-based metabolites (Pharmawati and Wrasiati, 2020). These substances are frequently reported in methanolic extracts because of their polarity and solubility, where many of them showed inhibition of α-glucosidase activity, indicating that they were effective in lowering blood glucose (Lee et al., 2024). Finally, low wavenumber region (<600 cm−1) usually indicates lattice vibrations or bending modes rather than organic functional groups. It may refer to metal oxides (Fe–O, Mg–O, Ca–O) or salts (e.g., NaCl, $MgSO_4$, $CaCO_3$) (Jiménez-Desmond and Pozo-Antonio, 2025). In all four extracts, prominent peaks observed (AEA: 574.79 cm^{-1}, MEA: 559.45 cm^{-1}, MES: 525.72 cm^{-1}, and AES: 491.31 cm^{-1}) commonly associated with inorganic compounds like metal–oxygen (M–O) bending in minerals or C–Br and C–Cl stretching (Jiménez-Desmond and Pozo-Antonio, 2025). Many studies reported that halophytes are known for accumulating metals and salts like Na^{+}, Mg^{2+}, Fe^{3+}, and Cl^{-} in their tissues (Lutts and Lefèvre, 2015; Nedjimi, 2022; Terebova et al., 2023). These inorganic vibrational bands may overlap with or mask weaker organic signals in this region, but their detection here highlights the mineral-rich nature of halophytes such as *A. halimus* and *S. mollis.* Similar reports align with our findings confirming the mineral richness of those plants (Nedjimi, 2018; Dessena and Mulas, 2021; Shahrokh et al., 2022), which at

low concentrations could enhance the antioxidant potential and anti-inflammatory properties of the plants (Kasote et al., 2015; Chouala et al., 2024).

In summary, FTIR characterization revealed that methanolic extracts (MEA and MES) showed a high number of identifiable peaks compared to the aqueous extracts (AEA and AES), indicating a richer chemical profile. This suggests methanol may extract a broader range of bioactive molecules, including more non-polar compounds such as terpenoids and certain flavonoids, which may enhance their antidiabetic and antioxidant potential. Additionally, both *A. halimus* and *S. mollis* shared major functional groups, including hydroxyls, aromatics, and ethers, supporting their observed biological activity. However, slight variations in peak positions and intensity may reflect differences in the specific polyphenolic or flavonoid constituents between the two species. These findings highlight the chemical complexity of both species and suggest that solvent polarity significantly influences their phytochemical yield and therapeutic potential.

Nevertheless, FTIR should be regarded as a preliminary phytochemical characterization technique. While it provides valuable information on the functional groups present in plant extracts, it does not permit the identification or quantification of individual compounds, and overlapping absorption bands may complicate the interpretation of complex plant matrices. Therefore, future studies should complement FTIR analysis with advanced analytical techniques.

2. Extraction yield, TPC, and TFC of plants extracts

Natural products are generally classified into two main groups: primary and secondary metabolites. The primary metabolites in plants play essential roles in growth and reproduction, as they are directly involved in fundamental cellular functions, while secondary metabolites are organic compounds that contribute primarily to the plant's defense mechanisms and environmental adaptability (Elshafie et al., 2023). Among these secondary metabolites, phenolic compounds are one of the largest and the most commonly distributed classes in the plant kingdom. Flavonoids, a major subgroup of phenolics, are particularly notable for their structural diversity and their wide range of biological activities. Understanding the extraction efficiency and content of these compounds is essential for assessing the therapeutic potential of halophytes (Dai and Mumper, 2010). In this study, the percent of extraction yield, TPC, and TFC were evaluated for both aqueous and methanolic extracts of *A. halimus* and *S. mollis*. These parameters provide insights into the solvent potential and the relative abundance of phenolic and flavonoid compounds, which are known to contribute significantly to antioxidant, antidiabetic, and other pharmacological activities. Results of the extraction yield and quantification of TPC and TFC revealed marked differences between solvents and plant species as illustrated in (Table IV).

Table IV. Extraction yield, total phenols and flavonoid contents in the plants extracts.

Extract	Extraction Yield (%)	TPC (mg GAE/g DW)	TFC (mg QE/g DW)
AEA	26.8	32.67±1.9	47.61±1.09
MEA	23.1	21.26±1.3	45.80±1.3
AES	14.18	19.30±1.3	80.67±1.3
MES	5.0	70.24±2.6	96.90±2.7

Values are presented as mean±SEM (n=3). g DW: Gram of extract's dry weight, GAE: Gallic acid equivalent, QE: Quercetin equivalent.

A. halimus extracts showed the highest extraction yield percentages, where the AEA yield percent was 26.8%, followed by the MEA at 23.1%. In contrast, *S. mollis* presented lower

yields, especially in the MES, which yielded only 5%, while the AES was 14.18%. In terms of TPC, the highest concentration was observed in MES (70.24 mg GAE/g DW), indicating that methanol was particularly effective at extracting phenolic compounds from *S. mollis*. This was followed by AEA (32.67 mg GAE/g DW), MEA (21.26 mg GAE/g DW), and AES (19.30 mg GAE/g DW). Interestingly, while the aqueous extract of *S. mollis* showed low TPC, it exhibited a very high TFC, reaching 80.67 mg QE/g DW, second only to MES, which had the highest TFC of 96.90 mg QE/g DW. In contrast, *A. halimus* extracts (AEA and MEA) had comparatively moderate flavonoid levels, with 47.61 and 45.80 mg QE/g DW, respectively.

These findings underline the influence of both plant species and solvent type on extraction efficiency and phytochemical composition. A previous studies reported a low extraction yield ratio in the aqueous extract of *S. mollis* (3.6%) collected in Al Jouf area and 24.2% of *A. halimus* collected in the region of Mascara (Amin and Musa, 2016; Zennaf et al., 2022). Similar findings were reported by a study that compared *A. halimus* from El Oued and Tlemcen, where the extraction yield varied slightly between regions, with 18.5% and 14.8% respectively (using methanol-acetone 60:40 in the extraction process) (Chaouche et al., 2021). Other study from M'Sila region reported a 20.33% yield ratio of the aqueous extract of *A. halimus* using a different extraction method (Bouaziz et al., 2021). The percent of a plant yield could be influenced by the polarity of the solvent and the used extraction method, as mentioned by El Mannoubi, (2023). However, according to our findings we suggest that the extraction yield can be influenced by several other factors, including the seasonal growth cycle in different ecological regions, and the maturity of the plant parts, as well as proper drying and storage conditions to prevent plant decomposition.

According to Gagman et al., (2020), the effectiveness of plant extracts largely depends on the phyto-constituent composition and type of solvent used for the extraction. This can be supported by our previous results from FTIR analysis, which revealed a greater number of

absorption peaks in the methanolic extracts compared to the aqueous ones, indicating a more diverse chemical composition. Additionally, variations in TPC and TFC between the different extracts of the two plants further explain this observation. While aqueous extraction was more effective for *A. halimus*, methanol proved to be a more suitable solvent for extracting phenolic and flavonoid compounds from *S. mollis*. This data aligns with previous study indicating that the TPC was 24.51 mg GAE/g DW in the 80% acetonic extract of *S. mollis* collected in Tunisia (Oueslati et al., 2012). Whereas a very low concentration of polyphenols (2.28 mg GAE/g DW) and of flavonoids (7.43 mg QE/g DW) were reported in the aqueous extract of the same plant collected in Al Jouf area (Amin and Musa, 2016). In the other hand, the total polyphenol content of *A. halimus* also has been reported to vary by region, with lower values observed in samples from El Oued (10.25 mg GAE/g DW) and Tlemcen (8.20 mg GAE/g DW) compared to our results (Chaouche et al., 2021). Additionally, TPC was 10.12 mg GAE/g DW in the methanolic extract of *A. halimus* from Bechar reported by Benhammou et al., (2009). Similarly, our results showed that the flavonoid content was also much higher than those reported in the Tlemcen samples (3.09 mg QE/g DW) and El Oued (1.82 mg QE/g DW) (Chaouche et al., 2021). These findings indicated that the plant's biotope as well as the mineral composition and physical properties of soil may greatly influence the variations of polyphenols and flavonoids rates through metabolic changes and transcriptional control, which in turn, affects the plant's stress tolerance and nutritional value (Heimler et al., 2017; Messaoudi et al., 2022).

3. Antioxidant activity of extracts (*In-vitro* assays)

A various assays have been used to assess the antioxidant potential of plants, often relying on spectrophotometric methods that either measure free radical scavenging or quantify the products of reactions involving a single electron or hydrogen atom transfer (Christodoulou et al., 2022). The antioxidant activity of the extracts from *A. halimus* and *S. mollis*, obtained using both aqueous and methanolic solvents, was evaluated using three complementary *in-vitro* assays: DPPH radical scavenging assay, the FRAP assay, and TAC assay. These methods were selected to assess different aspects of antioxidant action, including free radical scavenging activity, reducing power, and overall antioxidant potential, respectively. This multi-assay approach provides a comprehensive evaluation of the antioxidant properties of each extract.

3.1. DPPH scavenging activity of extracts

The DPPH assay is a simple, rapid, and highly sensitive method commonly used to assess the antioxidant activity of plant extracts. It measures the ability of antioxidants to donate hydrogen atoms to the stable DPPH radical, causing a color change from purple to yellow, which is detected by a decrease in absorbance at 517 nm. This change is directly proportional to the extract's radical scavenging capacity. Antioxidant strength is typically expressed as IC_{50} (the concentration required to reduce DPPH by 50%), where a lower value indicates higher activity (Moon and Shibamoto, 2009). The scavenging of the free radical DPPH by all extracts is showed in (Table V).

Table V. Antioxidant activities of plants extracts.

Parameters	AEA	MEA	AES	MES
IC_{50} (mg/mL)	1.34±0.001	1.32±0.02	0.39±0.005	0.79±0.002
EC_{50} (µg/mL)	324.59±0.03	980.57±0.05	434.65±0.009	84.71±0.006
TAC (mg AAE/g DW)	20.09±0.4	8.75±0.3	2.57±0.3	6.6±0.2

Values are presented as mean±S.E.M (n=3).

Among all samples, AES demonstrated the strongest DPPH scavenging activity with the lowest IC_{50} value of 0.39 mg/mL, followed by MES at 0.79 mg/mL. In contrast, both *A. halimus* extracts (AEA and MEA) exhibited higher IC_{50} values (1.34 and 1.32 mg/mL, respectively), indicating weaker radical scavenging capacity. These results suggest that *S. mollis* extracts possess superior free radicals scavenging power compared to *A. halimus*. Notably, this effect correlates with the high TFC observed in AES (80.67 mg QE/g DW) and MES (96.90 mg QE/g DW) previously discussed. This supports the notion that flavonoids such as catechin, epicatechin, quercetin, and luteolin, known to exhibit strong antioxidant properties by scavenging free radicals (Zahra et al., 2024), play a crucial role in neutralizing free radicals in this extract.

When comparing our results to previous studies, several *A. halimus* extracts demonstrated superior DPPH radical scavenging activity relative to the aqueous (AEA, IC_{50} = 1.34 mg/mL) and methanolic (MEA, IC_{50} = 1.32 mg/mL) extracts. Notably the (methanol/acetone) extract of same plant collected from Tlemcen exhibited an IC_{50} of 193 µg/mL, while the sample from El Oued showed an IC_{50} of 520 µg/mL (Chaouche et al., 2021), both reflecting higher antioxidant potential. Similarly, the aqueous-ethanolic extracts from Biskra and Mazagran demonstrated IC_{50} values of 845.64 µg/mL and 553.86 µg/mL, respectively (Ould Kaddour et al., 2019). Furthermore, the aqueous sample from M'Sila also indicated a better performance in scavenging DPPH radicals with IC_{50} = 0.95 mg/mL (Bouaziz et al., 2021). However, our extracts showed more effective antioxidant activity than several other reported samples of *A. halimus*. For instance, the methanolic extract from Bechar had a substantially lower activity with an IC_{50} of 31.83 mg/mL, which is markedly less potent than our MEA (1.32 mg/mL), their ethyl acetate (2.04 mg/mL) and butanolic (1.73 mg/mL) extracts showed relatively weak activity compared to the methanolic fraction (Benhammou et al., 2009). On the other hand, it was reported a lower IC_{50} values by Oueslati et al., (2012) and (Amin and Musa, 2016) for the

aqueous extract of *S. mollis* collected from different regions (IC50 = 2.5 µg/mL and 2.44 µg/mL, respectively), indicating a stronger free radicals scavenging potential compared to AES and MES.

3.2. Reducing power of plants extracts

Since antioxidants donate electrons to stabilize and neutralize free radicals, their reducing ability reflects their potential to counteract OS. The FRAP assay measures this by evaluating the reduction of ferric (Fe^{3+}) to ferrous (Fe^{2+}) ions in the presence of antioxidants. Therefore, it serves as a reliable and direct indicator of the total antioxidant power of a sample (Gohari et al., 2011). The ferric reducing ability of the extracts was assessed using the FRAP assay, and the results were expressed as EC_{50} (µg/mL) values (Table V). The methanolic extract of *S. mollis* exhibited the highest reducing capacity, with the lowest EC_{50} value of 84.71 µg/mL. This was followed by AES (434.65 µg/mL), AEA (324.59 µg/mL), and MEA, which showed the weakest reducing activity (980.57 µg/mL). The pronounced reducing power of MES is consistent with its high TPC and TFC values. This extract not only showed a high phenolic content but also a broad spectrum of chemical constituents, as indicated by its richer FTIR profile, which revealed a greater number of functional groups involved in redox reactions. These include phenolic hydroxyl groups, carboxylic acids, and conjugated double bonds, all contributing to its strong electron-donating capacity. This has been supported by the study conducted by Bougandoura and Bendimerad, (2013).

When compared to previous studies, our findings in AEA and MEA reveal superior antioxidant performance in ferric-reducing power. For instance, *A. halimus* from Tlemcen and El Oued showed EC_{50} values above 5 mg/mL, indicating lower activity (Chaouche et al., 2021). Similarly, EC_{50} values of 4.55 mg/mL for methanolic, 1.76 mg/mL for butanolic, and 1.51 mg/mL for ethyl acetate extracts of *A. halimus* collected from Béchar also reflect reduced antioxidant potential (Benhammou et al., 2009). However, our reported EC_{50} value for the ferric

reducing ability of AES was considerably higher than (EC_{50} = 130 µg/mL) reported in prior research using an 80% acetonic extract (Oueslati et al., 2012), in contrast MES showed a lower value resulting to greater reducing power. The reduced FRAP activity of AES could be attributed to its inability to solubilize some potent antioxidant compounds, which are more effectively extracted by organic solvents like methanol or acetone. This aligns with findings from other studies on medicinal plants, which demonstrated that the antioxidant activity of plant extracts is heavily influenced by the polarity of the solvent and its capacity to extract various antioxidant substances ((Lahmar et al., 2023; Tourabi et al., 2023).

3.3. Total antioxidant capacity

The TAC provides a global assessment of the antioxidant potential of plant extracts by evaluating their ability to reduce Mo (VI) to Mo (V). This assay is valuable for estimating the cumulative effect of both hydrophilic and lipophilic antioxidants present in the samples. The results presented in (Table V) revealed that AEA exhibited the highest TAC value (20.09 mg AAE/g DW), followed by MEA (8.75 mg AAE/g DW), MES (6.6 mg AAE/g DW), and AES (2.57 mg AAE/g DW).

In comparison to previously published values, the TAC of AEA and MEA was markedly higher than that reported by Chaouche et al., (2021) for (methanol/acetone) samples from Tlemcen (7.69 GAE/g DW) and El Oued (5.77 GAE/g DW). In addition, our results outperformed the TAC concentration of other extracts as the ethyl acetate (0.241 mg GAE/g DW), butanolic (0.112 mg GAE/g DW), and dichloromethane (0.110 mg GAE/g DW) fractions reported by Tahar et al., (2015). On the other hand, the TAC assay revealed a lower concentration in the AES and MES than the value of (23.29 mg AAE/g DW) observed in the acetonic extract from the aerial parts of Tunisian *S. mollis* (Oueslati et al., 2012). The noticed differences in the antioxidant activity across studies are likely due to variations in plant origin, environmental and seasonal conditions, and the specific parts used. Solvent polarity and

extraction methods significantly affect the efficiency of phenolic compound extraction. These factors directly influence the antioxidant potential and phytochemical composition of the plants. (Nazir et al., 2018; Hymery et al., 2021; Ayaz et al., 2022; Ferreira et al., 2024). Overall, our results reinforce the notable antioxidant potential of halophytic species

4. Acute toxicity test

The observations of acute toxicity test showed no behavioral changes, toxic symptoms, or fatalities were observed at any of the tested doses. The absence of acute toxicity up to 1000 mg/kg confirmed that the extracts of *A. halimus* and *S. mollis* are safe and well tolerated at the doses used in this study. These results supported the selection of 200 mg/kg (and 400 mg/kg for the combined treatment) as experimental doses for subsequent *in-vivo* assays in rats. This safety profile ensures that the antidiabetic, antioxidant, hepatoprotective, and nephroprotective effects observed later are attributed to genuine pharmacological activity rather than toxic stress. Nevertheless, since acute tests do not account for long-term administration, further sub-chronic and chronic evaluations would be required to fully establish their safety for prolonged therapeutic use.

5. Antidiabetic and antioxidant activity (*in-vivo* assays)

To assess the antidiabetic and antioxidant effects of *A. halimus* and *S. mollis*, both individually and in combination, twelve experimental groups were established. These included healthy control rats, diabetic control rats, and non-diabetic and diabetic groups treated orally and daily for 15 days with aqueous or methanolic extracts of either plant at 200 mg/kg body weight. Additionally, the effect of a combined aqueous extracts treatment (200 mg/kg of each plant extract; total 400 mg/kg) was evaluated in both normal and diabetic rats. This design allowed us to not only investigate the therapeutic potential of each extract but also to evaluate possible synergistic effects when both plants were administered together.

5.1. Effect of different extracts on blood glucose level

In the current study, DM was experimentally induced in adult Wistar rats using a single IP injection of STZ (60 mg/kg). Streptozotocin was freshly dissolved in distilled water at a concentration of 20 mg/mL, following the protocol of (Al-Hariri, 2012), in order to avoid the potential toxicity of citrate buffer (Ghasemi and Jeddi, 2023). The STZ injection successfully induced classic signs of diabetes, including polyuria, polydipsia, polyphagia, and a significant elevation in fasting blood glucose levels approximately 48h after injection over the experimental period. This hyperglycemia resulted from the selective cytotoxicity of STZ to pancreatic β-cells in the Langerhans's islets, leading to impaired insulin secretion and loss of glucose homeostasis (Noorafshan et al., 2004; Al-Hariri, 2012). Under normal conditions, elevated blood glucose levels stimulate pancreatic β-cells to release insulin, a key hormone in maintaining glucose homeostasis (Guo et al., 2023).

The effect of the different aqueous and methanolic plant extracts on blood glucose levels in STZ-induced diabetic rats is illustrated in (Fig. 23). Our findings showed that STZ administration leads to a notable increase on blood glucose level in (STZ) group compared to the (C) group, which remains consistently high (~5–6 g/L) throughout the experimental period, confirming the successful induction of hyperglycemia to rats. The treated groups: (STZ + MES), (STZ +AES), and (STZ +COMB) showed initial spike at day 1 (after STZ injection), followed by a progressive and notable decline in treatment period reaching near-normal levels by 5^{th} day. The combined treatment (STZ+COMB) appears to be the most effective in restoring normoglycemia. However, the methanolic and aqueous extracts of *A. halimus* (STZ+AEA) and (STZ+MEA) groups were relatively less effective, suggesting a limited capacity to normalize glycemia in diabetic rats.

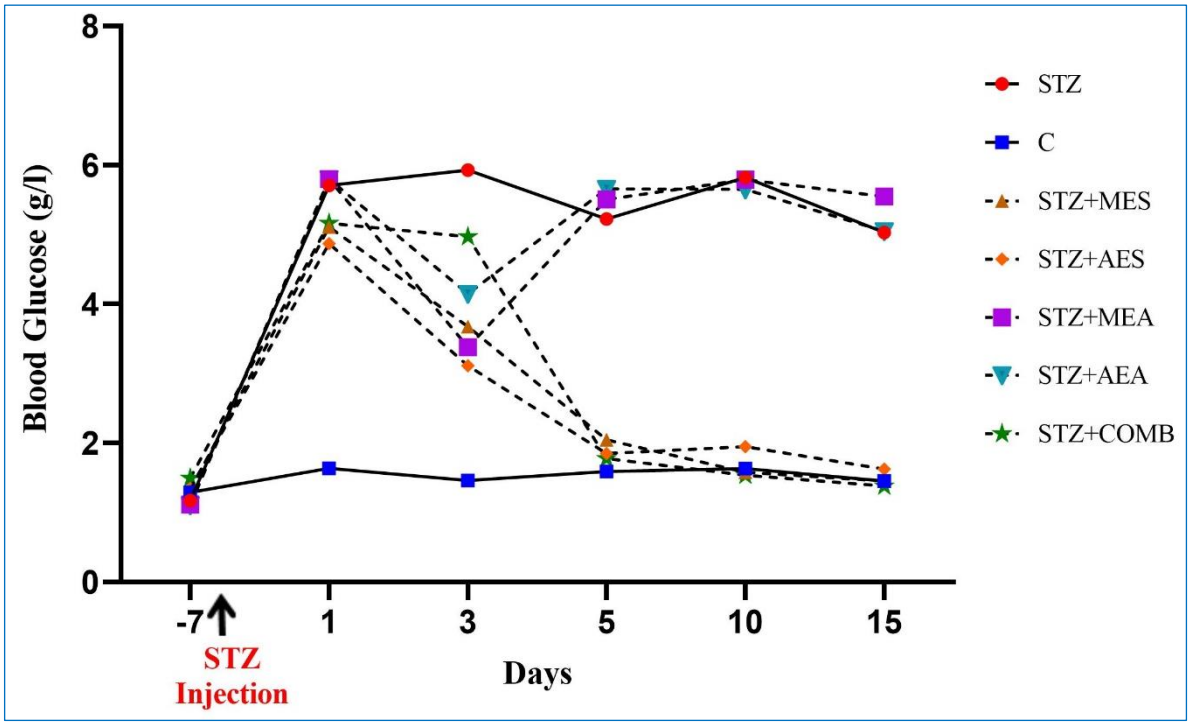


Figure 23. Variations of blood glucose levels during two-weeks of treatment in STZ-induced diabetic rats.

(C): control, (STZ): Diabetic rats, (STZ + MES): Diabetics treated with methanolic extract of *S. mollis*, (STZ + AES): Diabetics treated with aqueous extract of *S. mollis*, (STZ + MEA): Diabetics treated with methanolic extract of *A. halimus*, (STZ + AEA): Diabetics treated with aqueous extract of *A. halimus*, and (STZ + COMB): Diabetics treated with combination of the aqueous extracts of the two plants.

Table VI. Effect of the treatment with plants extracts on blood glucose levels (g/L) in diabetic and normal rats over 15 days.

		Period of treatment with the extracts				
Groups	**Day -7 (g/L)**	**Day 1 (g/L)**	**Day 3 (g/L)**	**Day 5 (g/L)**	**Day 10 (g/L)**	**Day 15 (g/L)**
C	1.29 ± 0.44	1.63 ± 0.33	1.46 ± 0.24	1.59 ± 0.38	1.63 ± 0.38	1.45 ± 0.44
STZ	1.17 ± 0.30	5.70 ± 0.41$^{(c)}$	5.92 ± 0.41$^{(c)}$	5.22 ± 0.81$^{(c)}$	5.82 ± 0.51$^{(c)}$	5.03± 0.85$^{(c)}$
MES	1.19 ± 0.34	1.11 ± 0.25$^{(f)}$	1.65 ± 0.19$^{(f)}$	1.29 ± 0.32$^{(f)}$	1.54 ± 0.31$^{(f)}$	1.18 ± 0.34$^{(f)}$
STZ+MES	1.31 ± 0.32	5.11 ± 0.92$^{(c)}$	3.68 ± 0.59	2.04 ± 0.92$^{(e)}$	1.58 ± 0.60$^{(f)}$	1.45 ± 0.64$^{(f)}$
AES	1.17 ± 0.38	1.25 ± 0.36$^{(f)}$	1.07 ± 0.15$^{(f)}$	1.03 ± 0.12$^{(f)}$	1.05 ± 0.15$^{(f)}$	1.05 ± 0.18$^{(f)}$
STZ+AES	1.35 ± 0.43	4.87 ± 0.67$^{(b)}$	3.11 ± 0.74$^{(d)}$	1.85 ± 0.93$^{(e)}$	1.95 ± 0.97$^{(f)}$	1.62 ± 0.67$^{(e)}$
MEA	1.11 ± 0.25	1.17 ± 0.38$^{(f)}$	1.17 ± 0.34$^{(f)}$	1.18 ± 0.34$^{(f)}$	1.18 ± 0.34$^{(f)}$	1.34 ± 0.37$^{(f)}$
STZ+MEA	1.11 ± 0.38	5.8 ± 0.67$^{(c)}$	3.38 ± 0.98	5.50 ± 0.70$^{(c)}$	5.79 ± 0.61$^{(c)}$	5.55 ± 0.66$^{(c)}$
AEA	1.10 ± 0.48	1.57 ± 0.30$^{(f)}$	1.44 ± 0.39$^{(f)}$	1.65 ± 0.58$^{(f)}$	1.59 ± 0.33$^{(f)}$	1.36 ± 0.37$^{(f)}$
STZ+AEA	1.13 ± 0.37	5.8 ± 0.67$^{(c)}$	4.15 ± 1.12$^{(a)}$	5.66 ± 0.63$^{(c)}$	5.65 ± 0.52$^{(c)}$	5.05 ± 0.76$^{(c)}$
COMB	1.09 ± 0.35	1.19 ± 0.34$^{(f)}$	1.54 ± 0.36$^{(f)}$	1.19 ± 0.34$^{(f)}$	1.47 ± 0.37$^{(f)}$	1.12 ± 0.26$^{(f)}$
STZ+COMB	1.5 ± 0.19	5.16 ± 0.92$^{(c)}$	4.97 ± 1.38$^{(c)}$	1.77 ± 0.80$^{(e)}$	1.53 ± 0.42$^{(f)}$	1.38 ± 0.53$^{(f)}$

Data are shown as mean±SEM (n=5). Letters indicate significant differences as follows: (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ vs. (C). (d) $p<0.05$, (e) $p<0.01$, (f) $p<0.001$ vs. (STZ).

The blood glucose levels of all groups and their statistical significance are presented in (Table VI). The STZ-induced diabetic group showed a highly significant increase ($p<0.001$ vs. C) in blood sugar levels, confirming the successful induction of hyperglycemia. Similar findings were found in many previous studies (Al-Jaghthmi et al., 2020; Zeid and Al Jaghthmi, 2020; Rehman et al., 2023). Started from the 5th day of extracts administration, treated diabetic rats in (STZ+MES), (STZ+ AES), and (STZ+COMB), showed a significant decrease in glucose levels ($p<0.01$ vs. STZ). On Day 15, our results recorded a nearly normalized glucose levels ($p<0.001$ vs. STZ) in (STZ+MES) and (STZ+COMB) groups and ($p<0.01$ vs. STZ) in (STZ+AES) group. These outcomes demonstrated that *S. mollis* and COMB has a hypoglycemic effect in diabetic rats. Plants are natural antioxidants and potent sources of phytotherapy, mainly because they contain antidiabetic compounds (flavonoids, phenols, tannins, and alkaloids), which improve pancreatic function by either increasing insulin secretion or decreasing glucose absorption in the gut (Kooti et al., 2016). Our previous phytochemical findings from AES and MES, have established that *S. mollis* leaves possessed a range of functional groups, with a significant presence of polyphenols, flavonoids and a possible amount of minerals. These bioactive compounds and minerals, especially the chromium and magnesium salts, from tissues of this plant regulate blood sugar by stimulating insulin secretion, increasing glucose uptake in peripheral tissues such as adipose and muscles, or inhibiting hepatic gluconeogenesis (Jeeva and Sheebha, 2014; Alfadhly et al., 2022). Moreover, combining different plant extracts can enhance hypoglycemic effects compared to using them individually. Studies have shown that certain combinations, like those of *Rhizophora mucronata* and *Avicennia marina*, or *Andrographis paniculata* and *Caesalpinia sappan*, can lead to stronger blood glucose-lowering effects. The synergistic effect often arises from different mechanisms of action within the combined extracts, potentially improving insulin sensitivity allowing the body to utilize glucose more effectively, or inhibiting glucose

absorption (Slavova et al., 2024; Wediasari et al., 2020; Zeid and Al Jaghthmi, 2020). In contrast, the (STZ+MEA) and (STZ+AEA) groups did not show any significant reduction in blood glucose, they showed a statistically high level (p<0.001 vs. C). Contrary, other studies reported that *A. halimus* extracts have an anti-hyperglycemic potential, but it was only observed after prolonged administration (four/seven weeks) (Bounouar et al., 2022; Chikhi et al., 2014). These results indicated that *A. halimus* has a time-dependent antidiabetic effect. On the other hand, the results observed in normal rats treated with MES, AES, AEA, MEA, and COMB (without STZ) remained within the normoglycemic levels highly significant (p<0.001 vs. STZ), reflecting the safety and non-hypoglycemic risk of the extracts in normal conditions.

5.2. Body weight changes

This study showed significant variations in BW across the experimental groups over the treatment period (Fig. 24, Table VII).

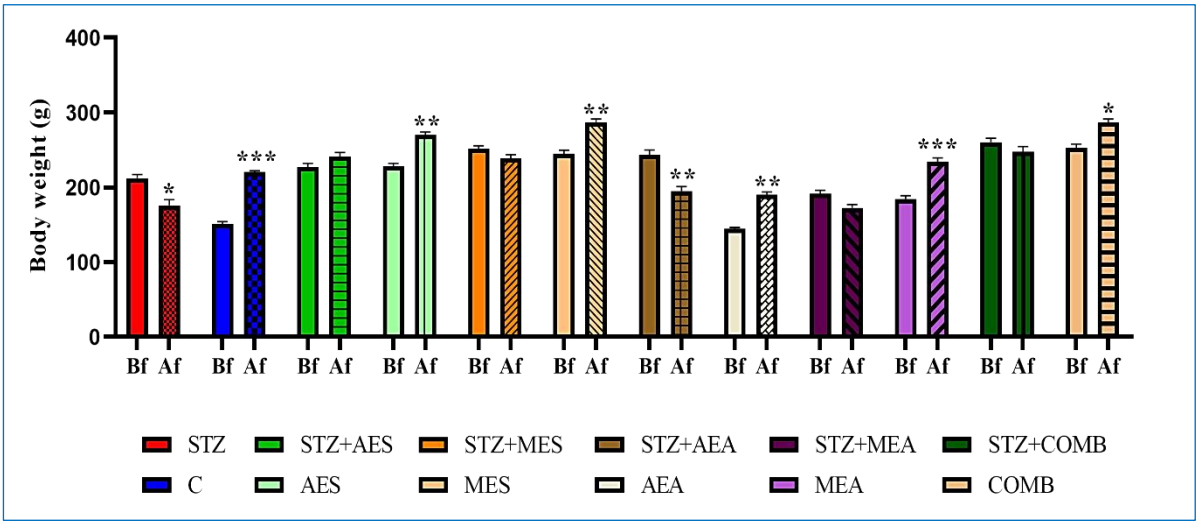


Figure 24. Body weight changes of rats before and after treatment with extracts. Significant differences over two-weeks (Before vs. After) are expressed as following: *p<0.05, **p<0.01, ***p<0.001.

Table VII. The mean of BW (g) before and after treatment, and net BW change (Δ) in the experimental groups.

Group	Initial Body weight (g)	Final Body weight (g)	Δ Body Weight (g)	Significance
STZ	212.2 ± 5.05	176.0 ± 7.45	-36.2	Weight loss (c)
C	151.2 ± 2.84	220.6 ± 1.61	+69.4	Weight gain
STZ + AEA	243.4 ± 6.5	195.2 ± 5.74	-48.2	(c), (f)
AEA	144.2 ± 2.2	190.0 ± 3.72	+45.8	(c), (f)
STZ + MEA	191.4 ± 4.75	172.6 ± 4.32	-18.8	(c), (f)
MEA	184.4 ± 4.74	234.4 ± 4.72	+50.0	(c), (f)
STZ + AES	227.0 ± 5	241.0 ± 5.43	+14.0	(c), (f)
AES	228.4 ± 3.5	269.8 ± 4	+41.4	(c), (f)
STZ + MES	251.8 ± 3.7	238.75 ± 5	-13.05	(c), (f)
MES	244.8 ± 5	286.6 ± 5	+41.8	(c), (f)
STZ + COMB	260.4 ± 5.33	247.5 ± 7.05	-12.9	(c), (f)
COMB	252.6 ± 5.12	286.6 ± 4.61	+34.0	(c), (f)

Δ Body Weight (g) = Final BW- Initial BW. All values are expressed as mean ± SEM (n = 5). The significant difference was expressed as follows: (c) $p<0.001$ vs. (C) group, (f) $p<0.001$ vs. (STZ) group.

Rats in (STZ) group exhibited a marked reduction ($p<0.001$ vs C) in body weight (−36.2 g), confirming the cachexic effect of STZ-induced diabetes. This observation is consistent with previous findings where STZ administration led to significant weight loss due to uncontrolled glucose levels. Additionally, muscle atrophy attributed to the catabolism of amino acids in muscle tissue, degradation of fat from adipose tissues, and degeneration of structural proteins, are known to be a major contributor to body weight loss (Eluehike and Onoagbe, 2018; Bencheikh et al., 2020; Tebboub and Kechrid, 2021). Furthermore, the excessive food intake has not led to weight gain as a result of insulin deficiency, because the destruction of pancreatic cells has considerably reduced the insulin levels (Akhtar et al., 2023). This has rendered the body cells unable to use glucose as an energy source, prompting compensatory utilization of muscle proteins and fats from adipose tissues for energy production (Riyahi et al., 2016; Singh

et al., 2022). In contrast, the (C) group showed a substantial weight gain (+69.4 g), reflecting normal growth and metabolism in rats.

Data from the non-diabetic rats treated with plants extracts showed that all groups demonstrated statistically significant weight gains ($p<0.001$) compared to (C) and (STZ) groups. Notably, less than the value in (C) group, MEA showed important weight gain (+50.0 g), closely followed by AEA (+45.8 g), MES with +41.8 g and AES with +41.4 g. The combination group (COMB) also promoted a weight gain (+34.0 g). However, in diabetic rats, treatment with the extracts attenuated diabetes weight loss to varying degrees: (STZ+MEA) and (STZ+MES) groups exhibited moderate weight loss (−18.8 g and −13.05 g, respectively), reflecting partial protection. The group (STZ+AES) was the only diabetic group that gained weight (+14.0 g), suggesting a notable therapeutic effect. The (STZ+COMB) group showed slight protection (−12.9 g), possibly indicating additive effects of both extracts in mitigating weight loss. Interestingly, the (STZ+AEA) group continued to show significant weight loss (−48.2 g), even more pronounced than the (STZ) group alone. This may be related to the limited hypoglycemic efficacy of the AEA extract observed in the glycemic control study, suggesting an inability to reverse diabetic cachexia, or possibly indicating a diuretic effect. These results may be attributed to the potential of *S. mollis* aqueous extract to reduce insulin resistance and enhance anti-inflammatory effects. Similar results found that some plants (*Holarrhena pubescens, Spondias mombin and Cichorium intybus*) can increase body weight in diabetic rats via there antihyperglycemic effect by reducing the blood sugar level and improving insulin sensitivity in cells (Saravanamuttu and Sudarsanam, 2012; Eluehike and Onoagbe, 2018; Akhtar et al., 2023). Body weight gain indicates that the anabolic effects have taken precedence over the catabolic ones (Al-Attar and Alsalmi, 2019). Contrary, some antidiabetic plants (such as *Bauhinia holophylla*) have decreased the body weight of diabetic animals, possibly due to their toxic effect (Pinheiro et al., 2017).

5.3. Organs relative weight changes

STZ-induced diabetes led to significant alterations in the relative weights of the pancreas (PRW), liver (LRW) and kidneys (KRW) compared to the normal (C) group, as illustrated in (Figs. 25-27). These changes reflect pathological hypertrophy or atrophy commonly associated with diabetes-induced organ dysfunction.

5.3.1. Pancreas

Diabetes caused a marked reduction in PRW ($p<0.05$ vs. C) (Fig. 25), indicative of β-cells destruction and pancreatic atrophy in accordance with many previous studies (Eluehike and Onoagbe, 2018; Shawky et al., 2020; Alsharif et al., 2023). They confirmed that β-cells in the pancreatic islets of Langerhans die after STZ-injection, confirming that the decrease in pancreatic relative weight is related to the degradation and atrophy of the islets, as found later in our histological study. Treatments with AES, AEA, MEA, and COMB in non-diabetic groups showed non-significant change in PRW (ns, $p>0.05$ vs. C), indicating the extract had no adverse effect on healthy tissue. Although, the (MES) group showed a slight increase in pancreatic mass compared to (C). When compared to (STZ) group, (STZ+AES) and (STZ+MEA) had no change in PRW. Similarly, a study found that the PRW remained unchanged because the pancreatic weight appeared to decrease proportionally with the overall reduction in body weight, rather than being directly influenced by the diabetic condition (Zafar and Naqvi, 2010). Whereas, our results revealed that (STZ+MES), (STZ+AEA), and (STZ+ COMB) rat groups had a notable increase in PRW compared to (STZ) group, demonstrating a possible hypertrophy in their pancreatic tissues.

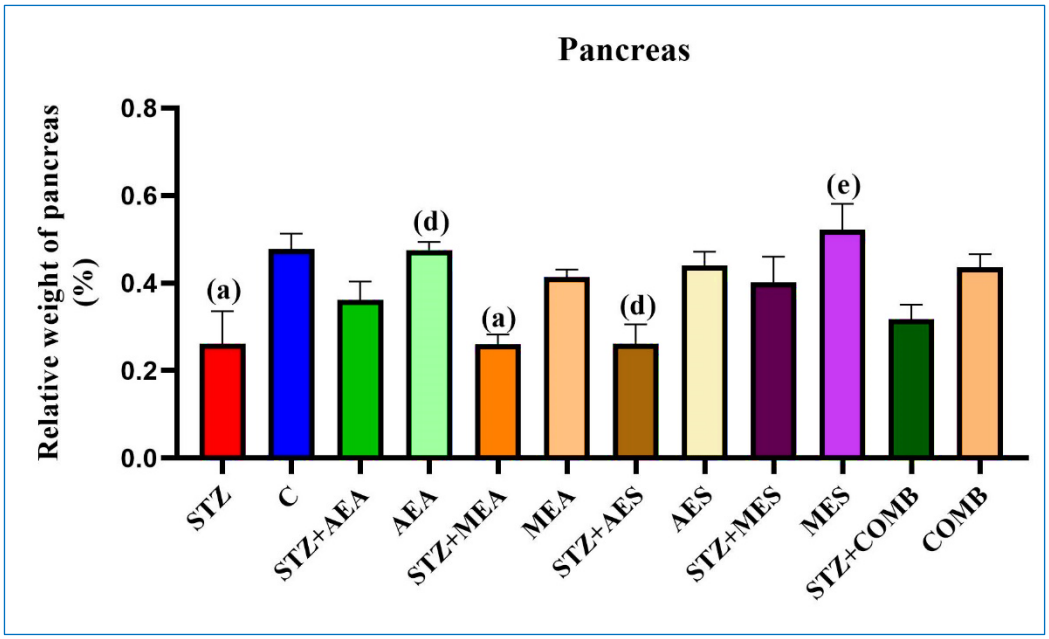


Figure 25. Effect of *A. halimus* and *S. mollis* extracts on PRW of normal and diabetic rats. Significance expressed as: (a) $p<0.05$ vs. (C); (d) $p<0.05$, (e) $p<0.01$ vs. (STZ).

5.3.2. Liver

As illustrated in (Fig. 26) STZ-induced diabetic rats exhibited an increase in LRW (ns, $p>0.05$ vs C) despite the fact that the mean weight of all the animals in (STZ) group has reduced. This result reflects hepatic hypertrophy which could be attributed to increased triglyceride accumulation leading to enlarged liver. Such lipid buildup is likely a result of increased fatty acid influx into the liver due to hypoinsulinemia, along with a reduced capacity for lipoprotein secretion caused by impaired apolipoprotein B synthesis (Zafar and Naqvi, 2010). A Histopathological study using electron microscopy revealed that the hypertrophy of hepatocytes due to an increase in number of intracytoplasmic acidophilic granules was common to STZ-induced diabetic rodents (Kume et al., 1994). The present findings of our study are in agreement with those reported that hepatic cells accumulate triglycerides as a result of impaired lipoprotein secretion, leading to hepatic steatosis and compensatory hyperplasia (Ohno et al., 1999; Zafar et al., 2009). On the other hand, treatment with the aqueous and methanolic extracts of both plants in diabetic groups resulted to a noticeable reduction in liver

weight, with significant differences observed particularly in (STZ+AES) and (STZ+ MES) groups (p<0.001 vs. STZ), and in (STZ+COMB) group (p<0.01 vs. STZ). These findings suggest a hepatoprotective effect, potentially attributed to the antioxidant and anti-inflammatory properties of the phytoconstituents present in these extracts. Similar study reported that the increase in liver weight in diabetic rats treated with *Moringa oleifera* may be due to enlargement of tubular cells lining and fatty infiltration of the liver (Omodanisi et al., 2017). Researchers declared that Curcumin can protect rat liver from damage caused by STZ-induced diabetes by counteracting OS and inhibiting stress response pathways, specifically p53 and MAPKs (Ghosh et al., 2015). Moreover, non-diabetic rats treated with the extracts exhibited a significant decrease on LRW as following: (p<0.001 vs STZ) in (AES), (MEA), and (COMB) groups, (p<0.01 vs STZ) in (AEA) group, and (p<0.05 vs STZ) in (MES) group. These findings suggest that the plant extracts did not induce hepatic enlargement cytotoxicity or stress in healthy animals. No significance was noticed compared to (C) group.

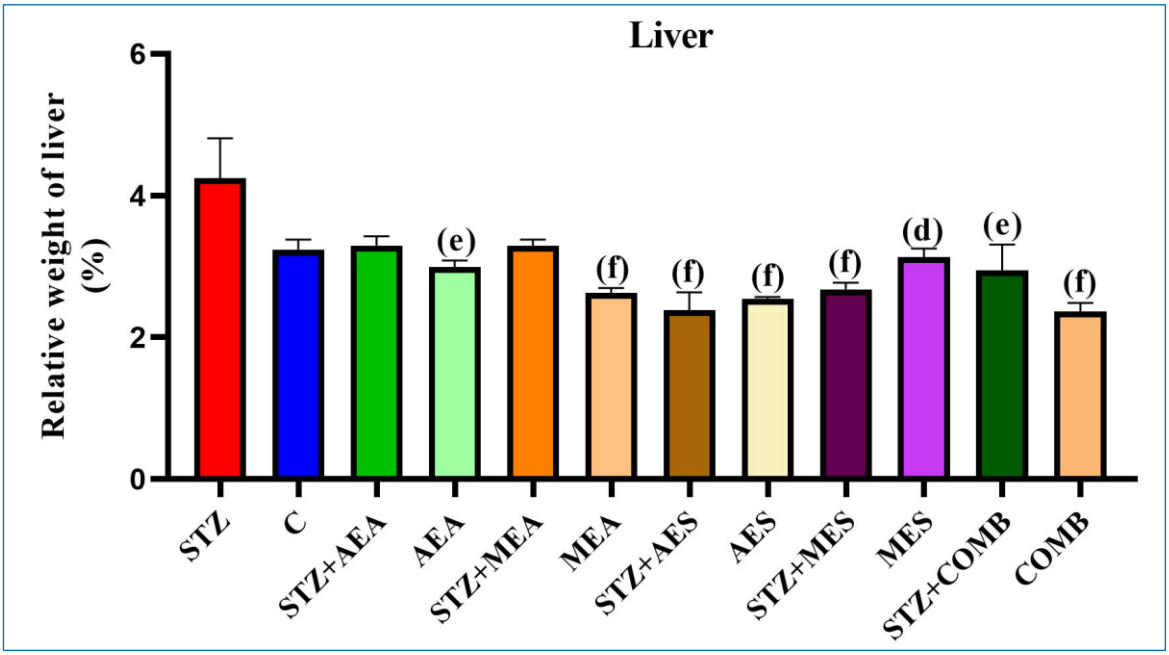


Figure 26. Effect of *A. halimus* and *S. mollis* extracts on LRW of normal and diabetic rats. Significance is presented as following: (d) p<0.05, (e) p<0.01, (f) p<0.001 vs. (STZ) group.

5.3.3. Kidneys

Results from KRW are presented in (Fig. 27). Despite the fact that the BW of (STZ) group rats in the end of experiment has decreased, they showed a marked increase ($p<0.001$ vs. C) in KRW. Similar findings reported that hyperglycemia directly upregulates TGF-β and Vascular Endothelial Growth Factor (VEGF) in renal tissues, leads to increase in glomerular, tubular and interstitial volume of diabetic animals compared with controls (Rasch and Dørup, 1997). Moreover, the increase in relative kidney weight in STZ-induced diabetic rats results from a combination of decreased protein degradation, increased protein synthesis, extracellular matrix expansion, functional hyperfiltration, and oxidative-inflammatory damage, all contributing to renal hypertrophy and pathological remodeling characteristic of diabetic nephropathy (Olbricht and Geissinger, 1992; Zafar and Naqvi, 2010). Furthermore, administration of plant extracts led to a moderate gain of kidneys weight in all non-diabetic groups where the highest significance elevation ($p<0.001$ vs. C) was noted in (MES) group. The diabetic rats treated with (AEA, MEA, MES, and COMB) showed a statistically significant increase in KRW ($p<0.001$ vs. C). However, when compared to the (STZ) group, the observed increases of KRW in *A. halimus*-treated diabetic groups (STZ+AEA) and (STZ+MEA) were not statistically significant, which means the change could be due to random variation rather than a real effect of the treatment, it may not be potent enough under the current experimental conditions (short duration, low dose etc.). Interestingly, the (STZ+AES) group presented a significant reduction in KRW ($p<0.05$ vs. STZ). This may imply a protective or regulatory effect of AES in preventing kidney hypertrophy or pathological enlargement often associated with diabetes, in accordance with other studies (Grover et al., 2001; Mestry et al., 2016).

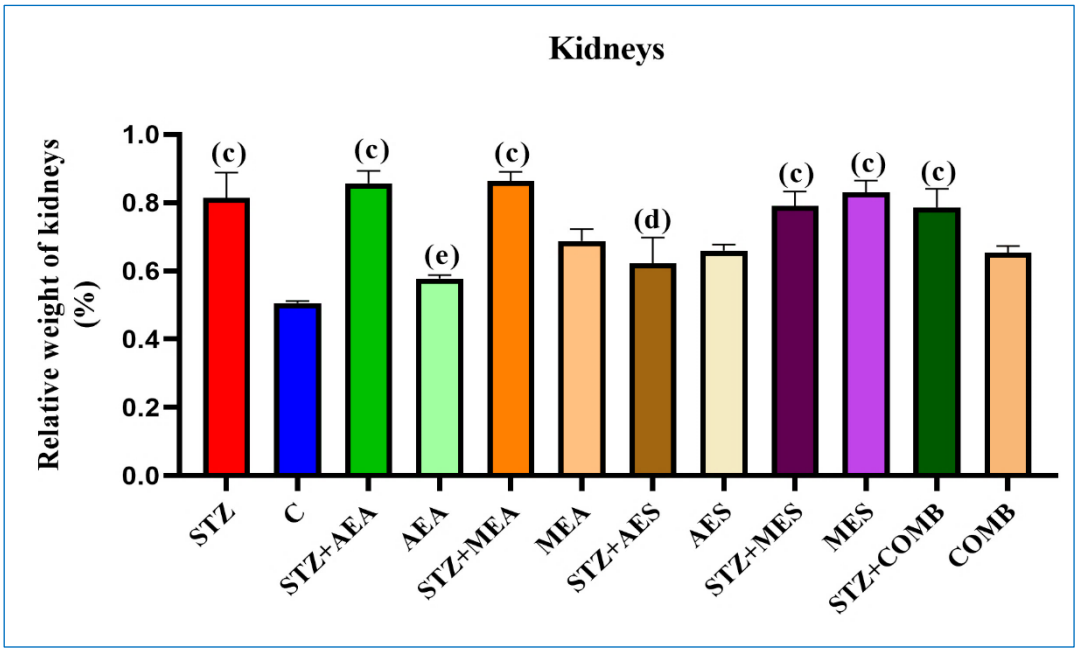


Figure 27. Effect of different treatments on KRW of healthy and STZ-induced diabetic rats. Significance is presented as: (c) $p<0.001$ vs (C) group; (d) $p<0.05$, (e) $p<0.01$ vs. (STZ) group.

5.4. Biochemical parameters

Biochemical parameters serve as critical indicators of metabolic and organ function, especially in experimental models of DM. In STZ-induced diabetic rats, alterations in serum biomarkers such as liver transaminases (ASAT and ALAT), kidney function markers (creatinine and uric acid), and protein profiles (total protein and albumin) are commonly observed due to the OS and tissue damage associated with hyperglycemia. Evaluating these biochemical markers allows for a comprehensive assessment of the systemic impact of diabetes and the possible therapeutic effects of plant extracts. In this study, the effects of aqueous and methanolic extracts of *A. halimus* and *S. mollis*, both individually and in combination, was examined to determine their influence on biochemical disturbances induced by STZ administration.

5.4.1. Hepatic biomarkers (ALAT and ASAT)

Diabetes is a metabolic disorder that can cause damage to hepatocytes. Injury to these liver cells is associated with the release of intracellular components into the bloodstream. The

assessment of serum levels of hepatic enzymes serves as a reliable indicator for diagnosing liver cells damage. In the present study, a significant increase (p<0.001 vs. C) in ASAT and ALAT levels was observed in the (STZ) group (Fig. 28), indicating hepatic injury induced by STZ. This hepatotoxicity is likely a result of OS and inflammatory processes triggered by hyperglycemia (Hajam and Rai, 2019; Fagbohun et al., 2020; Rehman et al., 2023). Treatment with both aqueous and methanolic extracts of *S. mollis* and COMB resulted in a notable reduction in ASAT and ALAT levels compared to the (STZ) group, with significance ranging from (p<0.05) to (p<0.001), demonstrating potent hepatoprotective activity. However, AEA and MEA were ineffective and failed to counteract STZ-induced hepatotoxicity, showing a highly significant increase (p<0.001 vs. C) in both enzymes. This elevation was higher than (STZ) group, suggesting that the extract may not have exerted a protective effect on the liver, may be because the highly damage of liver cells, the body dehydration, or because their hepatoprotective efficacy in diabetic conditions is a dose or duration dependent. These outcomes concorded with those reported that a long-term treatment with *Nigella sativa* oil was effective in reducing the increased serum ASAT and ALAT in STZ-induced diabetic rats (Al-Logmani and Zari, 2011). Conversely, other reports note that some plant extracts may cause an increase or slight elevation in ALAT and ASAT activities relative to (STZ). For instance, treatment with *Balanites aegyptiaca* extract showed increased levels on these enzymes (Zaakouk et al., 2018).

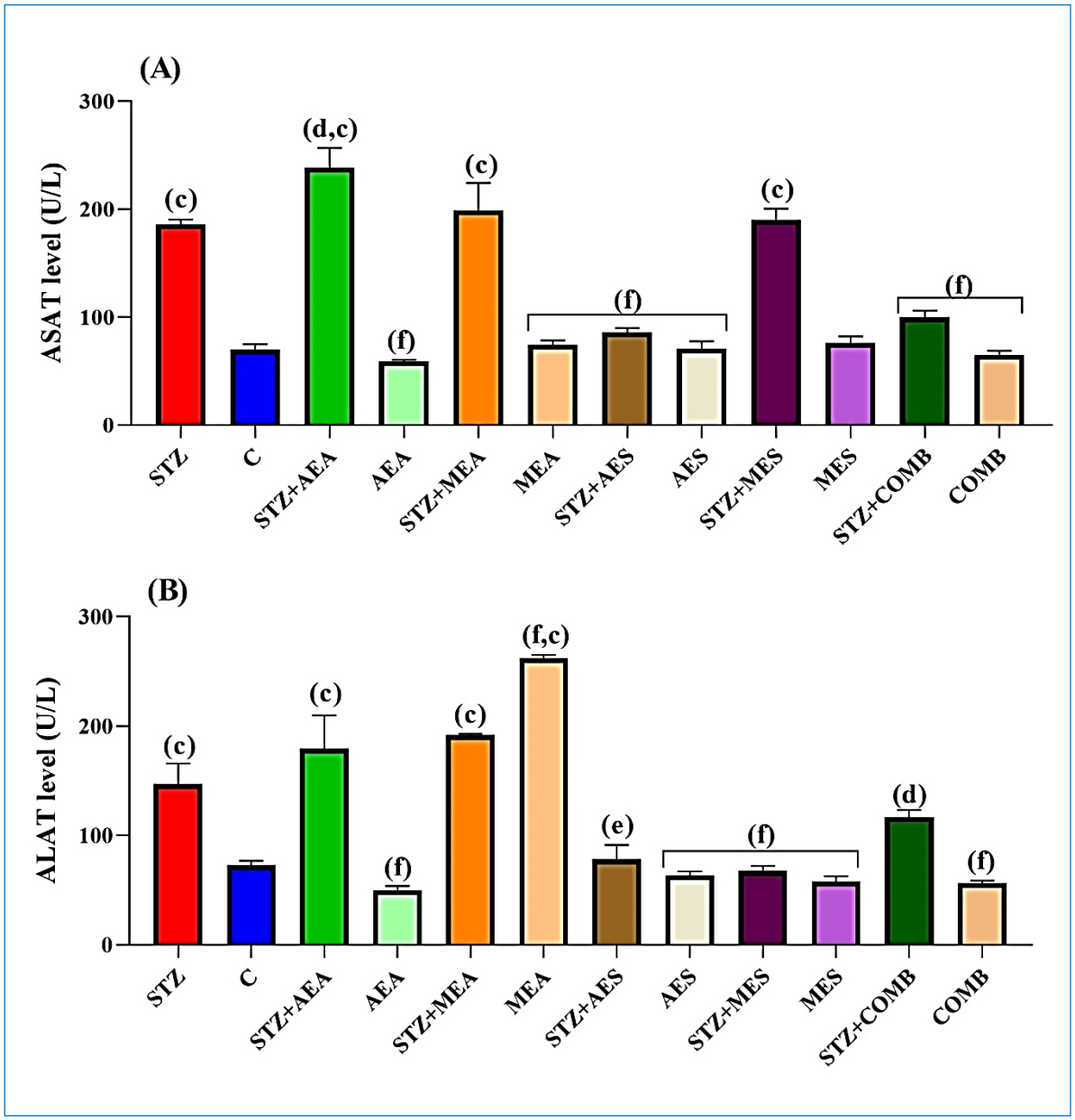


Figure 28. Effect of different treatments on hepatic enzymes of healthy and diabetic rats. (A): ASAT level, (B): ALAT level. Significance is presented as following: (c) $p<0.001$ vs. (C) group; (d) $p<0.05$, (e) $p<0.01$, (f) $p<0.001$ vs. (STZ) group.

5.4.2. Renal function biomarkers (creatinine and uric acid)

Impaired kidney function and increased protein catabolism are associated with higher creatinine and uric acid concentrations. Results from renal biomarkers are shown in (Fig. 29).

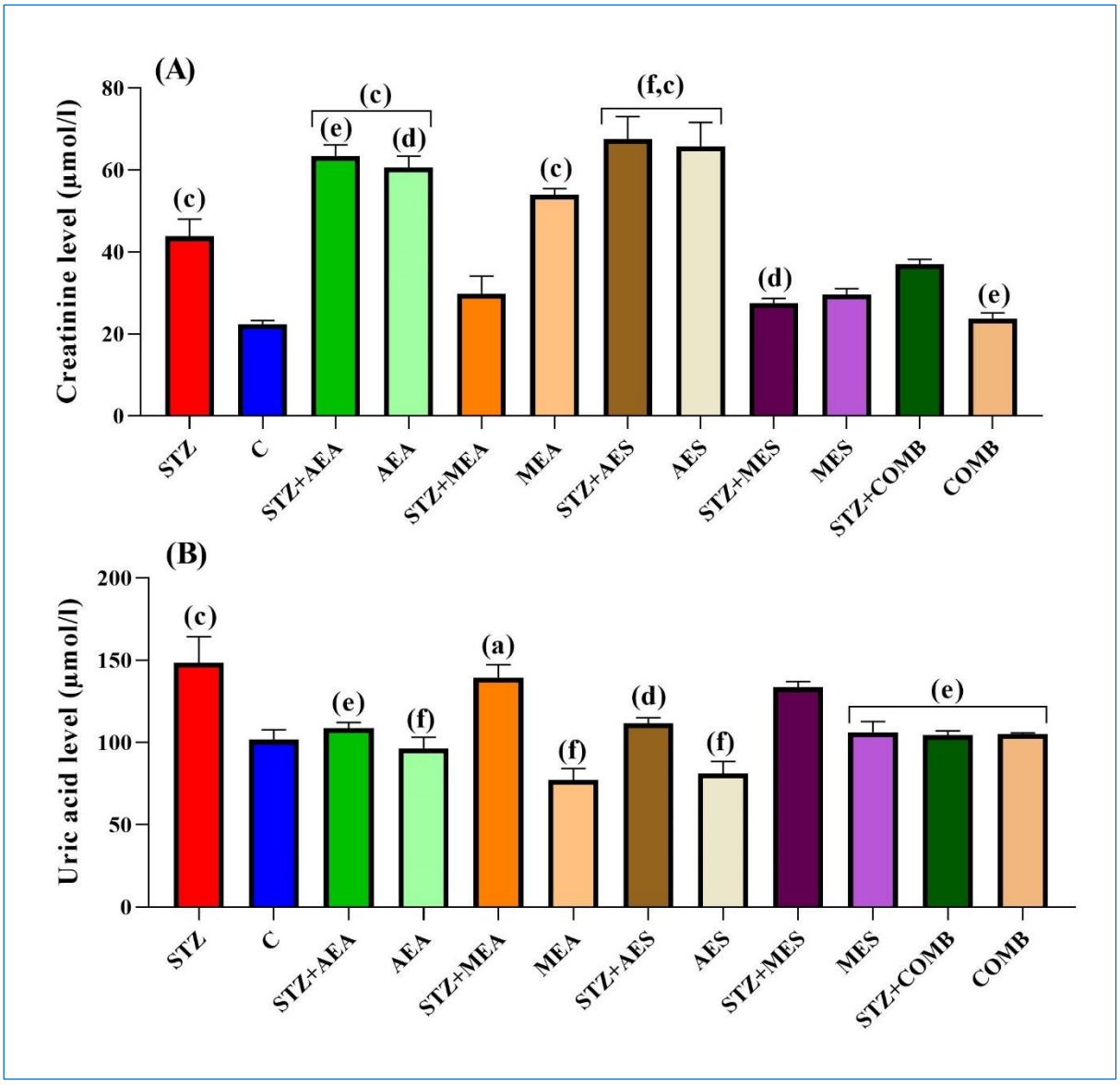


Figure 29. Effect of different treatments on the renal biomarkers of healthy and diabetic rats. (A): Creatinine level, (B): Uric acid level. Significance is presented as following: (a) $p<0.05$, (c) $p<0.001$ vs (C) group; (d) $p<0.05$, (e) $p<0.01$, (f) $p<0.001$ vs. (STZ) group.

In this study, the STZ-induced diabetic group exhibited a significant increase in both creatinine and uric acid levels ($p<0.001$ vs. C). Similarly to previous studies, this result indicates an impaired renal function likely due to nephrotoxicity caused by STZ-induced OS and glomerular damage (Alq and Hussein, 2021; Rehman et al., 2023; Mughal et al., 2024). In treated diabetic rats particularly (STZ+MES) and (STZ+COMB) groups, administration of the extracts led to a noticeable reduction in creatinine and uric acid levels compared to the diabetic

group with values approaching normal levels ($p<0.05$, and $p<0.01$). Many plant extracts have been shown to reduce elevated serum creatinine levels in STZ-diabetic rats, indicating nephroprotective effects. For example, treatment with *Punica granatum* leaf extract significantly decreased serum creatinine (Mestry et al., 2016). Similarly, ethanol extracts of *Citrullus colocynthis* and *Momordica charantia* fruits alone and combined have lowered serum creatinine levels compared to untreated diabetic group (Tehseen et al., 2024), consistent with our findings. The methanolic extract of *A. halimus* produced a non-significant decrease in creatinine level compared to (STZ) group, and no effect on uric acid level with a significant deference of ($p<0.05$ vs. C). On the other hand, treatment with AEA and AES in both diabetic and non-diabetic rats induced a statistically highly significant increase in serum creatinine level ranging from $p<0.05$ to $p<0.001$ compared to (STZ). However, the treatment in (STZ+AEA) and (STZ+AES) caused a reduction of uric acid level ($p<0.01$ and $p<0.05$, respectively) compared to (STZ) group. Creatine phosphate in muscle degrades to produce creatinine which is released by the body muscles at a fairly constant rate. This creatinine is filtered by the kidneys and thus changes in creatinine level reflects renal damage. Uric acid is the waste product of purine metabolism and is also excreted through urine. Therefore, changes in the levels of these markers are used to estimate renal dysfunction (Indu et al., 2019). When kidney function is impaired due to nephrotoxicity, creatinine accumulates in the blood, resulting in elevated serum creatinine levels (Kim and Moon, 2012). The unexpected results of our study induced by AEA and AES are possibly due to high salt or secondary metabolite concentrations typical of halophytic species. Halophytes naturally accumulate both salts (like sodium and chloride) and osmolytes (like proline and betaine) within their cells, which may exert diuretic effects or increase osmotic load (Slama et al., 2015). This can potentially worsen dehydration and indirectly elevate serum creatinine levels if not properly metabolized or filtered, even in the presence of beneficial bioactive compounds in the plants. However, this effect may also be

transient or dose-dependent. Some plants, such as *Aristolochia* and *Rhubarb*, have been associated with nephrotoxicity and may contribute to increased creatinine levels in some contexts (Pearson et al., 2022), which aligns with our findings. Overall, these findings suggest that *S. mollis*, especially the methanolic fractions, and COMB exhibit potent nephroprotective effects in STZ-induced diabetic rats compared to other extracts, which were unable to restore renal parameters to normal range.

5.4.3. Protein profile (total protein and albumin)

Proteins are vital biomolecules important to all cells in the body, circulate in blood where two major classes of proteins are present: albumin and globulins. Albumin is an important protein synthesized in the liver; its production is associated with proper energy supply. Thus, albumin is a significant clinical marker to predict disease status in individuals (Indu et al., 2019). Results of total protein and albumin levels are presented in (Fig. 30). We recorded a non-significant change in total protein level in (STZ) group rats compared to rats in (C) group. Similar results are observed in treated diabetic rats with different extracts: AEA, MEA, AES, MES, and COMB. However, (STZ) group showed a slight elevation in albumin level ($p<0.01$ vs. C), in accordance with findings noted a 23.4% elevation in albumin level of diabetic rats (Al-Attar and Alsalmi, 2019). Treated diabetic rats: (STZ+AEA), (STZ+AES), (STZ+MES), and (STZ+COMB) groups showed a notable efficacy of extracts in restoring albumin levels to near normal with significance varying from $p<0.05$ to $p<0.001$ when compared to (STZ) group. These observations are in agreement with other investigations (Almalki et al., 2019; Indu et al., 2019; Zeid and Al Jaghthmi, 2020; Mughal et al., 2024).

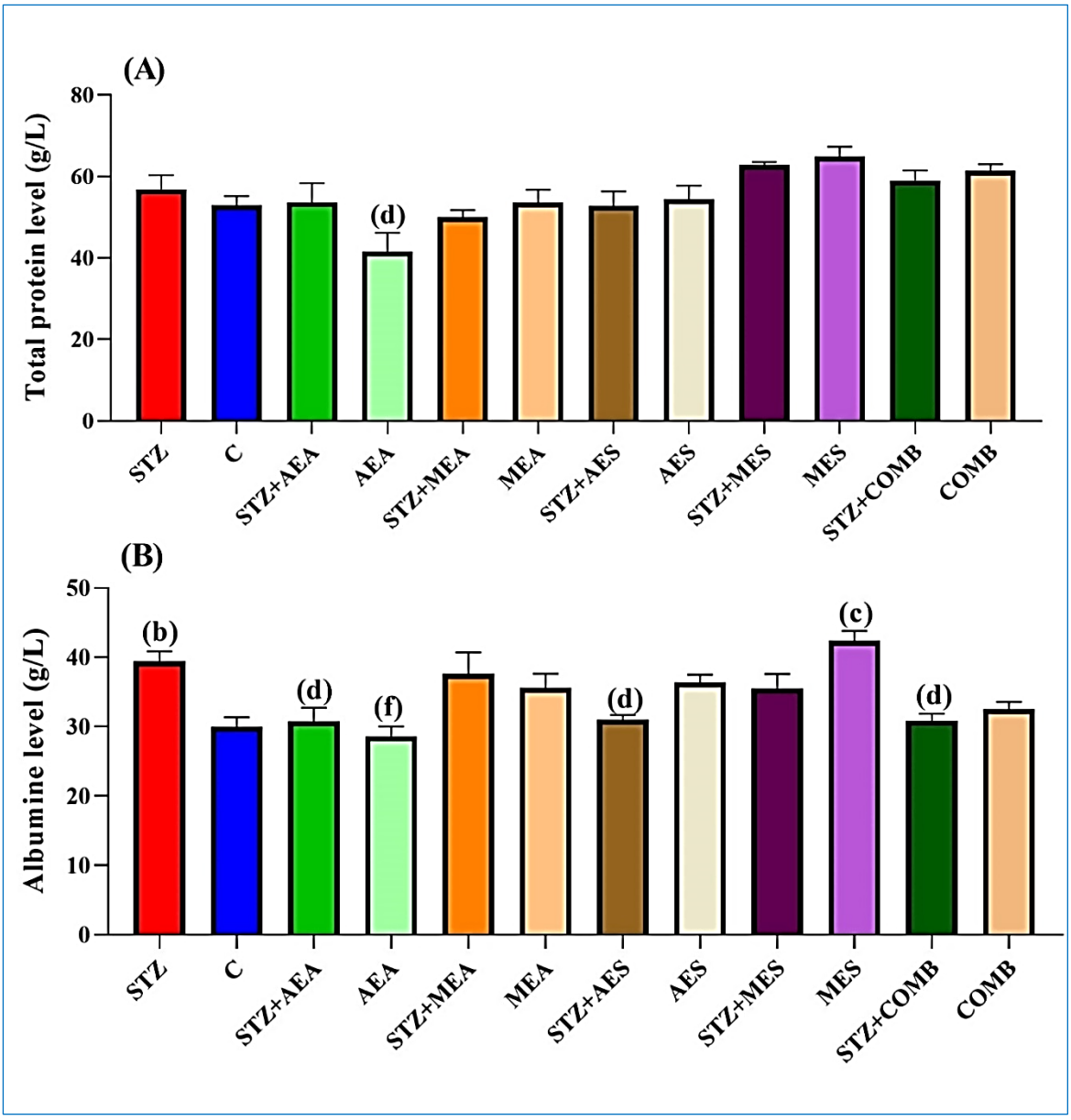


Figure 30. Effect of different treatments on proteins profile of healthy and diabetic rats. (A): Total protein, (B): Albumin level. Significance is presented as following: (b) $p<0.01$, (c) $p<0.001$ vs. (C) group; (d) $p<0.05$, (f) $p<0.001$ vs. (STZ) group.

5.5. Effects of extracts on hematological parameters

It has been reported that various hematological parameters could be a useful indicator in assessing the harmful effects of drugs as well as medicinal plants, which may also vary during diabetes (Mahmoud, 2013). The effects of STZ-induced diabetes and treatment with different extracts on the complete blood count (CBC) is represented in (Fig. 31).

Our results showed a significant decrease in the count of WBC ($p<0.05$ vs. C) and LY ($p<0.001$ vs. C), besides a statistically highly significant increase of MO ($p<0.001$ vs. C) and RBC ($p<0.05$ vs. C) levels in (STZ) group. However, no significant changes have been noticed in the other hematological parameters (GR, HCT, HGB and PLT) in (STZ) group. These results are in consonance with findings by earlier researches (Fagbohun et al., 2020; Rehman et al., 2023). The increased monocytes level might be due to high blood sugar level, which prompted the bone marrow to generate more monocyte progenitor cells, leading to monocytosis (Kanter et al., 2020). Additionally, the decrease in LY and WBC counts can be attributed to the body's stress response following the injection of STZ (Helal et al., 2005). Prolonged hyperglycemia can lead to an increase in RBC level and HCT count, likely reflects a combination of hemoconcentration due to fluid loss and compensatory erythropoietic activity in response to hyperglycemia-induced OS. However, such elevations may not persist in long-term or severe diabetes, where anemia tends to dominate due to damage to the cytoskeleton of the RBC's membrane. This damage leads to a low-grade inflammation that is linked to many complications of diabetes (Simmons, 2010; Williams et al., 2023). Administration of both aqueous (AEA) and methanolic (MEA) extracts of *A. halimus* led to a notable decrease in all measured hematological parameters (WBC, LY, MO, GR, RBC, HCT, HGB, and PLT), with significance ranged from ($p<0.05$ to $p<0.001$) in STZ-induced diabetic rats, when compared to (STZ) and (C) groups. On the other hand, we noticed in (STZ+MES) and (MES) groups a significant increase ($p<0.05$, $p<0.01$, and $p<0.001$) in WBC, LY, RBC, HCT, HGB, and PLT

count compared to (STZ) and (C) groups. Phytotherapy using the AES showed a decrease in the levels of: LY (p<0.001 vs C), MO (p<0.01 vs. STZ), HGB (p<0.001 vs. STZ and C) and PLT (p<0.01 vs. C). Contrary, there was a notable increase of GR level (p<0.001 vs. STZ and C). Interestingly, treatment with the combined aqueous extracts of the two plants appeared to exert a normalizing effect on certain hematological parameters in STZ-induced diabetic rats, particularly LY, RBC, and HCT. This suggests a possible synergistic interaction between the bioactive constituents of both plants, potentially reduced OS, or restored erythropoietin and immunomodulatory activity disrupted by STZ induction. Moreover, in (AES), (STZ+MES), (MES), (STZ+COMB), and (COMB) groups we recorded an increase on the PLT number (p<0.05) with significance ranging from p<0.05 to p<0.001 compared to both (STZ) and (C) groups. Other studies showed that some antidiabetic plants can lead to reduced HGB and PLT level as a compensatory mechanism of antioxidant and anti-inflammatory effects of the plants (Esmail Al-Snafi et al., 2019; Yılmaz et al., 2022). The aqueous extract of stem bark of the antidiabetic plant *Afzelia Africana* has increased LY, MO and PLT in diabetic (Oyedemi et al., 2011). Besides, in some contexts, the reduction in blood glucose level may correlate with lower hemoglobin levels particularly in the plants influence RBC production or its survival (Esmail Al-Snafi et al., 2019). The RBC level and HCT ratio might be normalized by using vital nutrients of the plant, which support blood cell formation (hematopoiesis), protect the red cells from OS damage, and maintain their integrity and function (Cherrada et al., 2024).

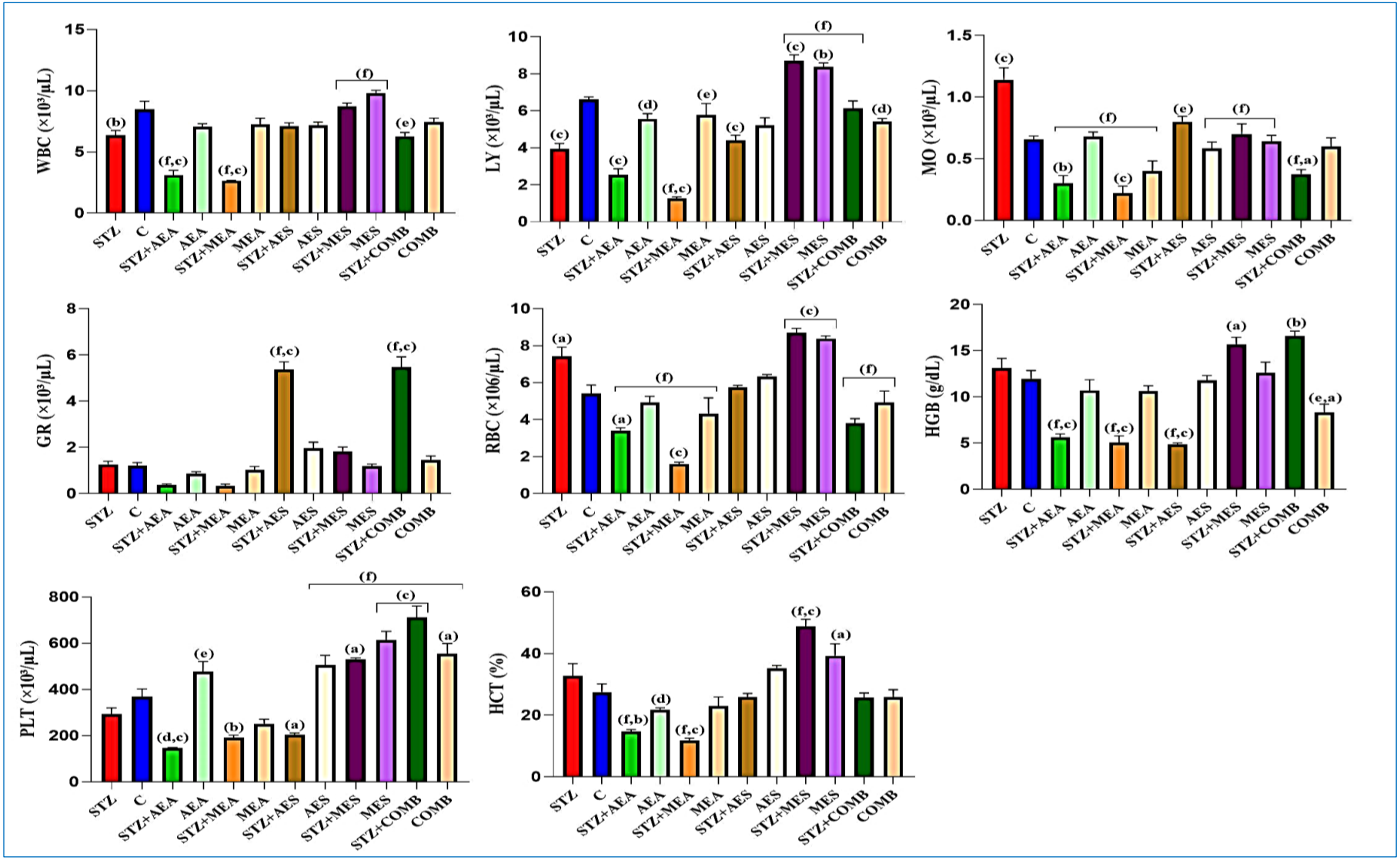


Figure 31. Comparative analysis of hematological indices in normal, diabetic, and treated rats.
Significance is presented as following: (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ vs. (C) group; (d) $p<0.05$, $p<0.01$, (f) $p<0.001$ vs. (STZ) group.

5.6. Evaluation of oxidative stress biomarkers in organs

Hyperglycemia promotes the generation ROS, leading to OS, which plays a major role in the pathogenesis of diabetes, particularly in STZ-induced models. Besides, it contributes to the complications linked to diabetes (Bhatti et al., 2022). To evaluate the oxidative damage caused by diabetes and the potential protective effects of plant extracts, we measured five key OS markers: MDA, GSH, GSH-Px, SOD, and CAT in the pancreas and liver, and MDA, GSH, GSH-Px, in kidneys. The influence of each treatment on these biomarkers in different organs is presented below.

5.6.1. Malondialdehyde (MDA) Levels

Malondialdehyde (MDA), a key marker of LPO, was quantified to assess oxidative damage in the pancreas, liver, and kidneys of all experimental groups (Fig. 32).

Experimental diabetes induced by STZ led to a highly significant increase in MDA level of liver ($p<0.001$) and non-significant in pancreas and kidneys of the (STZ) group compared to the (C) group, indicating an intensification of LPO and OS. Persistent hyperglycemia in diabetes leads to elevated production of oxygen free radicals, resulting in LPO, which generates MDA and increases membrane fluidity and permeability (Kakkar et al., 1995). Compared to the (STZ) group, a non-significant increase in MDA levels was observed in the pancreas of (STZ+MEA) and (AEA) rats' groups, while a highly significant increase ($p<0.001$) was detected in the (STZ+AES), (STZ+MES), (STZ+COMB), (MES), (COMB) groups, and ($p<0.01$) in the (MEA) group. Furthermore, when compared to the (C) group, all of the aforementioned groups exhibited a significant increase in pancreatic MDA levels ($p<0.001$), except for the (AEA) group, which showed a milder but still significant elevation ($p<0.05$).

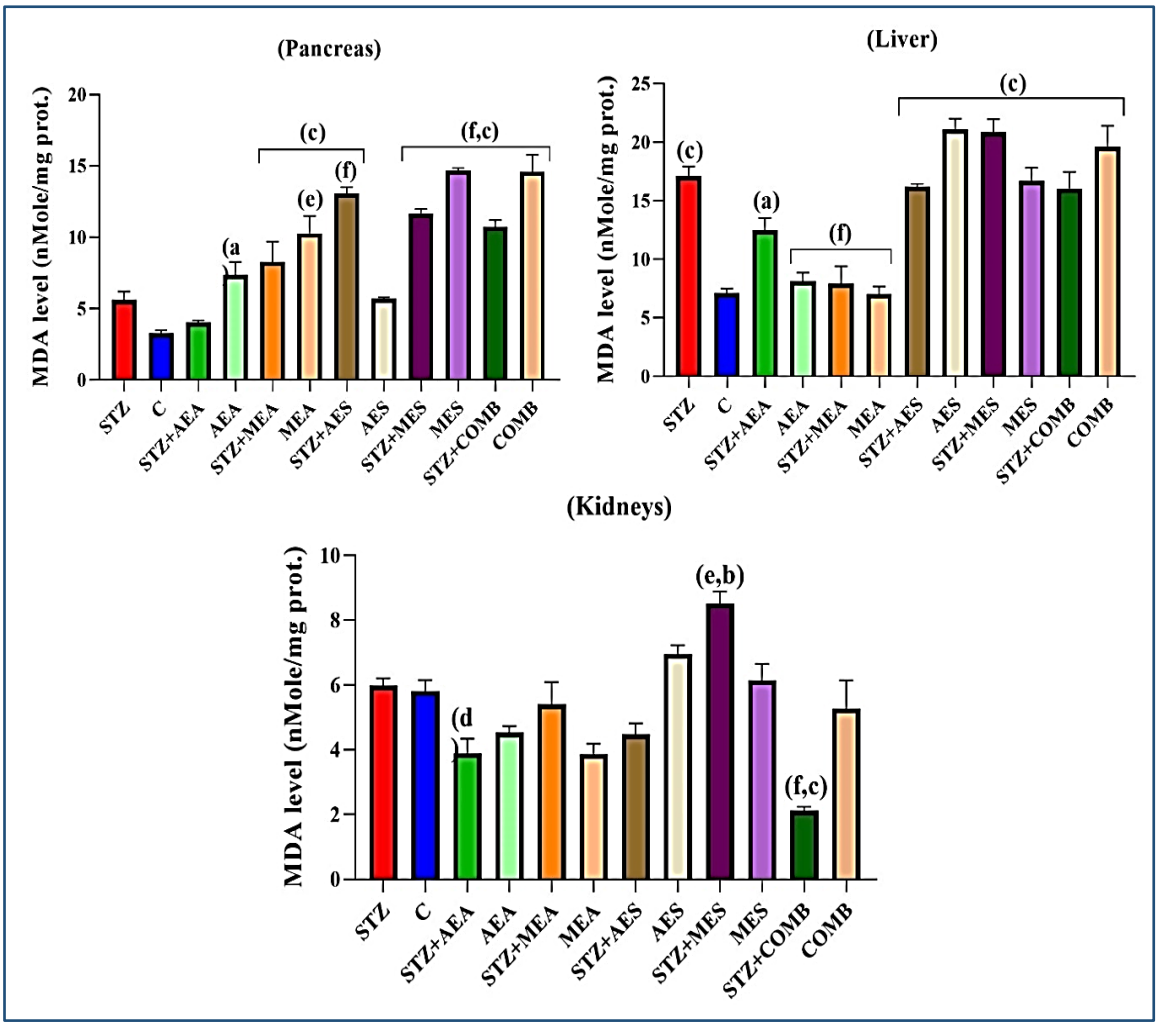


Figure 32. Effects of diabetes and extracts supplementation on MDA of different organs. (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ vs. (C) group. (d) $p<0.05$, (e) $p<0.01$, (f) $p<0.001$ vs. (STZ).

In the liver, several treatments exhibited a protective effect. Significant reductions in MDA levels compared to the (STZ) group were noted in the (AEA), (STZ+MEA), and (MEA) groups ($p<0.001$), while the (STZ+AEA) group showed a non-significant decrease. However, compared to the (C) group, MDA levels remained significantly elevated ($p<0.001$) in the (STZ+AES), (AES), (STZ+MES), (MES), (STZ+COMB), and (COMB) groups, indicating persistent OS despite treatment. These results underline the stronger antioxidant effect of AEA and MEA in hepatic tissues.

Regarding the kidneys, a slight but significant reduction ($p<0.05$ vs. C) of MDA levels was observed in the (STZ+AEA) group, and a much stronger decrease ($p<0.001$ vs. STZ and C)

was noted in the (STZ+COMB), highlighting the notable nephroprotective potential of the combined extracts. In contrast, the (STZ+MES) group displayed a significant elevation (p<0.01 vs. STZ and C) in renal MDA levels, suggesting a possible pro-oxidative effect of this treatment in kidney tissue.

When MDA presents at elevated levels, it enhances glucose-stimulated insulin secretion in pancreatic islets by upregulating the expression of key genes like glucokinase, GLUT2 and Pancreatic Duodenal Homebox 1 (PDX1) (Wang et al., 2014). Researchers have indicated that following to STZ exposure, GLUT2 improves β-cell survival, while STZ reduces GLUT2 expression, impairing glucose-stimulated insulin secretion and leading to β-cell dysfunction. Although some β-cells may survive the initial STZ injury, their reduced functionality due to lower GLUT2 levels creates a negative feedback loop, worsening hyperglycemia and lowering β-cell activity (Hosokawa et al., 2001; Hahn et al., 2020). Moreover, MDA affects the intracellular ATP/ADP ratio and cytosolic calcium levels, which are essential for insulin secretion (Wang et al., 2014). A previous study proposed that MDA, a marker of OS and LPO, serves as a possible therapeutic target for preserving pancreatic β--cell function, playing a role in diabetes-related complications (Angie et al., 2024). This suggests that MDA might play a dual role, contributing to both β-cell dysfunction after STZ exposure and compensatory mechanisms that temporarily boost insulin release and glucose regulation.

5.6.2. Reduced glutathione (GSH) levels

Reduced glutathione, a key intracellular antioxidant, was assessed to evaluate the redox balance in diabetic and treated rats (Fig. 33).

In the (STZ) group, GSH levels showed a significant increase in the pancreas (p<0.001 vs. C) and liver (p<0.01 vs. C), while the kidneys displayed a non-significant change. This rise in GSH, particularly in the pancreas and liver, may represent a compensatory defense mechanism in response to the elevated OS induced by STZ. Higher levels of GSH may safeguard cellular proteins from oxidation via GSH redox cycle to neutralize ROS generated by STZ induced diabetes (Soliman et al., 2015). Furthermore, GSH is recognized for its ability to neutralize hydrogen and lipid peroxides (Bhatti et al., 2022).

In the pancreas, treatments with the extracts in the groups (STZ+AEA), (STZ+MEA), and (STZ+COMB) led to a highly significant reduction in GSH levels (p<0.001 vs. STZ), suggesting improved oxidative balance due to effective antioxidant action of the extracts. Conversely, both the (STZ+MES) and (MES) groups exhibited a significant increase in pancreatic GSH (p<0.001 vs. STZ), possibly indicating overcompensation or stress-induced upregulation. Comparing to (C) group, highly significant elevation on pancreatic GSH levels were found in the (AEA), (MEA), (STZ+AES), (AES), (STZ+MES), and (MES) groups (p<0.001), supporting the idea that these treatments may enhance the antioxidant defense system. These results are in agreement with previous reports highlighting the role of polyphenols and flavonoids rich extracts in the increase of cellular GSH levels, and upregulating GSH synthesis and recycling pathways (Myhrstad et al., 2002; Moskaug et al., 2005). In the liver, multiple treatments resulted in increased GSH levels relative to (C) group. Specifically, (STZ+AEA), (MEA), (STZ+AES), (AES), (STZ+MES), (MES), (STZ+COMB), and (COMB) groups showed highly significant increases (p<0.001), while (AEA) and (STZ+MEA) showed moderate increases (p<0.01). These findings suggest that most of the

plant extracts contribute to restoring hepatic redox homeostasis and improving antioxidant status. In the kidneys, (STZ+MEA) and (MEA) groups exhibited a significant increase (p<0.001 vs. STZ and C) in GSH levels indicating a strong reno-protective antioxidant effect. The (STZ+COMB) group also showed an elevation of GSH levels (p<0.05 vs. STZ), and the (COMB) group had a moderate but significant increase (p<0.05 vs. C). These enhancements suggest that MEA and the combination of extracts were particularly effective in strengthening renal antioxidant defenses.

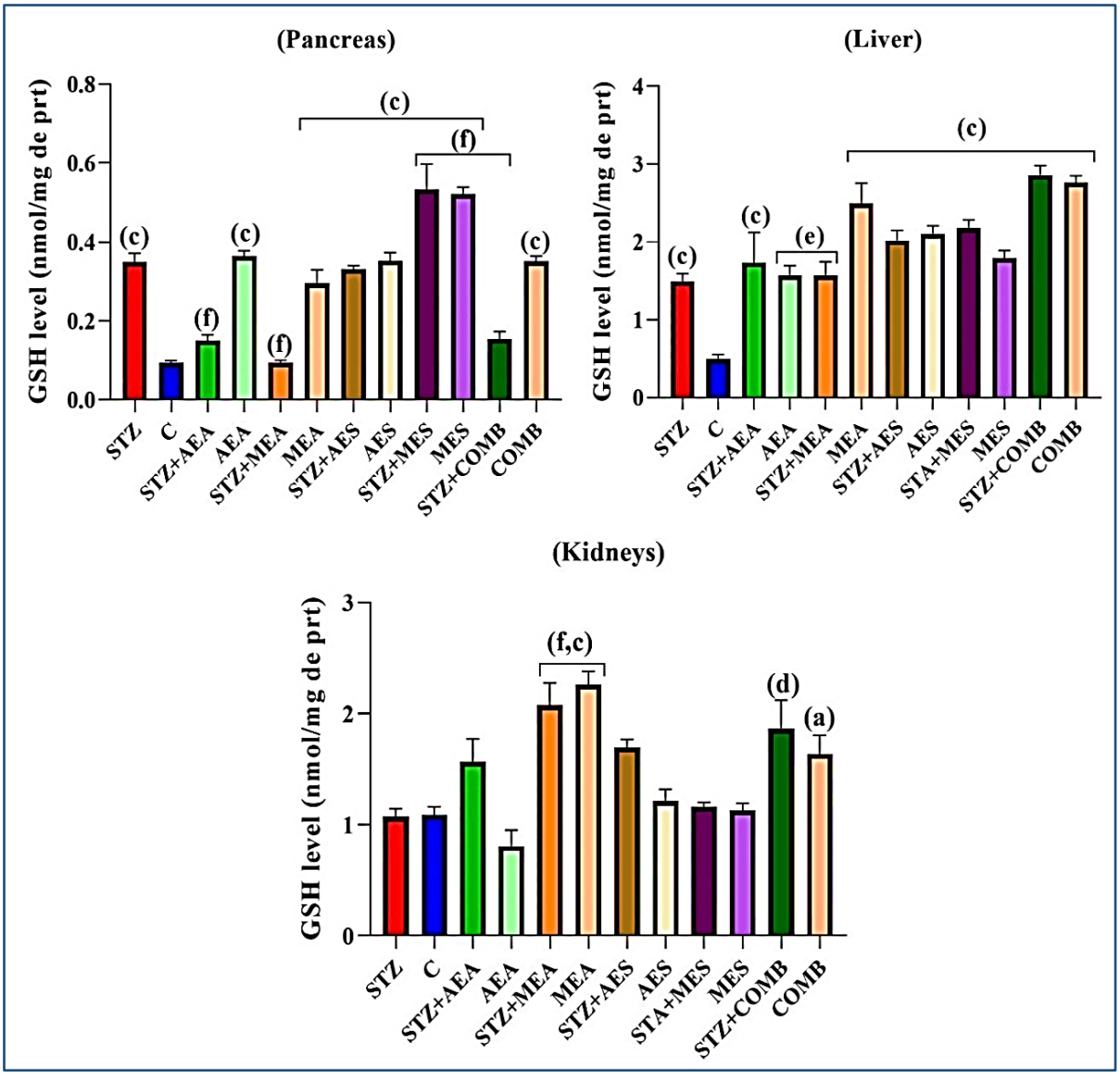


Figure 33. Effects of diabetes and extracts supplementation on GSH of different organs. (a) p<0.05, (b) p<0.01, (c) p<0.001 vs. (C) group. (d) p<0.05, (e) p<0.01, (f) p<0.001 vs. (STZ) group.

Overall, these findings reveal that GSH levels were dynamically modulated by diabetes and the administered plant extracts in an organ-specific manner. Researchers suggested that the bioactive compounds such as polyphenols, flavonoids and terpenoids present in antidiabetic plants could lower ROS, boost the antioxidant enzymes activities and improve insulin sensitivity (Alam et al., 2022; Krawczyk et al., 2023). However, the persistently elevated GSH in some groups, particularly with MES treatment may also reflect ongoing oxidative burden or feedback dysregulation which need further investigations.

5.6.3. Glutathione peroxidase (GSH-Px) activity

Glutathione peroxidase is an essential antioxidant enzyme that catalyzes the reduction of H_2O_2 and lipid peroxides, protecting cells from oxidative damage. In this study, GSH-Px activity was evaluated across the pancreas, liver, and kidneys to assess the antioxidant response to diabetes and the therapeutic effects of various plant extracts treatments (Fig. 34). In the pancreas, a significant elevation of GSH-Px was detected in the (STZ) group (p<0.001) compared (C) group, likely reflecting a compensatory response to the STZ-induced OS. Consistent with current findings, some studies reported that STZ-induced diabetes triggers elevated GSH-Px activity in pancreatic tissues as an adaptive response to OS (Kakkar et al., 1995; Shahraki et al., 2020). Indeed, high glucose levels contribute to increased OS in pancreatic β-cells. The overexpression of GSH-Px boosts its activity and shields Langerhans's islets from harmful effects including the accumulation of H_2O_2 and lipid hydroperoxides by facilitating their breakdown with GSH as a co-substrate (Salazar-García & Corona, 2021). However, treatment with most extracts led to a notable decrease in GSH-Px activity. Specifically, (STZ+AEA) group showed a significant reduction (p<0.01), while (MEA) and (STZ+AES) showed moderate decreases (p<0.05). A stronger decline in GSH-Px levels (p<0.001) was observed in the groups: (AES), (STZ+MES), (MES), (STZ+COMB), and (p<0.05) in the (COMB) group when compared to the (STZ) group. These results suggest that

the extracts (particularly in their methanolic and combined forms) effectively attenuated oxidative pressure, reducing the need for overexpression of endogenous GSH-Px in the pancreas. This aligns with earlier studies where plant bioactive compounds such as *Gardenia latifolia* reduced oxidative burden, allowing antioxidant enzyme levels to normalize (Alshabi and Shaikh, 2022). For instance, Rosmarinic acid treatment in high-fat diet plus STZ-induced diabetic rats significantly restored decreased GSH-Px, SOD, and CAT activities in the pancreas, suggesting that the antioxidant attenuated oxidative damage and rebalanced endogenous defenses (Govindaraj & Sorimuthu Pillai, 2015).

In the liver, GSH-Px levels remained significantly increased ($p<0.05$ vs. C) in the (STZ) group, a finding that supports the concept of OS-induced upregulation of antioxidant enzymes in diabetic conditions. Streptozotocin is known to generate ROS, leading to hepatic OS and stimulating the expression of endogenous antioxidants such as GSH-Px. This compensatory elevation has been consistently observed in diabetic models, as reported in recent studies where STZ administration caused marked increases in hepatic GSH-Px, SOD, and CAT activities (El-Demerdash et al., 2022). However, some studies also show a decrease in GSH-Px activity in diabetic rats, particularly with long-term STZ administration (Genet et al., 2002; Goyal et al., 2011). The exact effect of STZ on GSH-Px can vary depending on the dose, duration of treatment, and other factors (Yang et al., 2013). Compared to (C) group, many groups exhibited significantly ($p<0.001$) elevated GSH-Px levels: (STZ+AES), (STZ+MES), (MES) and (STZ+COMB), along with a moderate rise ($p<0.05$) in the (AES) and (COMB) groups. These results suggest that despite their antioxidant potential, the plant extracts did not reduce GSH-Px levels to baseline but rather maintained or even enhanced antioxidant enzyme expression, likely due to residual OS or through activation of Nrf2-related antioxidant pathways. Similar outcomes were reported with *Actinidia deliciosa* aqueous extract, which significantly enhanced

hepatic GSH-Px activity in diabetic rats, presumably by promoting glutathione metabolism and mitigating oxidative damage (El-Demerdash et al., 2022).

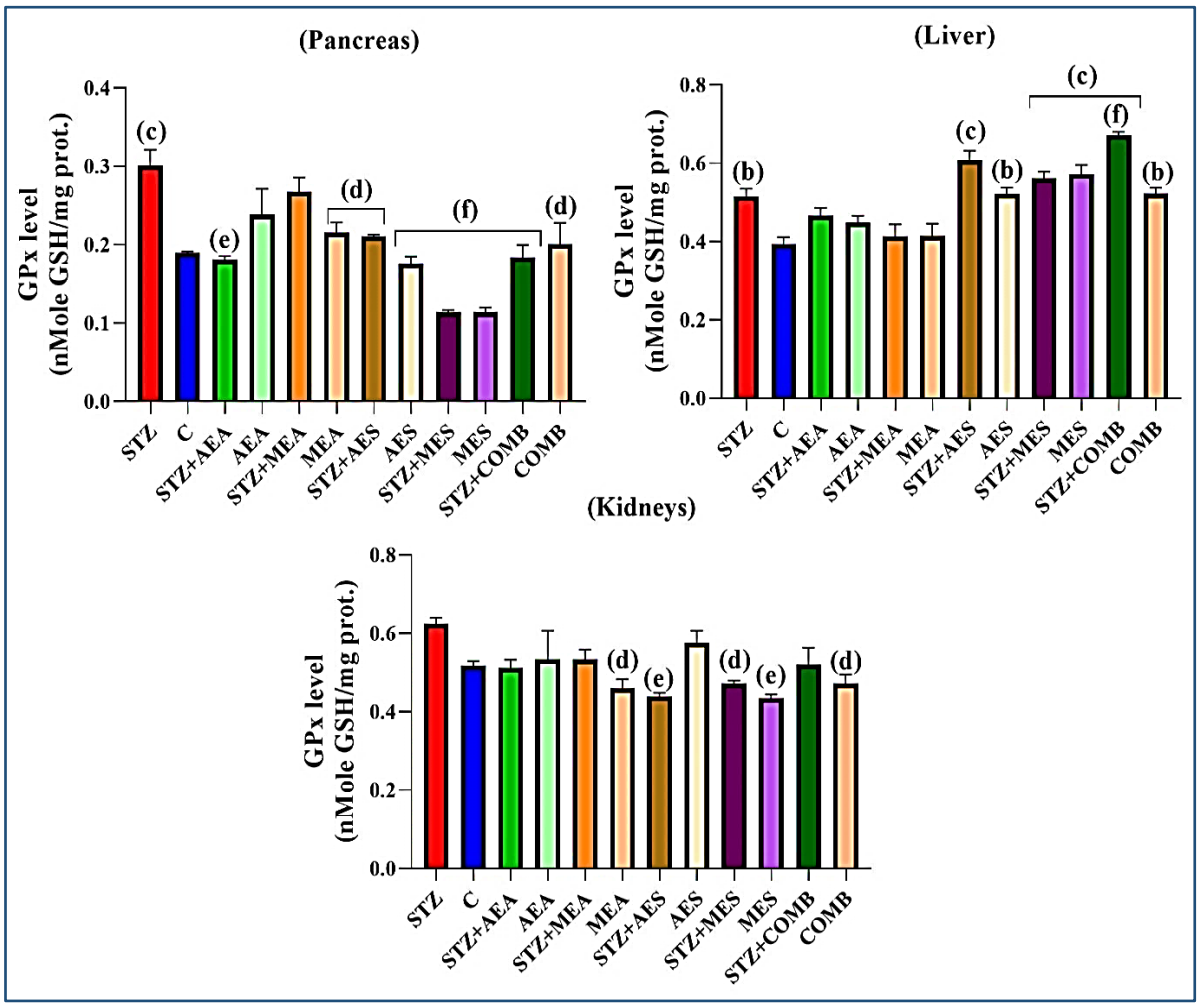


Figure 34. Effects of diabetes and extracts supplementation on GSH-Px of different organs. (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ vs. (C). (d) $p<0.05$, (e) $p<0.01$, (f) $p<0.001$ vs. (STZ).

Interestingly, when compared to the (STZ) group, only the (STZ+COMB) group maintained a significant increase in GSH-Px ($p<0.001$). This observation mirrors recent findings with polyphenol-rich plants combinations, which were found to enhance enzymatic antioxidant activities more effectively than single-plant treatments (Putra et al., 2024). The persistent elevation of GSH-Px in the (STZ+COMB) group may reflect the dual action of antioxidant restoration and active enhancement of hepatic defense systems, possibly due to high polyphenol and flavonoids content and ROS-scavenging activity of the combined extracts.

These observations are consistent with the antioxidant properties of phenolic compounds, which are known to modulate endogenous enzymatic defense mechanisms depending on the oxidative status of the tissue (Jin et al., 2023).

In the kidneys, GSH-Px activity was not significantly altered in the (STZ) group, implying a weaker enzymatic response to oxidative injury in this organ. However, several treatments produced a significant decrease in GSH-Px compared to the (STZ) group: (MEA), (STZ+MES), and (COMB) showed moderate reductions ($p<0.05$), while (STZ+AES) and (MES) demonstrated a more pronounced decrease ($p<0.01$). These findings suggest that the extracts especially MES and AES may contribute to restoring redox equilibrium, thereby reducing GSH-Px demand in the kidneys.

5.6.4. Catalase (CAT) and superoxide dismutase (SOD)

To further evaluate the antioxidant defense mechanisms affected by diabetes and treatment, the activities of SOD and CAT, two crucial enzymatic antioxidants were analyzed in the pancreas and liver tissues (Fig. 35). In the pancreas, diabetic rats of (STZ) group showed a significant increase ($p<0.001$ vs. C) in SOD activity, indicating a reactive upregulation of enzymatic defenses in response to OS resulted by STZ induction. The literature presents contrasting findings, with some studies reporting a decline in SOD activity, whereas others have noted enhanced levels of this antioxidant enzyme (Maritim et al., 2003; Almalki et al., 2019; Shahraki et al., 2020).

Notably, SOD activity was significantly reduced **(**$p<0.001$**)** in the **(**STZ+AEA), **(**AEA), **(**AES)**, (**STZ+MES)**, (**MES) and **(**COMB) groups; as well as in **(**STZ+AES) and **(**STZ+COMB) groups ($p<0.01$) compared to (STZ) group. These reductions likely reflect improved redox status, resulting in less oxidative burden and hence lower need for SOD activity. Plant extracts are rich in antioxidant compounds, such as polyphenols and other phytochemicals, which can neutralize free radicals, chelate pro-oxidant metal ions, and modulate antioxidant enzyme

activity. By enhancing the body's ability to manage OS, these bioactive constituents contribute to maintaining redox balance and may reduce the reliance on endogenous defenses like superoxide dismutase (SOD) to counteract oxidative damage (Kumar et al., 2021). Conversely, both **(**STZ+MEA) and **(**MEA) groups displayed a significant increase **(***p*<0.001 vs C) in SOD levels, suggesting that the methanolic extract may activate antioxidant defenses not only under diabetic stress but also in normal physiological conditions. This response may be attributed to the presence of bioactive compounds, such as polyphenols and flavonoids, which can trigger redox-sensitive pathways like Nrf2 or induce mild oxidative signaling, leading to an adaptive increase in SOD expression even in healthy pancreatic tissues (Alrawaiq et al., 2014; Ebrahimi et al., 2025).

CAT activity in the pancreas remained mostly unchanged in the (STZ) group, but showed significant increases **(***p*<0.001 vs STZ and C**)** in **(**STZ+MEA), **(**MEA**)**, and **(**MES) groups. In addition, **(**AES) and **(**COMB) groups also showed elevated CAT levels relative to the (C) group (*p*<0.01 and *p*<0.001, respectively). Similarly to our findings, administration of *Teucrium polium* extract to STZ-induced diabetic rats resulted in significantly increased pancreatic GSH content accompanied by enhanced activities of CAT and SOD (Harlev et al., 2013). The **(**COMB) group also showed a significant increase **(***p*<0.01**)** when compared to the (STZ) group. These findings suggest that while some treatments restored redox balance (leading to normalization of SOD), others stimulated enzymatic pathways such as CAT, possibly due to phytochemical specific responses. In the liver, a significant reduction (*p*<0.01 vs. C) in SOD activity was observed in the **(**STZ) group confirming hepatic oxidative damage. These decreases continued in several treated groups. When compared to the (STZ) group, a significant reduction (*p*<0.01) in hepatic SOD was recorded in (MEA), (MES), and (COMB) groups and highly significant decrease (*p*<0.001) in (STZ+AES), (AES), (STZ+MES), and (STZ+COMB) group. These results reflect tissue-specific variations in antioxidant responses. As highlighted

in recent research, the bioactive constituents of the extracts can modulate the antioxidant defense system by enhancing pathways that are less dependent on SOD activity (Bouyahya et al., 2024). Compared to (C) group rats, animals in the groups: **(**AEA) **(**p<0.01), **(**STZ+MEA) **(**p<0.05**), (**MEA)**, (**STZ+AES)**, (**AES)**, (**STZ+MES)**, (**MES)**, (**STZ+COMB), and (COMB) (p<0.001) all exhibited significantly lower SOD levels. This supports the concept (previously discussed) of tissue-specific and condition-dependent modulation of enzymatic antioxidants by plant-derived compounds. Antioxidants neutralize ROS through three main mechanisms: prevention, interception, and repair. Enzymes such as SOD and CAT function primarily in prevention by limiting ROS generation, SOD catalyzes the conversion of O_2^- into H_2O_2, which is then broken down into water by CAT. Interceptors, also known as free radical scavengers, directly neutralize ROS, while repair enzymes help restore biomolecules that have been damaged by OS (Kumar et al., 2021).

As for CAT activity in the liver, no significant change was found in the (STZ) group, but notable increases were observed in the (STZ+AEA), (STZ+MEA), (AES), and (STZ+COMB) groups (p<0.05 vs. C). Compared to the (STZ) group, CAT activity increased significantly in (STZ+AEA) and (STZ+COMB) groups (p<0.05) and in (STZ+MEA) (p<0.01), further supporting the protective role of these treatments in modulating hepatic OS responses. The rise in CAT activity is attributed to increased generation of H_2O_2, as reduced insulin levels enhance fatty acyl CoA oxidase activity, which triggers the oxidation of fatty acids and H_2O_2 production (Kakkar et al., 1995). Studies have indicated that catalase plays a role in detoxification by facilitating the decomposition of H_2O_2 into H_2O and O_2, thereby providing protective effects against oxidative damage (De duve and Baudhun, 1966; Bhatti et al., 2022).

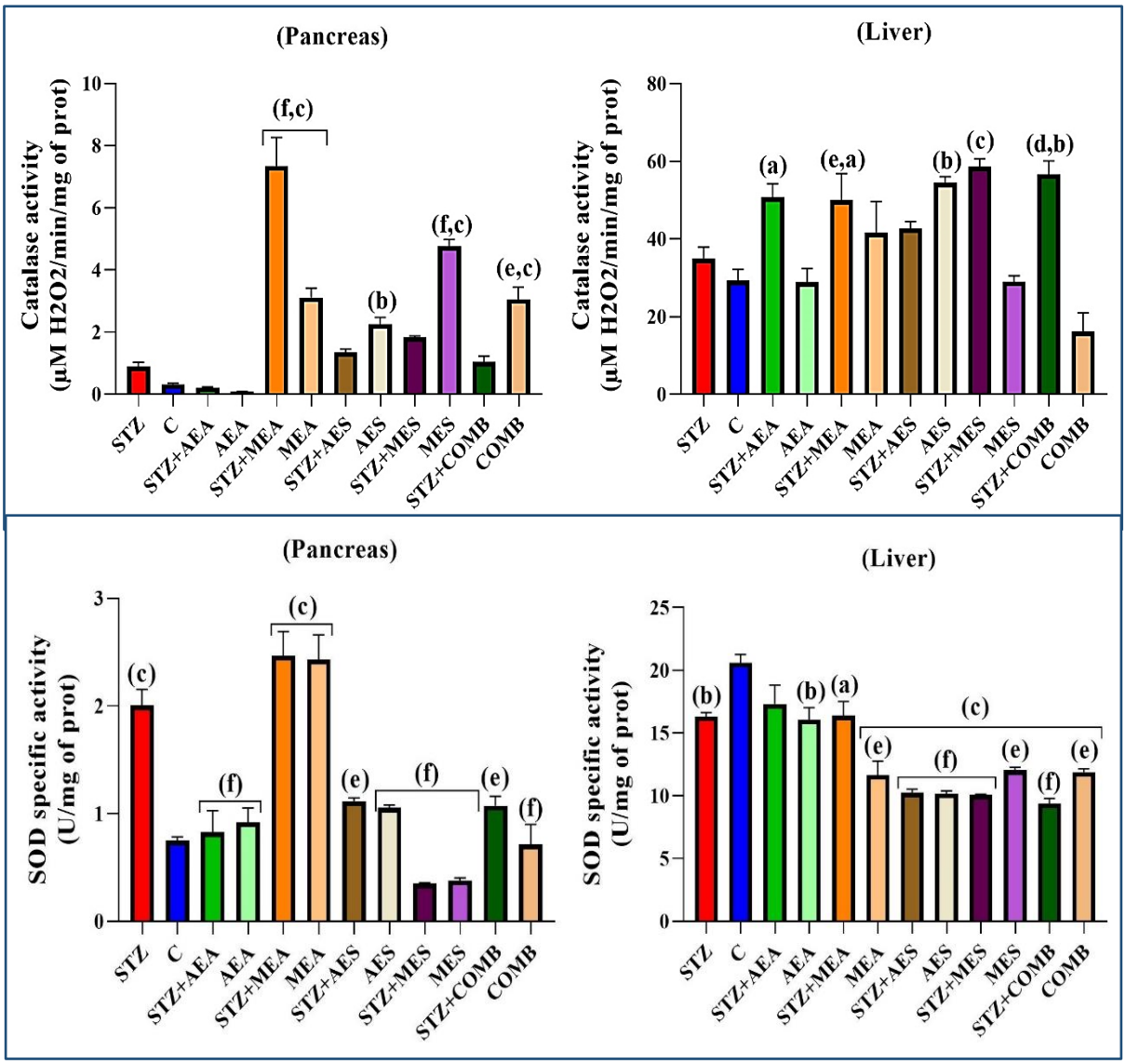


Figure 35. Effects of diabetes and extracts supplementation on CAT and SOD of pancreas and liver. (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ vs. (C). (d) $p<0.05$, (e) $p<0.01$, (f) $p<0.001$ vs. (STZ).

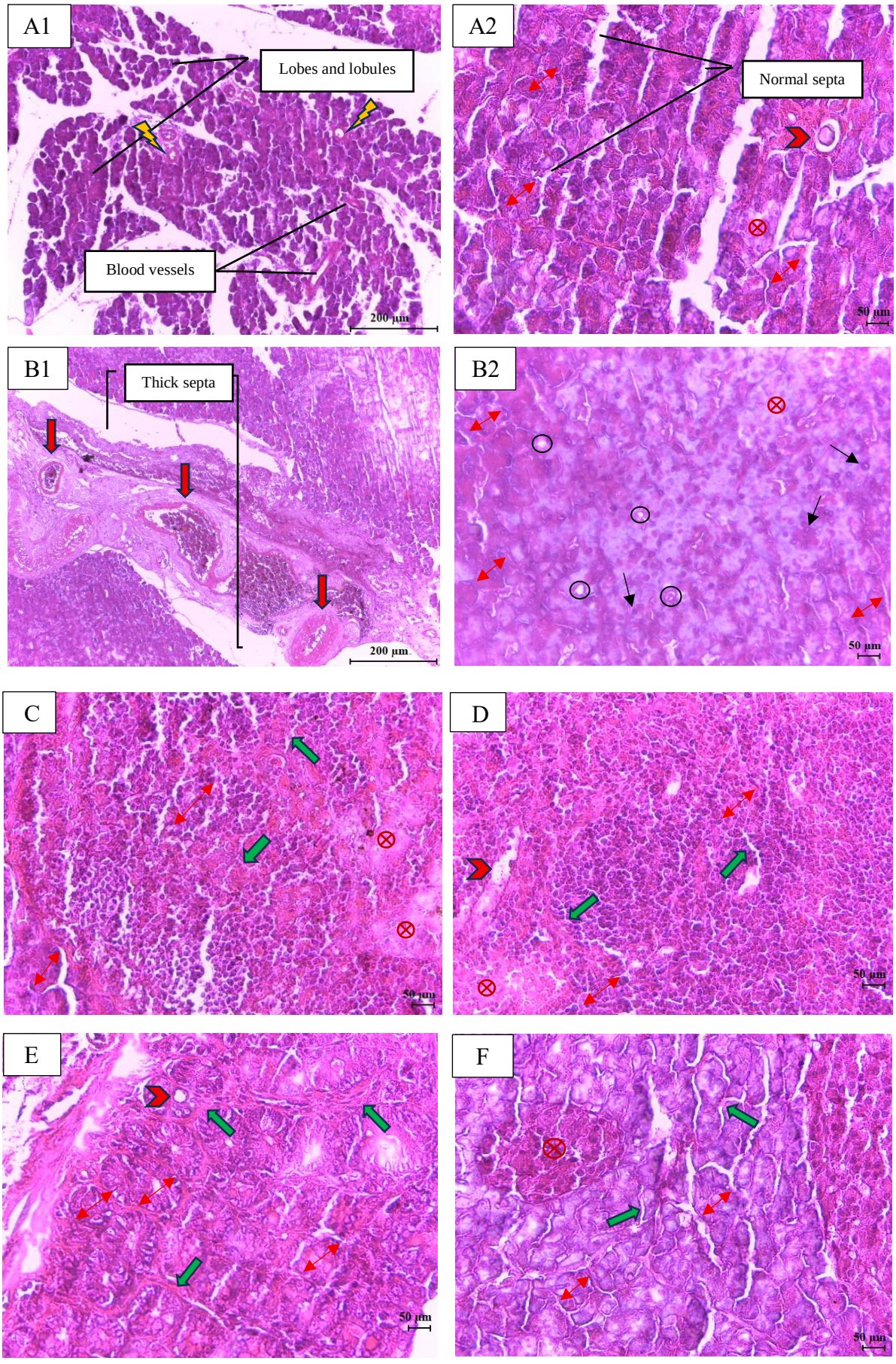
5.7. Histological study

Histological evaluation revealed distinct structural damage in the pancreas, liver, and kidneys of diabetic rats induced by STZ, whereas plant extract treatments produced varying degrees of tissues protection and restoration across different groups.

5.7.1. Pancreas histology

Histopathological examination of the pancreas from different groups are shown in (Fig. 36). The photomicrographs (A1 and A2) of (C) group revealed a well-organized pancreatic tissue architecture with a clear acinar cells clusters, and islets of Langerhans appeared distinct with normal cell density. No visible signs of inflammation edema or fibrosis. Conversely, a several histopathological alterations were observed in the (STZ) group micrographs (B1 and B2). The general architecture seemed disrupted compared to normal pancreas, including necrosis and shrunken in the islets of Langerhans and reduced cellular density with some areas appearing pale pink staining which indicates β-cell damage, pyknotic nucleus and some vacuolation. Other parts were lysed and fibrous connective tissue were increased around islets and ducts. In addition, the exocrine parenchymal portion showed atrophy, degeneration and dissociation of the acinar tissue. These findings are consistent with earlier reports, where similar degenerative changes were noted following STZ-induced diabetes (Barakat et al., 2020; Indu et al., 2019). The images (C-G2) represent the pancreatic tissues of the rats after treatments with the aqueous and methanolic extracts of *A. halimus*, *S. mollis,* and the combination of the two plants. We observed a normal and intact tissues architecture without any signs of necrosis, inflammations or cell damage. Presence of a dense clusters of acinar cells with round and dark nuclei, and well-organized pancreatic islets (lighter areas) were visible in some groups. Interestingly, histological examination of pancreatic sections from STZ-induced diabetic rats treated with various plant extracts (AEA, MEA, AES, MES, and COMB) revealed varying degrees of morphological improvement compared to the untreated diabetic (STZ) group. Key regenerative

features included partial restoration of islet architecture in some groups, reduced necrotic areas, and decreased cytoplasmic vacuolation within the exocrine acini. However, certain regions still displayed persistent necrosis (pyknotic nuclei), vacuolated cells, and disrupted acinar organization (condensed purple stain), indicating incomplete tissue recovery within the two-week treatment period. Thickening of the interlobular connective tissue septa was evident in several treated groups as observed in: (STZ+AEA), (STZ+MEA), and (STZ+MES) groups, indicator of reparative fibrosis, a common response to persistent injury and inflammation in the pancreas. These findings are consistent with previous reports on plant-derived antioxidants, such as *Panax ginseng* and *Salvia officinalis*, which have demonstrated β-cell protective and regenerative effects, attenuation of OS, and partial reversal of STZ-induced pancreatic damage (Ashkani-Esfahani et al., 2021; Yin et al., 2024). While none of the extracts fully reinstated normal histological architecture of the pancreas, the observed regeneration of islet boundaries in (STZ+AES) and (STZ+COMB) groups may reflect partial recovery of β-cells mass or enhanced functional capacity of residual β-cells and possibly improved insulin secretory activity, which align well with the notable hypoglycemic and antioxidant effect observed previously of those extracts, supporting the idea that the plant's beneficial effect may be through enhancing insulin synthesis and secretion. Similar outcomes were reported using the Watermelon peels (20%) as a treatment to STZ induced diabetic rats (Rezq, 2017). The protective mechanisms of many extracts are thought to involve scavenging of ROS, modulation of inflammatory signaling pathways, and promotion of β-cell proliferation or neogenesis (Simeone et al., 2006; Nugent et al., 2008).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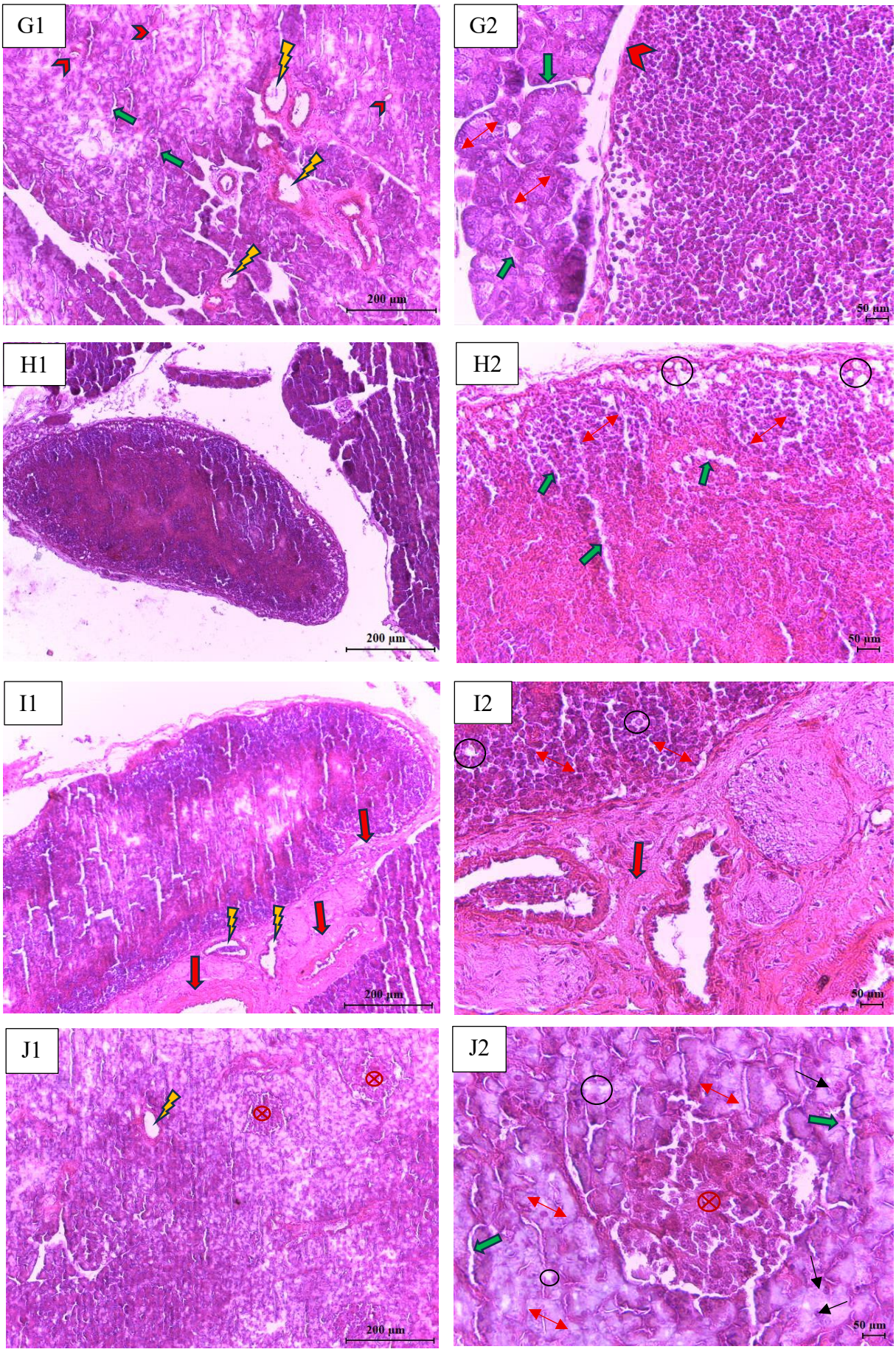
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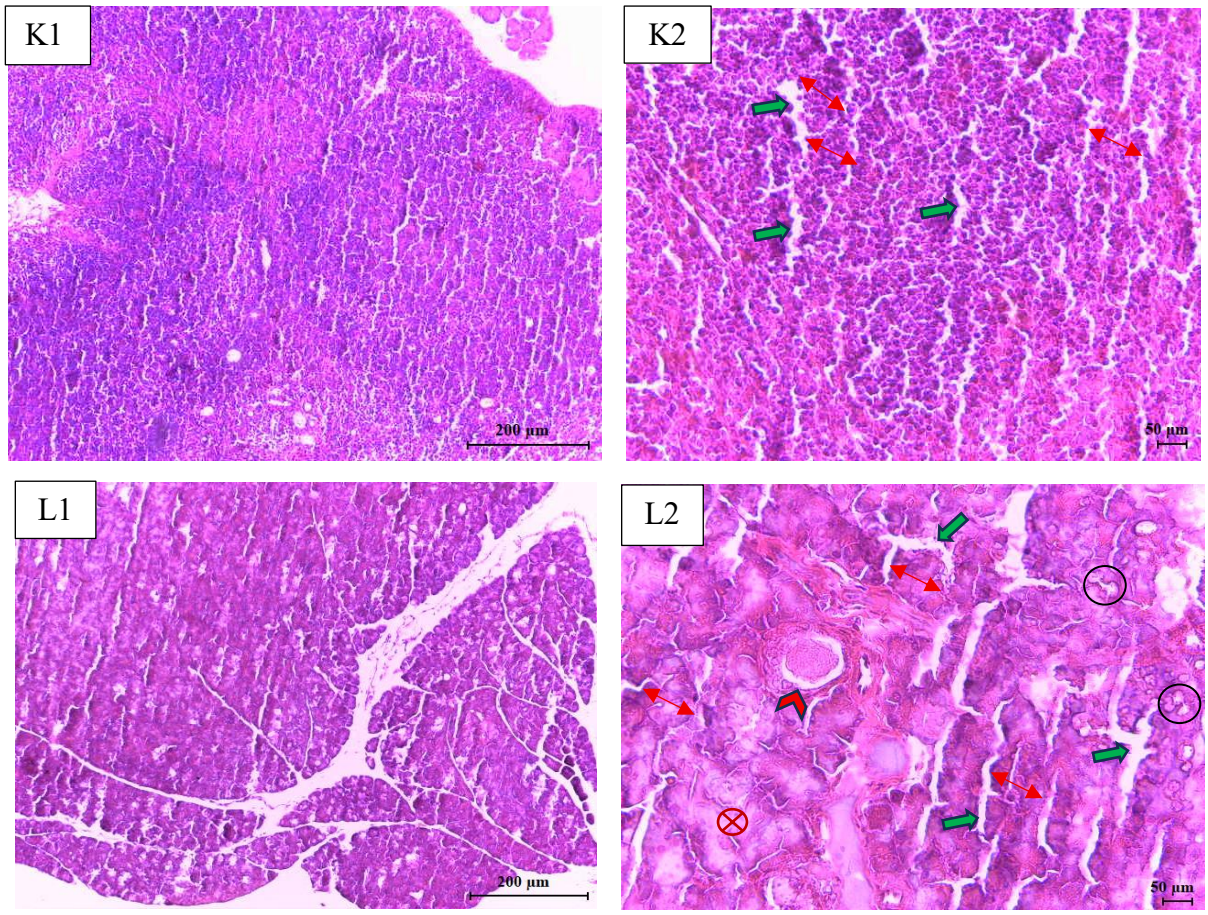


Figure 36. Photomicrographs (A1–L2) demonstrates the histological sections of the pancreas tissues from different groups stained by H&E [Magnification 10X and 40X]. (A1 and A2): Sections of pancreas from (C) group showing normal pancreatic structure. (B1 and B2): (STZ) group shows altered pancreatic architecture, (C): Group (AEA), (D): Group (MEA), (E): Group (AES), (F): Group (MES), (G1 and G2): Group (COMB), (H1 and H2): Group (STZ+AEA), (I1 and I2): Group (STZ+MEA), (J1 and J2): Group (STZ+AES), (K1 and K2): Group (STZ+ MES), (L1 and L2): Group (STZ+COMB).

Signs signification:

(⊗): Islet of Langerhans.
(➡): Normal intralobular septa.
(○): Vacuolation.
(➡): Intralobular duct.
(↔): Cluster of acini (group of acinar cells).
(→): Pyknotic nuclei.
(⚡): Interlobular duct.
(➡): Fibrosis (fibrous connective tissue).

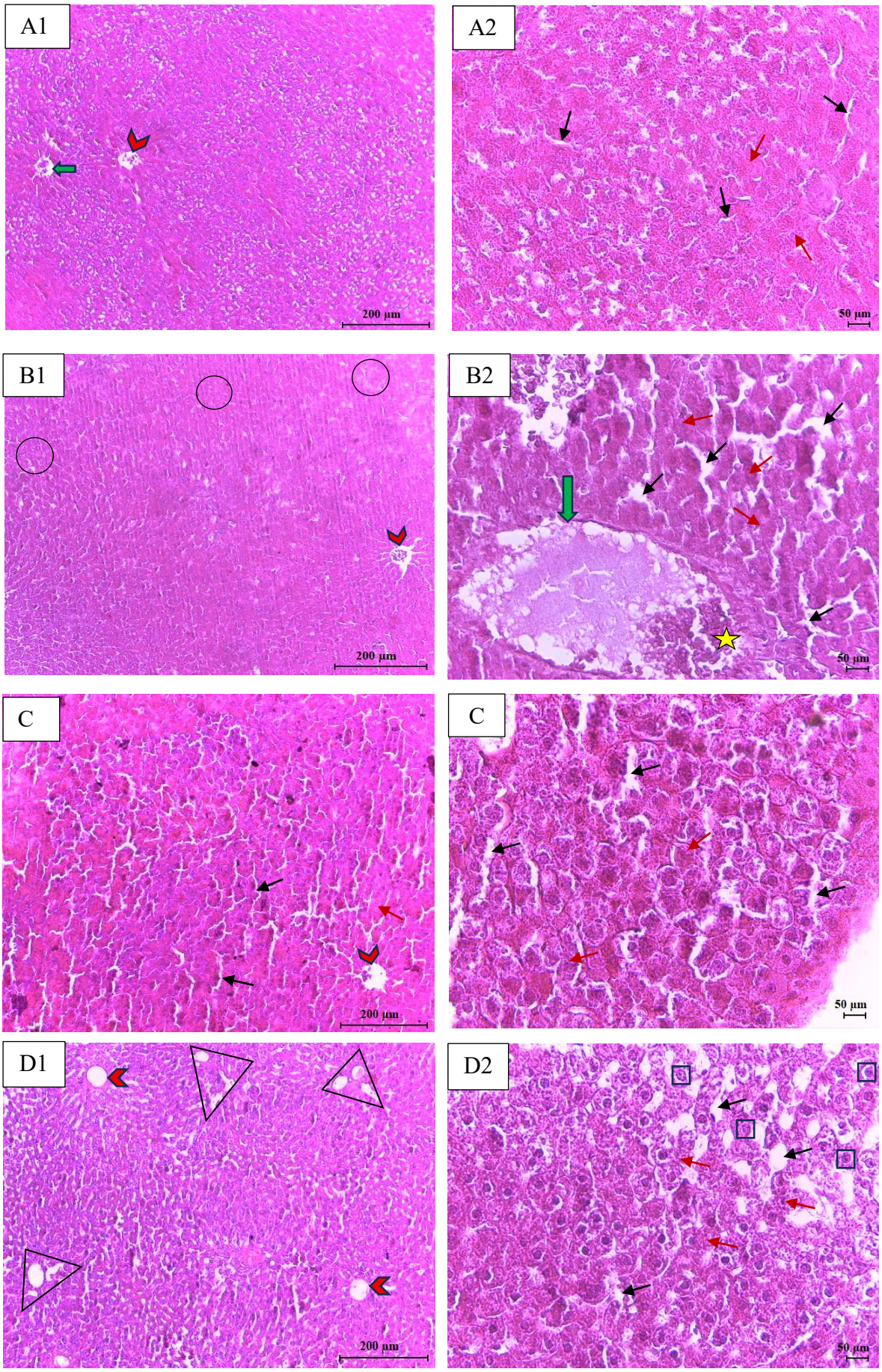
5.7.2. Liver histology

The liver is a key organ in maintaining glucose homeostasis, as it regulates essential metabolic pathways such as glycogenesis, glycogenolysis, glycolysis, and gluconeogenesis. Histopathological micrographs of the liver from different groups are shown in (Fig. 37). Histological examination of liver sections revealed distinct differences between the experimental groups. In the (C) group, hepatic lobular architecture appeared normal, with well-organized central veins surrounded by radially arranged hepatocyte cords. Hepatocytes exhibited polygonal morphology with eosinophilic cytoplasm and centrally located round nuclei, while sinusoids were regularly distributed and patent. No signs of necrosis, vacuolization, or inflammatory infiltration were detected. The STZ-induced diabetic group exhibited severe histopathological alterations. Hepatic lobular disorganization was evident, with marked sinusoidal dilation, vascular congestion, and areas of hepatocellular degeneration. Hepatocytes displayed cytoplasmic vacuolization and irregular nuclear morphology, while focal necrotic patches and inflammatory cell infiltration were observed. These findings reflect significant hepatic injury associated with STZ-induced diabetes which aligns with several other reports (Zafar et al., 2009; Al-Jaghthmi and Zeid, 2020). Liver injury observed in diabetic conditions is closely linked to OS generated by persistent hyperglycemia. Excess glucose promotes ROS production, which disrupts carbohydrate, protein, and lipid metabolism and triggers inflammatory responses (Yazdi et al., 2019). These events cause vascular congestion and sinusoidal endothelial damage, ultimately leading to sinusoidal obstruction and interlobular vessel dilation (Alsharif et al., 2023). These histopathological alterations in liver sections are consistent with the elevated ASAT and ALAT activities, and correlate closely with the disturbances in hepatic OS markers observed in the (STZ) group. Treatment with *A. halimus* extracts in (STZ+AEA) and (STZ+MEA) groups resulted in partial recover against STZ-induced hepatic damage. In both groups, lobular architecture was better preserved compared

to the (STZ) group, with reduced sinusoidal congestion and fewer necrotic areas. Nevertheless, mild cytoplasmic vacuolization in hepatocytes, severe vascular dilation and fibrous tracts were still evident in some portal areas of the liver from (STZ+AEA) group. In (STZ+MEA) group, we observed injured bile duct which looks unclear with lack of normal cuboidal epithelial lining indicating a persisted damage in portal area. Presence of binucleated cells and disorganization in hepatocytes cords. Similar patterns have been reported in previous studies, where some therapies conferred partial hepatoprotection against STZ-induced damage but failed to fully normalize biochemical markers or restore hepatic architecture (Eluehike et al., 1970; Indu et al., 2019). This suggests that *A. halimus* extracts mitigate OS and structural alterations, though their hepatoprotective effects remain moderate or may require prolonged treatment period for complete recovery. On the other hand, the aqueous and methanolic extracts of *S. mollis* improved liver morphology in (STZ+AES) and (STZ+MES) groups relative to the (STZ) group. Hepatic lobules were more distinct and the overall tissue integrity was better preserved. The portal triads were relatively well defined in the (STZ+AES) group, the bile ducts and hepatic arteries were clearly identifiable. Hepatocytes surrounding the portal areas showed reduced vacuolar degeneration compared to the (STZ) group. Although mild vascular congestion persisted around the portal vein, and the surrounding parenchyma maintained a more preserved lobular organization with less extensive necrosis. Sinusoids appeared moderately dilated but not severely disrupted, suggesting partial recovery of vascular architecture under aqueous extract treatment. In the (STZ+MES) group, lobular organization was notably improved, with clearer delineation of hepatic cords radiating from central veins toward portal areas. Compared to the (STZ) group, The portal area showed bile ducts and vessels with reduced fibrous expansion. Hepatocytes retained better cytoplasmic staining, though some cells displayed mild vacuolization and nuclear alterations. Inflammatory infiltration was still present, but overall parenchymal preservation was greater than in (STZ)

group and slightly superior to the (STZ+AES) group, indicating a stronger hepatoprotective effect of the methanolic extract. These results may be attributed to the high levels of phenolic and flavonoid compounds in the MES, as indicated previously in phytochemical and FTIR analysis. Many studies reported that administering plants extracts rich in polyphenols to STZ-induced diabetic rats can restore liver enzymes levels, reduce markers of apoptosis, and improve liver histology (Sheweita et al., 2016; Barakat et al., 2020). Flavonoids enhance cell survival pathways, promote hepatocyte proliferation, and support pancreatic β-cell function, thereby improving insulin secretion and reducing fasting blood glucose level (Al-Khayri et al., 2022). Polyphenols contribute additional antioxidant protection by reducing OS and LPO (Krawczyk et al., 2023), which collectively help maintain hepatic and pancreatic integrity under diabetic conditions. Remarkably in the (STZ+COMB) group, liver histology was almost completely restored to normal. Hepatic lobular organization was clearly maintained, central veins and hepatocyte cords were intact, and sinusoids were regularly distributed without marked dilation. Hepatocytes appeared polygonal with eosinophilic cytoplasm and centrally located nuclei, with occasional binucleated cells reflecting active regeneration. Only minimal vacuolization was noted, and no inflammatory infiltration was present. The synergy between *A. halimus* and *S. mollis* may reflect complementary antioxidant, anti-inflammatory, and cytoprotective mechanisms that counteract hyperglycemia-induced hepatic stress. This superior efficacy of the combined treatment highlights a synergistic interaction that may offer greater therapeutic benefit than individual extracts. These observations align with the biochemical data showing improved liver enzyme profiles (reduced ALAT and ASAT), thereby confirming the consistency between structural and functional recovery of the liver in (STZ+COMB) group. In non-diabetic rats treated with extracts (AEA, MEA, AES, MES, and COMB), hepatic architecture remained intact and comparable to the (C) group. Hepatocytes preserved their morphology with no necrotic or inflammatory changes. While the other extracts

showed completely normal histological features, only the MEA and MES groups exhibited mild cytoplasmic vacuolization and binucleated cells, reflecting increased cell activity for regular cell regeneration. These findings confirm the hepatic safety of both individual and combined plant extracts in normal rats.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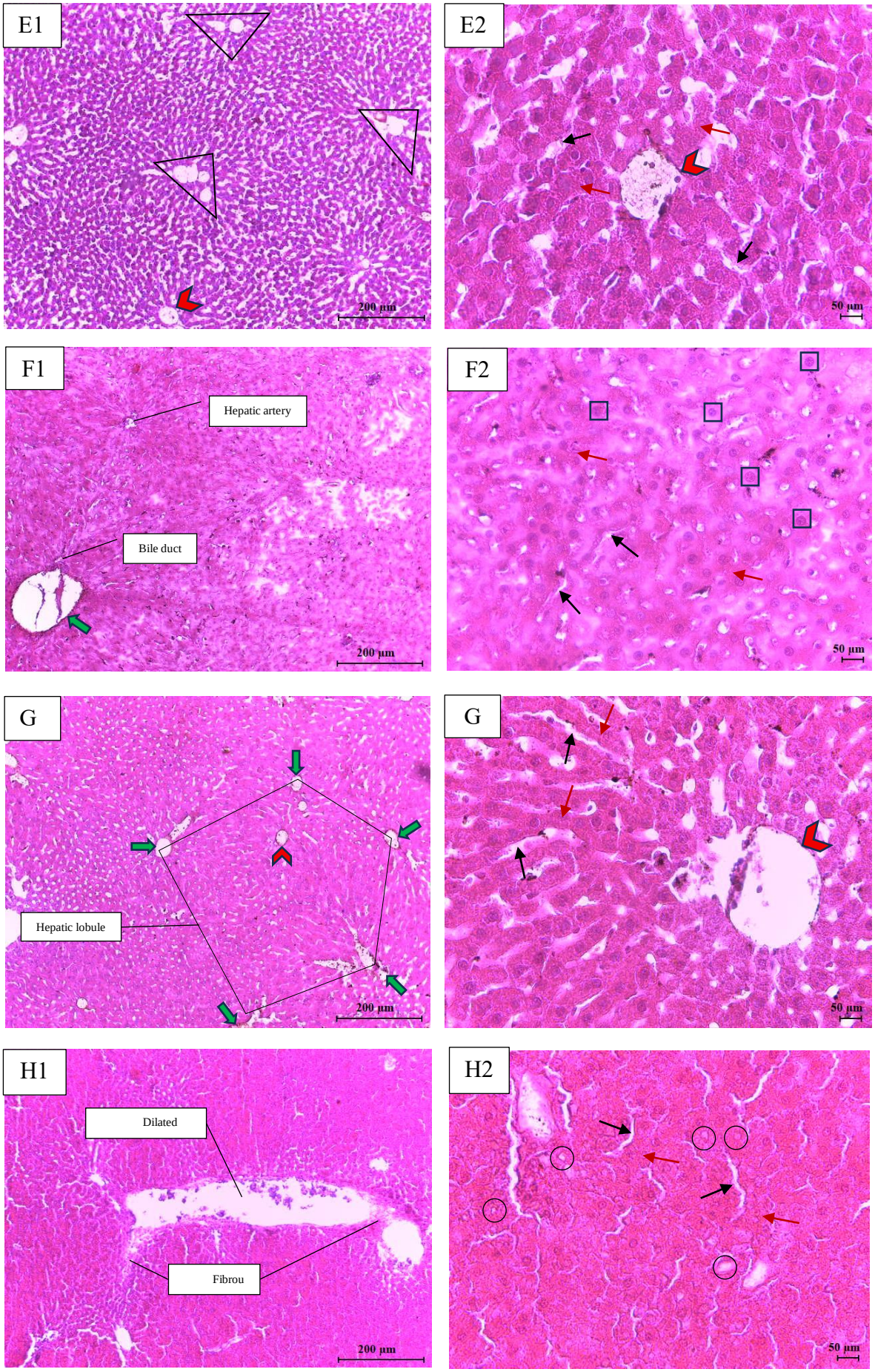
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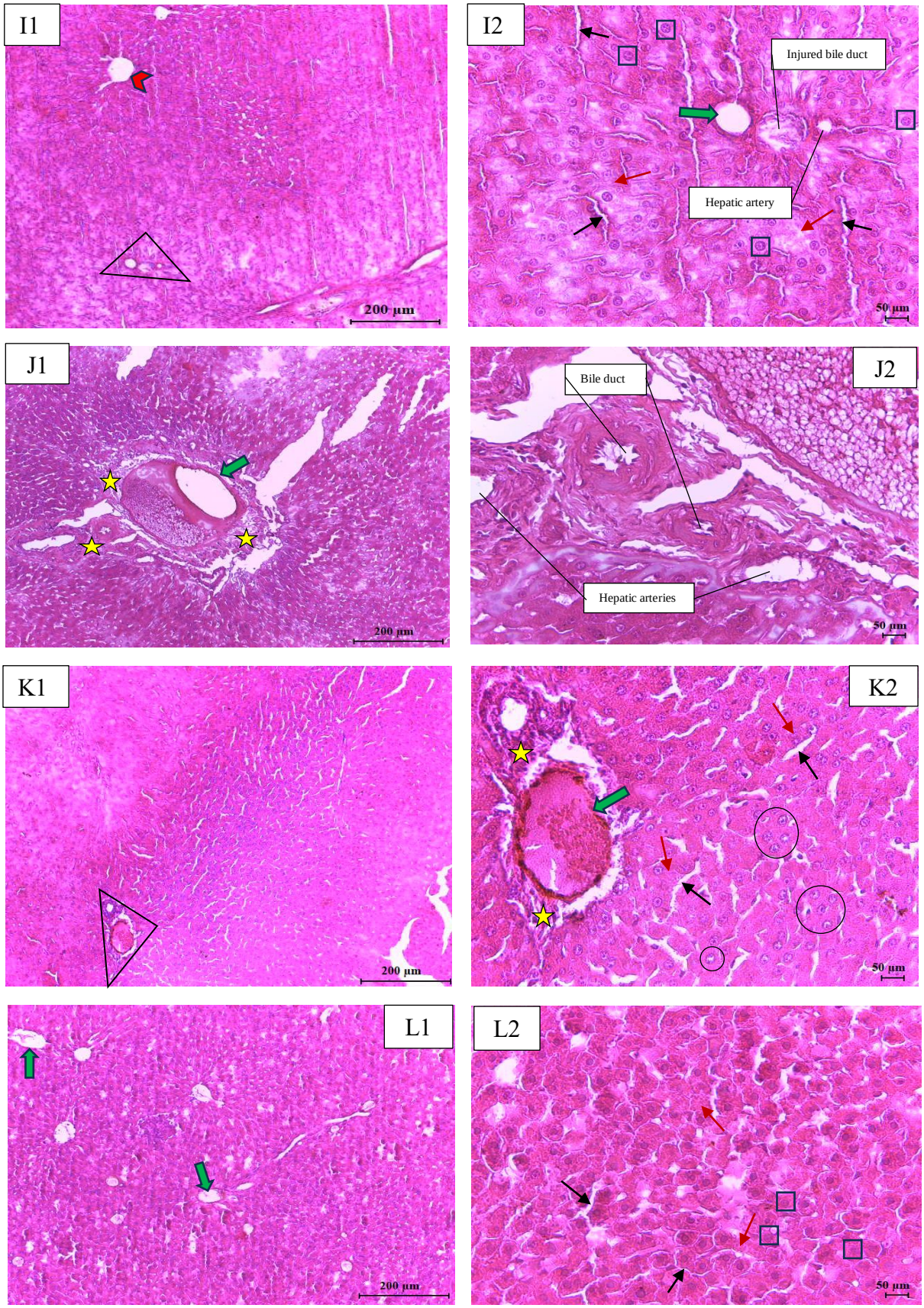


Figure 37. Photomicrographs (A1–L2) demonstrates the histological sections of the liver tissues from different groups stained by H&E [Magnification 10X and 40X].

(A1 and A2): Sections of liver from (C) group, (B1 and B2): Diabetic group (STZ), (C1 and C2): Group (AEA), (D1 and D2): Group (MEA). (E1 and E2): Group (AES), (F1 and F2): Group (MES), (G1 and G2): Group (COMB), (H1 and H2): Group (STZ+AEA), (I1 and I2): Group (STZ+MEA), (J1 and J2): Group (STZ+AES), (K1 and K2): Group (STZ+ MES), (L1 and L2): Group (STZ+COMB).

Signs signification:

(□): Binucleated hepatocytes.
(➡): Portal vein.
(◯): Vacuolization in cells.
(➡): Central vein.
(➡): Hepatocytes cords.
(➡): Sinusoids.
(☆): Periportal fibrosis infiltrated with inflammatory cells.
(△): Portal triad area.

5.7.3. Kidney histology

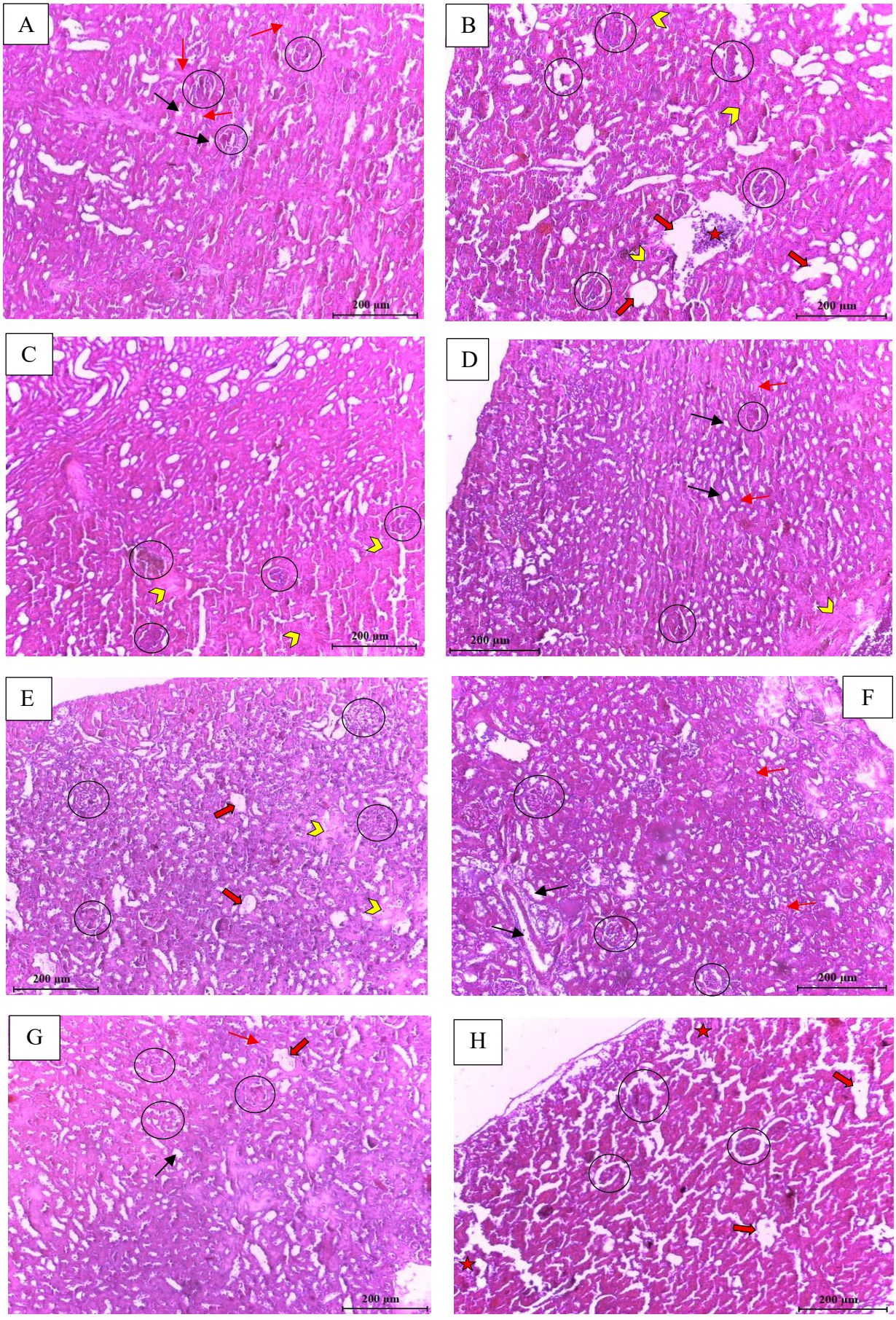
The kidney plays a central role in diabetes, not only by regulating glucose reabsorption and excretion but also as a vulnerable site to hyperglycemia-induced OS and inflammation, which promote tissue damage and impair renal function. Histological analysis of kidney tissues of experimental groups is shown in (Fig. 38). In the (C) group, renal morphology appeared normal, the glomerulus shape was preserved with well-defined capillary lumen, clear Bowman's spaces, and intact tubular structures, while no congestion, necrosis, or inflammatory infiltration was noted. In contrast, kidneys from the (STZ) group showed severe pathological changes characterized by shrunken and distorted glomeruli with widened Bowman's spaces in some areas, while in other areas we observed an expansion of mesangium and thickening inside the glomerulus. Tubular epithelial was dilated, with interstitial edema, vascular congestion, and focal inflammatory infiltration, reflecting classical features of diabetic nephropathy induced by STZ. Previous works reported similar signs of altered kidney function and tissue integrity in STZ-induced diabetic rats, which are commonly associated with persistent hyperglycemia, OS, and inflammation leading to glomerular and tubular damage (Barakat et al., 2020; Fagbohun et al., 2020; Akoul, 2024).

In normal rats treated with AEA produced mild histological changes compared to (C), including tubular dilation, and vascular congestion, with some glomeruli appearing less compact and presence of small collagen deposits. Whereas the MEA maintained nearly normal architecture with intact glomeruli and tubules, indicating its better renal safety. A similar trend was observed with AES caused focal tubular dilation, mild epithelial degeneration, and slight congestion, whereas the MES preserved kidney structure with minimal changes.

Interestingly, these microscopic findings contrasted with the biochemical data, since creatinine levels were markedly elevated in (AEA) and (AES) groups, even exceeding those observed in the (STZ) group. The rise in creatinine level observed with aqueous extracts, despite the preserved renal architecture, is likely due to their high mineral and salt content (as we suggested previously in the biochemical findings), which may disrupt fluid and electrolyte balance, or to certain phytoconstituents capable of inducing osmotic stress on renal tubules, thereby elevating creatinine levels in the absence of true kidney damage. Several studies support this interpretation, as aqueous fractions of halophytes, while rich in polyphenols, often contain high levels of inorganic salts, oxalates, or saponins that may exert negative effects and cause serious health issues (Chaiyarit and Thongboonkerd, 2020; Ullah et al., 2024).

The combination of both extracts in healthy rats (COMB) showed no significant histological alterations. In the (STZ+AEA) group, treatment led to partial improvement, with some preserved glomeruli and reduced congestion, but persistent tubular dilation and epithelial degeneration, which contrasted with the biochemical data since creatinine remained elevated. Similarly, the treatment in (STZ+AES) group produced limited recovery, as glomeruli were only partially preserved and tubular dilation and congestion persisted, again consistent with high creatinine levels. On the other hand, the methanolic extract in (STZ+MEA) group provided better amelioration of kidney tissues, restoring glomerular and tubular architecture close to normal with only mild interstitial fibrosis, consistent with improved biochemical

markers. In (STZ+MES), however, the MES demonstrated strong nephroprotection, with well-preserved glomeruli, near-normal Bowman's spaces, and minimal vascular changes, restoring the kidney structure almost completely. These findings are in line with previous researches on ethanolic extracts of *Artemisia annua* and *Artemisia turanica*, which were reported to improve renal biochemical parameters and mitigate diabetes-induced structural damage in renal tissue (Yazdi et al., 2019; Akoul, 2024). Finally, the combination treatment in diabetic rats (STZ+COMB) resulted in nearly normal renal morphology, with intact glomeruli and tubules and minimal signs of congestion, closely resembling the (C) group. Taken together, these observations with the biochemical results confirmed that methanolic extracts of both plants, and particularly MES and COMB, exerted the most pronounced nephroprotective effects against STZ-induced renal damage, while aqueous extracts induced morphological and biochemical disturbances in renal function.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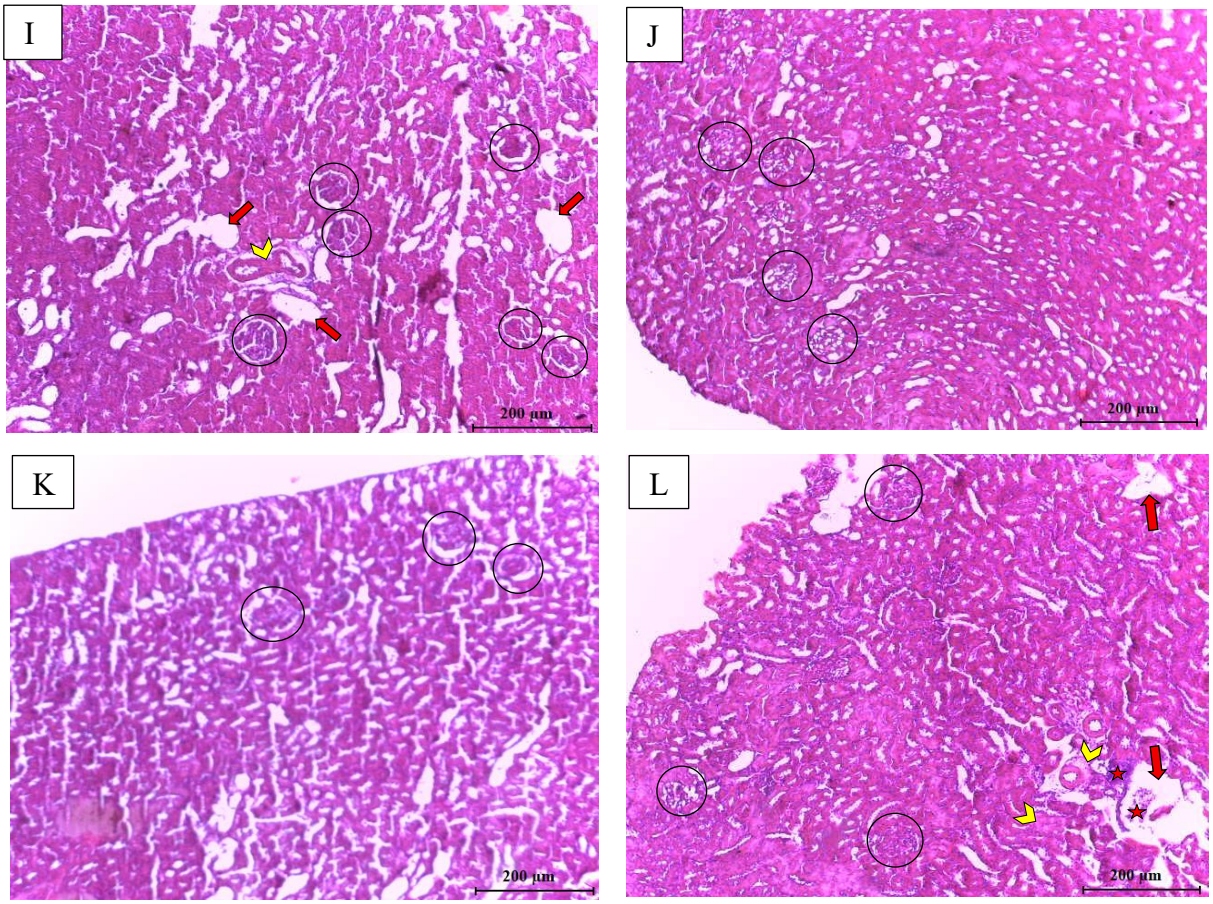

Figure 38. Photomicrographs (A–L) demonstrates the histological sections of the kidney tissues from different groups stained by H&E [Magnification 10X and 40X].
(A): Section of the kidney from (C) group. (B): Diabetic group (STZ). (C): Group (AEA). (D): Group (MEA). (E): Group (AES), (F): Group (MES), (G): Group (COMB), (H): Group (STZ+AEA), (I): Group (STZ+MEA), (J): Group (STZ+AES), (K): Group (STZ+ MES), (L): Group (STZ+COMB).

Signs signification:

(◯): Glomerulus.
(→): Distal convoluted tubule.
(→): Proximal convoluted tubule.
(➡): Renal tubular dilation.
(≫): Fibrosis.
(★): Cells infiltration or inflammation.

General discussion

The comprehensive evaluation of *A. halimus* and *S. mollis* extracts successfully established the phytochemical basis, *in-vitro* antioxidant potential, and *in-vivo* therapeutic efficacy of both plants in managing STZ-induced diabetes and its associated complications arising from hyperglycemia and OS. A clear correlation emerged between the specific chemical profile of each extract and its biological activity, highlighting the critical influence of solvent polarity and demonstrating a notable synergistic effect when the plants were combined.

The FTIR analysis provided the foundational evidence for the observed biological activities, confirming the widespread presence of functional groups associated with bioactive compounds, including hydroxyls, aromatics, and C-O stretching, indicative of polyphenols, flavonoids, and terpenoids. Critically, the methanolic extracts (MEA and MES) exhibited a richer chemical diversity than their aqueous counterparts (AEA and AES). The choice of extraction solvent significantly impacted the yield and composition, which in turn governed antioxidant capacity. Methanol proved to be the superior solvent for extracting total phenolic compounds and flavonoid from *S. mollis*, resulting in MES having the highest TPC (70.24 mg GAE/g DW) and TFC (96.90 mg QE/g DW). The high TFC in *S. mollis* extracts (AES and MES) directly translated to their superior radical scavenging power in the DPPH assay, reinforcing the role of flavonoids as key free-radical scavengers. Conversely, the AEA extract, despite moderate TPC/TFC and weaker performance in the DPPH and FRAP assays, showed the highest TAC (20.09 mg AAE/g DW). This suggests that aqueous extraction yields a unique profile of hydrophilic antioxidants (such as polysaccharides or glycosides) that contribute significantly to the overall capacity but are less active in single-electron transfer assays.

In parallel with the *in-vitro* findings, the results were directly reflected in the *in-vivo* antidiabetic and organ-protective outcomes. Regarding glycemic control, the extracts from *S. mollis* (MES, AES) and COMB were highly effective in achieving a rapid and significant

reduction in blood glucose, reaching near-normalized levels by Day 15. This potent hypoglycemic effect is attributed to the high concentration of bioactive compounds, including polyphenols, flavonoids, and potentially essential minerals, capable of stimulating insulin secretion or enhancing glucose utilization. Body weight results further supported the metabolic recovery, demonstrating that AES was the only extract that achieved weight gain (+14.0 g) in diabetic rats, suggesting a strong anti-catabolic and anabolic effect alongside its glycemic control. Conversely, the minimal hypoglycemic effect of AEA correlated with a severe inability to mitigate diabetic cachexia, resulting in the most pronounced weight loss (-48.2 g).

The efficacy of the extracts in controlling hyperglycemia and preventing its complications is fundamentally rooted in their capacity to restore the body's redox balance. Across all examined organs, the OS profile revealed a coordinated restoration of redox balance that reflects the global metabolic improvements induced by the extracts. The modulation of OS markers varied by tissue, reflecting specific protective strategies exerted in the pancreas, liver, and kidneys. In the pancreas, the most bioactive treatments (MES, AES, and COMB) acted to stabilize the acute oxidative response, lowering the reliance on endogenous enzymes such as GSH-Px and SOD and supporting the recovery of β-cell function. Critically, the pronounced rise in pancreatic MDA observed in these strong hypoglycemic groups warrants a nuanced interpretation: it suggests a potential transient adaptive signal to upregulate key genes like GLUT2 and PDX1, thereby enhancing insulin-secretion pathways rather than indicating persistent oxidative damage. In the liver, the aqueous and methanolic extracts of *A. halimus* (AEA and MEA) were particularly effective in reducing lipid peroxidation (LPO) and replenishing GSH stores. MEA and COMB further strengthened enzymatic detoxification. This systemic reduction of hepatic OS markers provided the mechanistic basis for the observed hepatoprotection and successful mitigation of STZ-induced hypertrophy (elevated LRW) and near-complete restoration of the hepatic architecture, especially in the MES and COMB groups.

Finally, in the kidneys, the strongest protection was provided by MES, AES and COMB, which markedly reduced renal LPO (MDA) and increased GSH levels. This strong correlation with the OS profile underscored their effectiveness in preventing the structural deterioration (KRW) typical of diabetic nephropathy, leading to near-normal renal histology.

Taken together, these results indicate that the extracts do not exert a uniform antioxidant effect; rather, they restore redox homeostasis through a complementary blend of mechanisms: direct radical scavenging (notably by MES), enhanced detoxification (by MEA and COMB), and controlled oxidative signaling (by MES, AES, and COMB). The COMB treatment consistently offered the most comprehensive systemic recovery, often surpassing the efficacy of the best single extract (MES). Its ability to simultaneously decrease OS enzyme reliance in the pancreas, increase GSH reserves in the liver and kidney, and significantly reduce MDA in the kidneys highlights a powerful synergistic effect. This synergy, where the rapid glycemic control and potent radical scavenging of *S. mollis* are complemented by the high TAC and broader spectrum of components from *A. halimus*, provides a definitive mechanistic basis for the complete metabolic and structural protection observed in the target organs.

CONCLUSION

Interest in halophyte plants has grown considerably in recent years due to their richness in bioactive metabolites and their potential as natural alternatives for managing chronic metabolic disorders. The present study was undertaken to investigate the phytochemical profile and therapeutic potential of *A. halimus* and *S. mollis* extracts, individually and combined, in STZ-induced diabetic rats.

Phytochemical characterization revealed clear differences between aqueous and methanolic fractions. FTIR spectra indicated the presence of multiple functional groups present in phenolic, flavonoid, and other bioactive compounds. Extraction yields were generally higher for aqueous fractions, whereas methanolic extracts displayed a greater diversity of identifiable peaks, suggesting a richer phytochemical composition. Consistently, methanolic extracts exhibited superior total phenolic and flavonoid contents, as well as higher antioxidant potential. These features provide a strong chemical basis for the observed biological activities.

Biological investigations confirmed that STZ-induced diabetes produced severe hyperglycemia, weight loss, organ hypertrophy, OS, and tissue injury in the pancreas, liver, and kidneys. Among treatments, *S. mollis* extracts and COMB significantly reduced blood glucose, counteracted diabetic cachexia, and supported weight recovery. In contrast, *A. halimus* extracts showed limited hypoglycemic effect, with the aqueous fraction associated with further body weight decline. Biochemical markers supported these findings: *S. mollis* and COMB attenuated hepatic hypertrophy and reduced transaminase leakage (ALAT, ASAT), indicating hepatoprotective activity. Whereas, *A. halimus* extracts failed to provide similar protection. Renal function tests revealed that MES and COMB normalized creatinine and uric acid levels, while aqueous extracts of both plants increased creatinine in normal and diabetic rats. Protein

profile analysis showed that although total protein remained unchanged, albumin levels were significantly restored, pointing to improved protein metabolism under treatment with the extracts.

Hematological analysis further demonstrated that STZ-induced diabetes suppressed WBC and LY while elevating MO and RBC. *A. halimus* extracts aggravated these alterations, whereas *S. mollis*, particularly MES, restored WBC, RBC, HGB, and PLT counts. The combined extract also exerted a synergistic effect, highlighting enhanced immune and erythropoietic regulation.

Oxidative stress markers revealed organ-specific modulation. STZ increased hepatic LPO, while extracts showed differential antioxidant effects: AEA and MEA reduced liver MDA, indicating some protective capacity. COMB treatment markedly improved renal oxidative balance, whereas MES showed paradoxical pro-oxidant effects in kidneys. Glutathione levels and antioxidant enzyme responses (GSH-Px, SOD, CAT) reflected compensatory adaptations, with MEA and COMB providing the most consistent renal protection, and AEA/MEA contributing to pancreatic redox stabilization.

Histopathological evaluations corroborated biochemical findings. AES and COMB partially preserved pancreatic islet morphology, while COMB achieved near-complete hepatic recovery, with MES and AES also offered substantial protection. In the kidneys, MES and COMB were particularly effective in maintaining glomerular and tubular architecture.

Overall, these findings demonstrate that *S. mollis*, particularly its methanolic extract, and COMB exerted potent antidiabetic, antioxidant, hepatoprotective, and nephroprotective effects. In contrast, *A. halimus* showed weaker efficacy, with its aqueous extract potentially associated with adverse hepatic and renal effects.

Future perspectives

Future research should aim to:

- Isolate and identify the active phytoconstituents responsible for the observed effects, particularly in *S. mollis* methanolic extract. Advanced techniques such as HPLC, LC-MS/MS, and NMR can help to characterize the major antioxidant and antidiabetic constituents.
- Although the plant extracts showed no signs of acute toxicity in this study, chronic toxicity assessments and dose optimization are essential for evaluating their long-term safety profiles.
- Measuring HbA1c: to assess long-term glycemic control beyond fasting glucose levels.
- Evaluating insulin resistance (HOMA-IR index): to determine the effect of treatments on insulin sensitivity and β-cell function.
- Analyzing immunological markers (anti-insulin antibodies and interleukins): to explore the inflammatory and immunometabolic pathways involved in diabetes and its modulation by plant extracts.
- Integrating molecular or histochemical approaches: to confirm the protective mechanisms at the cellular and tissue levels.

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Hypoglycemic and antioxidant effects of the aqueous extract of *Suaeda mollis (Desf.) Delile* in Streptozotocin-induced diabetic rats.

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Abstract

Diabetes is a metabolic disorder marked by chronic hyperglycemia and oxidative stress, leading to severe health complications. In search of alternative treatments, researchers are investigating medicinal plants with unstudied therapeutic potential, *Suaeda mollis* is one such plant that remains insufficiently explored. This study aimed to assess the antidiabetic and antioxidant properties of its aqueous leaf extract (AES) in both healthy and streptozotocin-induced diabetic rats. The study used the Fourier Transform Infrared Spectroscopy analysis (FTIR) to identify functional groups of phytochemicals, quantified polyphenols and flavonoids, and assessed antioxidant activity via DPPH, FRAP, and TAC assays. The hypoglycemic effect of AES was tested in STZ-induced diabetic Wistar rats over two weeks. Serum biochemical and hematological parameters were measured, and oxidative stress markers (MDA, SOD, CAT, GSH, GPx) in pancreatic homogenates and pancreatic histopathology changes were evaluated. FTIR analysis identified five functional groups in AES, which also exhibited high polyphenol and flavonoid contents and strong antioxidant activity. The extract significantly reduced blood glucose and enhanced antioxidant defenses in diabetic rats. However, it increased serum creatinine and pancreatic MDA levels. Histopathological analysis showed partial restoration of pancreatic islet structure. *Suaeda mollis* shows promising antidiabetic and antioxidant effects, but further research is needed to confirm its safety as a therapeutic agent.

Keywords: Antidiabetic- Antioxidants- FTIR- Oxidative stress- STZ- induced diabetes- *Suaeda mollis*.

Introduction

Diabetes mellitus (DM) is a devastating chronic and metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin or its action, which can lead to severe complications including cardiovascular disease, neuropathy, and nephropathy (Reddy, 2018).

Findings from the International Diabetes Federation 10th edition (IDF) confirmed that diabetes is one of the major health emergencies. It is estimated that 537 million people have diabetes, and this number is projected to reach 643 million by 2030 (IDF, 2021). As the global prevalence of diabetes continues to rise, there is an urgent need for effective therapeutic strategies that not only manage blood glucose levels but also mitigate the associated oxidative stress, a key factor in the progression of diabetic complications (Kooti et al., 2016). Oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses. In the context of diabetes, elevated blood glucose levels can exacerbate oxidative stress, causing cellular damage and accelerating the development of diabetic-related issues (Gerber and Rutter, 2017; Salazar-García and Corona, 2021). Antioxidant mechanisms, therefore, play a crucial role in neutralizing ROS and protecting against oxidative damage, making them a vital component in the management of diabetes (Bhatti et al., 2022). Nutritional antioxidant derived from dietary sources have gained significant attention due to their potential to improve antidiabetic therapy (Krawczyk et al., 2023). For centuries, there has been growing interest in the use of natural products, particularly plant-based therapies, for managing diabetes and its complications through antihyperglycemic, antioxidant and anti-inflammatory mechanisms (Wasana et al., 2021). Many plants, traditionally used in folk medicine, have been found to possess potent antidiabetic and antioxidant properties. These natural remedies offer a promising alternative to synthetic drugs, which often come with undesirable side effects (Alam et al., 2022). Antioxidant plants, especially halophytes, provide a renewable source of bioactive compounds for food, cosmetics, and medicinal applications (Ksouri et al., 2012). Recent research indicates that these plants have multiple biological impacts due to their high concentrations of secondary metabolites, including polyphenols, which have shown potential in reducing oxidative stress (Hymery et al., 2021). *Suaeda mollis (Desf.) Delile*, a halophytic plant belonging to the Amaranthaceae family grown throughout arid and semi-arid range lands of Mediterranean basin, is one such plant that has garnered attention for its medicinal properties (Nedjimi, 2018). Traditionally used in various cultures for its purported health benefits, *S. mollis* has been reported to exhibit anti-inflammatory, anticancer, and antioxidant activities (Oueslati et al., 2023). The antidiabetic and antioxidant effects of *S. mollis* have not been fully explored *in vivo*, particularly in the context of diabetes induced by Streptozotocin (STZ), a compound commonly used to induce experimental diabetes in animal models. The primary objectives of this study were to identify the functional groups of the

bioactive compounds found in the aqueous extract of *S. mollis* (AES), quantify the polyphenol and flavonoid contents, and assess the antioxidant potential of the extract. Additionally, this research aimed to investigate the hypoglycemic effects of AES on STZ-induced diabetic rats, analyze oxidative stress markers in pancreatic homogenate and examine the histological changes of the pancreas, which provides a comprehensive insight to the therapeutic benefits of the extract for managing diabetes and oxidative stress.

Material and methods

Chemicals and reagents

All chemical products used in this study were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).

Plant material

Suaeda mollis (Desf.) Delile was collected in the Djellal area (34.92° N, 6.89° E; Khenchela-Algeria) and identified by Dr. Boughediri Larbi from the Department of Biology at Badji Mokhtar University, Annaba-Algeria, basing on the descriptions provided by (Ozenda, 1991). Only the leaves of the plant were utilized, they were cleaned and air-dried at room temperature in a shaded area to prevent degradation of bioactive compounds. Once fully dried, the leaves were ground into a fine powder using an electric grinder. The prepared powder was stored in an airtight container at room temperature until further use.

Preparation of the aqueous extract

The aqueous extract was prepared by adding 10 g of plant powder to 100 mL of distilled water, and putted on magnetic stirring for 24 hours. The mixture was then filtered to separate the micelle from the marc using Whatman cellulose filter papers. The filtrate was evaporated in an oven to obtain the dried extract, which was stored at 4°C in the dark for future use. For *in vivo* experiments, the extract was freshly prepared daily, with a concentration of 200 mg of the dried extract per 1 kg of rat body weight (BW), dissolved in 1 mL of water.

In vitro study

Fourier transform infrared resonance analysis (FTIR)

Functional groups in AES were detected using (FTIR; Agilent Cary 630, USA spectrometer). The measurements were performed between 25°C and 27°C and recorded from 400 to 4000 cm^{-1} with a spectral resolution of 4 cm^{-1}. This technique was used to determine the functional groups of the bioactive chemicals present in the extract, which was separated by its peak's wavenumbers. FTIR

transmittance spectrum was designed via Origin 2019b 64 Bit version, in which the spectrum was reprocessed using a baseline correction and smoothing to reduce the noise.

Determination of the total phenols content (TPC)

The polyphenols are determined using Folin-Ciocalteu reagent, according to the technique described by (Agbor et al., 2014). The absorbance is measured at 765 nm, and the total amounts of phenols are expressed in milligram of gallic acid equivalent per gram of extract's dry weight (mg GAE/g DW) based on a gallic acid standard curve.

Determination of the total flavonoids content (TFC)

Flavonoids were determined using the aluminium chloride colorimetric method (Pourmorad et al., 2006). The measurement of absorbance was carried out at 415 nm, and the flavonoids content is expressed in milligrams of quercetin equivalent per gram of extract's dry weight (mg QE/g DW) based on a quercetin standard curve.

Assessment of antioxidant activities

The antioxidant potential of AES was evaluated using the following spectrophotometric methods:

The Radical scavenging evaluation

To evaluate the scavenging ability of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, the adopted approach was suggested by (Kabir et al., 2016). Quercetin has been used as a standard, and absorbance was measured at 517 nm. The result was shown as the amount of extract required to capture 50% of radicals (IC50 mg/mL).

The Ferric Reducing Antioxidant Power (FRAP) was measured using the technique described by (Yildirim et al., 2001). This method is based on the extract's ability to deliver an electron while converting ferric iron from ferric tripiridyl (Fe^{3+}) to a ferrous form (Fe^{2+}). When antioxidants are present in the extract, this reaction produces a detectible blue color at 700 nm. As a result, a high absorbance indicates that the extract possesses strong reducing potential. The result was presented as (EC50 µg/mL), which is the half-maximum effective concentration necessary to achieve a greater potency.

The Total antioxidant capacity (TAC)

The phosphomolybdenum assay is based on the reduction of molybdenum Mo (VI) present in the form of molybdate ions MoO_4^{2-} to molybdenum Mo (V) MoO^{2+} in the presence of the extract or an antioxidant agent. At an acidic medium, this reduction results in the creation of a greenish complex (phosphate/Mo (V)). The increase of this complex coloration in the presence of an

antioxidant is detected at 695 nm (Prieto et al., 1999). Ascorbic acid is used as a standard and the results obtained are expressed in milligram of ascorbic acid equivalent per gram of the extract's dry weight (mg AAE/g DW).

***In vivo* study**

Animals

Adult male Wistar rats, weighing 150 - 300g from Pasteur Institute in Algiers- Algeria were selected and housed under standard environmental conditions (24±1°C), with 12 h light and 12-h dark cycles. The rats had a free access to standard food pellets and water *ad libitum*. The Ethical Committee of the Directorate General for Scientific Research and Technological Development at Algerian Ministry PNR/SF 08/2012 approved all healthcare procedures.

Induction of experimental diabetes

Streptozotocin was injected intraperitoneal (IP) as a single dose of 60mg/kg to the rats after an overnight fasting. For this purpose, distilled water was used to dissolve STZ, the solution was freshly prepared to reach final concentration of 20 mg/mL just before use (Al-Hariri, 2012). After 1h, all the injected rats received glucose to avoid the hypoglycemic effect of STZ. After 3 days, only rats with a fasting glucose level of 2.5 g/l were selected for the group of diabetics.

Groups design

The study was conducted using 20 adult rats, which were divided into four groups, each containing five rats. The groups were formed based on the rats' body weight, ensuring that the animals in each group had similar weights:

Group 1 (Control group): Normal, healthy rats with no treatment, serving as the baseline for comparison.

Group 2 (STZ): The diabetic control, rats in this group were injected with STZ via a single IP dose (60mg/kg) to induce diabetes. The purpose of this group was to observe the influence of STZ on rats.

Group 3 (AES): Normal rats treated orally with (200 mg/kg) of AES, assessing the extract's effects on non-diabetic rats.

Group 4 (STZ+AES): Rats received STZ (60mg/kg) than treated orally with (200 mg/kg) of AES for two-weeks, evaluating the therapeutic effects of the extract on diabetes conditions.

The body weight of rats (BW) was recorded and blood glucose levels were measured by a reflective glucometer (Vital-Check, MM1200) in the 1^{st}, 3^{rd}, 5^{th}, 10^{th} and 15^{th} days of the experiment.

Blood collection

After two-weeks of the experiment, rats were fasted an overnight before being sacrificed by cervical decapitation to avoid animal stress, and the total blood was separated into tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant, and tubes without EDTA. The tubes with EDTA were utilized for hematological analysis (counts of the White Blood Cells (WBC), Lymphocytes (LY), Monocytes (MO), Granulocytes (GR), Red Blood Cells (RBC), Hemoglobin (Hb), and Platelets (PLT), which were measured using an automated cell counter (ERMA INC-PCE 210; Japan). The tubes without anticoagulant were centrifuged at 3000 rpm for 15 minutes at 4°C. The resulting serum was then stored in the Eppendorf tubes at -20°C for biochemical analysis (the serum levels of creatinine, uric acid, albumin, total proteins, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT), were estimated using an automated biochemical analyzer (VITROS® 5600 Integrated System, Quidel Ortho Corporation; USA).

Histology

Animals were dissected, the pancreas was quickly removed, carefully cleaned from fat, and weighted before being preserved in 10% formaldehyde. Pancreatic samples were rinsed, dehydrated with an increasing concentration of ethanol (70%, 95%, and 100%), and cleared in cyclohexane. After 12 h of paraffin impregnation in an incubator at 60C°, samples were then embedded in paraffin blocks. Subsequently, the blocks were sliced using a (Leitz 1512) rotary microtome (Marshall Scientific, Hampton, NH 03842, USA). After dewaxing and rehydration, the sections were stained with hematoxylin and eosin (Hould, 1984). The resulting slides were then observed under a light microscope (Leica Microsystems, DM 1000 LED) and the digital camera (Leica ICC50 HD) was used to take micro-photographs for histopathology study.

Determination of oxidative stress biomarkers

In order to prepare the pancreatic homogenate, the fresh pancreas samples were homogenized at a rate of 1:2 w/v in a Tris-Buffered Saline (TBS): 50 mm Tris, 150 mm NaCl, pH 7.4, and centrifuged (9000xg/15 minutes/4°C). The obtained supernatant was conserved at -20°C for the assessment of oxidative stress markers.

The glutathione (GSH): The assay was performed following the method developed by (Weckbecker and Cory, 1988). It is based on measuring the optical absorbance at 412 nm of the 2-nitro-5-mercapturic acid resulting from the reduction of 5,5-dithio-bis-2-nitrobenzoic acid (DTNB) by the (-SH) groups of glutathione.

The glutathione peroxidase (GPx): The enzymatic activity of GPx was assessed using the method of (Flohé and Günzler, 1984), which relies on the reduction of hydrogen peroxide (H_2O_2) in the presence of GSH. Optical densities were measured at 412 nm.

The superoxide dismutase (SOD): This assay was assessed using the nitro blue tetrazolium (NBT) method relies on the photo-reduction of the riboflavin/methionine complex, which generates superoxide anions (O^{2-}) (Beyer and Fridovich, 1987). The oxidation of NBT by O^{2-} is employed for detecting the presence of SOD. In an aerobic environment, the combination of riboflavin, methionine, and NBT results in a bluish coloration. The presence of SOD hinders the oxidation of NBT. The absorbances of the samples are measured at 560 nm.

The malondialdehyde (MDA): This assay was performed using the method of (Esterbauer et al., 1991). It is based on the condensation of MDA in an acidic and hot environment with thiobarbituric acid (TBA), resulting in the formation of a pink pigment. This chromogen can be measured at 530 nm.

Catalase (CAT): It was determined using the technique of (Aebi, 1984). Absorption was recorded at 240 nm every 15 seconds for 1 minute.

The Bradford test was used to determine pancreatic protein concentrations (He, 2011). Serum bovine albumin (BSA) was utilized as a standard.

Statistical analysis

The data is presented as (mean±SEM). Results were analyzed using one-way (Sidak test for multiple comparisons) or two-way (Tukey's post hoc test) analysis of variance (ANOVA) using GraphPad prism 8.0.2 (263) (Graph-Pad Inc., San-Diego, CA, USA). $p<0.05$ or less was considered statistically significant.

Results

Fourier transform infrared resonance analysis (FTIR)

The FTIR analysis of AES is illustrated in Figure 1. The results from the spectrum showed the presence of 5 elongation bands. The presence of a broad and strong rounded band at 3338.76 cm-1 was due to hydrogen bonding vibration of the hydroxyl (O-H) group. Alkyne (C≡CH) group is shown by the presence of a weak elongation band at 2109.21 cm-1. The intense elongation band in 1610.68 cm-1 indicated the (C=C) stretching vibration from the aromatic rings of phenols. (C-H) group bending vibration was assigned in 1360.25 cm-1. We noticed also an elongation with a

wavenumber of 1072.54 cm-1 which referred to (C-O) function group. At 491.31 cm-1 we observed a simple final band that could be associated with inorganic components.

Phytochemical compounds (TPC and TFC)

The extraction yield (%), TPC and TFC in AES are showed in Table 1. Using the method of maceration to obtain the dry water extract, we found that the percentage of extraction yield was 14.18 %. The assessment of the phenolic compounds and flavonoid concentrations revealed that TPC and TFC were (19.30 mg GAE/g DW and 80.66 mg QE/g DW respectively).

Anti-radical and antioxidant activities of AES

According to the estimation of in vitro antioxidant activity using the DPPH and FRAP scavenging methods, and TAC showed in the Table 2, our results revealed that the AES had a strong DPPH radical scavenging power of 0.39 mg/mL, an important ferric reduction ability of 434.65 µg/mL, and the TAC was assessed at 2.57 mg AAE/g DW.

Effect of treatment on blood glucose level

The effect of two-weeks treatment with AES on blood glucose levels is given in the Figure 2. After 48 hours of administering STZ (60 mg/kg), the blood glucose levels of (STZ+AES) rats group exhibited a statistically highly significant increase ($p<0.001$) compared to the control group. Similar results were observed on the (STZ) group during the entire experimental period. On the other hand, daily oral intake of AES in (STZ+AES) group induced a significant decrease ($p<0.01$) in the blood glucose level after 3 days of treatment compared to (STZ). It remained consistently decreased ($p<0.001$) started from the 5th day of the treatment until the end of the experiment.

Variation of body weight (BW) and pancreatic relative weight (PRW)

Body weight and pancreatic relative weight changes are illustrated in the Table 3. Concerning the change in BW during the experimental period, our results showed that the average BW of (STZ) group decreased significantly ($p<0.001$; -16.34%) in comparison to the control group. In the (STZ+AES) and (AES) groups, we observed a significant increase in BW ($p<0.001$; +6.20% and +18.11%, respectively). However, this increase was lower than that noticed in the control group (+46.18%). Whereas, the treatment with AES increased significantly ($p<0.001$) the BW in (STZ+AES) group compared to (STZ) group. Our data indicated a notable significant reduction ($p<0.05$) in the PRW for both groups the treated (STZ+AES) and untreated (STZ) diabetic rats compared to the (C) group. There were no significant changes observed on PRW of (AES) group.

Hematological study

The effects of STZ-induced diabetes and AES treatment on the complete blood count (CBC) is represented in the Table 4. Our results showed a significant decrease in the count of WBC ($p<0.05$) and LY ($p<0.001$), besides a statistically highly significant increase ($p<0.001$) of MO and RBC in (STZ) group compared to control. However, no significant differences have been noticed in the other hematological parameters (GR, Hb and PLT) in (STZ) group. The phytotherapy using the AES has increased GR level ($p<0.001$) but decreased significantly the levels of MO ($p<0.01$), Hb ($p<0.001$) and RBC ($p<0.05$). On the other hand, compared to control group, the daily oral intake of AES produced a significant decrease on LY ($p<0.001$) and PLT ($p<0.01$) in (STZ+AES) group. Moreover, in (AES) group we recorded a significant decrease on the level of LY ($p<0.05$) and an increase on the PLT number ($p<0.05$).

Biochemical parameters

Table 5 shows the effects of STZ induced diabetes and AES supplementation to biochemical compounds in the serum of diabetic and treated rats after two-weeks of treatment. Diabetic rats showed a significant increase on creatinine ($p<0.05$), uric acid ($p<0.05$), ASAT ($p<0.001$), ALAT ($p<0.01$), albumin ($p<0.001$) and total protein ($p<0.05$) compared to control rats. However, the treatment of diabetic rats with the AES has significantly decreased ($p<0.001$) ASAT, albumin, total protein, and ALAT ($p<0.01$) levels compared to (STZ) group. Comparing (STZ+AES) to control group, the assessment of a daily AES consumption exhibited a significant increase of creatinine ($p<0.001$) but a decrease on the total protein level ($p<0.01$). in (AES) group, we noticed that the plant's extract produced an increase on the level of albumin ($p<0.01$), and creatinine ($p<0.001$), however, it significantly decreased ($p<0.01$) the level of ASAT and total protein compared to control.

Oxidative stress parameters

The effects of STZ and AES on enzymatic antioxidants, reduced-GSH and MDA levels of pancreas homogenate are illustrated in Figure 3. In (STZ) group, there were a significant high levels of pancreatic antioxidant enzymes ($p<0.001$; GPx, SOD) and CAT ($p<0.05$). The same results were observed in the concentrations of GSH ($p<0.001$) and MDA ($p<0.01$) compared to the control group. On the other hand, it was noticed that the treatment in (STZ+AES) exhibited a significant decrease ($p<0.001$) of SOD and GPx levels. However, a highly statically significant increase was recorded on the level of MDA ($p<0.001$) compared to (STZ) group. in (AES) group, the oral administration of AES caused an obvious augmentation in MDA ($p<0.01$), GSH and CAT

(p<0.001) levels. Additionally, we observed a significant increase (p<0.001) on pancreatic CAT, GSH, MDA and SOD (p<0.05) levels in (STZ+ AES) group compared to control.

Histological study

Figure 4 presents photomicrographs highlighting the histological changes in the pancreas of the different experimental groups after two weeks of AES treatment in both normal and diabetic rats. In the control group (Figure 4. A), the pancreatic islets showed a typical histological architecture without any visible abnormalities. In contrast, (Figure 4. B) reveals that the pancreas of rats in the (STZ) group exhibited severe histopathological changes representing a degeneration and necrosis of pancreatic cells, with many cells showing pyknotic nuclei (indicated by red circles). The (Figure 4. C) demonstrates the pancreas of normal rats treated with AES, shows well-preserved pancreatic tissues with intact acinar cells and normal islet structure. Finally, (Figure 4. D) illustrates the pancreas from the (STZ+AES) group, showing a partial restoration of the Langerhans islets' normal structure with a slight hypertrophy and near-normal cellular composition (red arrow).

Discussion

Our research has focused on diabetes mellitus, which is one of the most frequent metabolic and endocrine disorders. We have investigated the hypoglycemic and antioxidant properties of AES in both, normal and diabetic rats. The application of traditional medicinal plants is proving to be the solution to the researches of scientists for the good management of diabetes. In order to identify the functional groups of the bioactive compound present in the plant and responsible of its possible effects, we used the Fourier-Transform Infrared spectroscopy as a potent and specific analytical technique. The result from the FTIR analysis spectrum revealed the existence of five peaks for various functional groups. Our results showed that AES contains a hydroxyl (O-H) group (broad signal at 3338.76 cm^{-1}) and aromatic carbons (C=C) which were noticed as a sharp elongation at 1610.68 cm^{-1}. These vibration signals are similar to those reported in the literature cited that these functional groups might come from phenolic compounds existed in this extract (Fatiqin et al., 2021; Mughal et al., 2024; Ramírez-Hernández et al., 2019). Moreover, AES also contained an alkyne (C≡CH) group (2109.21 cm^{-1}) and aldehyde (C-H) bending (1360.25 cm^{-1}). The band in 1072.54 cm^{-1} of (C-O) functional group, which is referred to aromatic ethers (acids and flavonoids likely flavanone) as reported by many authors (Hafizah et al., 2017; Noh et al., 2017). The final elongation band at 491.31 cm^{-1} showed the presence of some minerals as well as certain metal ions complexes. Using gamma-ray spectrometry, Nedjimi (2018), revealed that Suaeda mollis contains

a high quantity of calcium, potassium, cobalt, and sodium (Nedjimi, 2018), which at low concentrations could enhance the antioxidant potential and anti-inflammatory properties of the plants (Chouala et al., 2024; Kasote et al., 2015).

In our phytochemical study, we evaluated the % of the extraction yield and the amount of polyphenols and flavonoids in AES. We found an extraction yield percentage that was a fourfold higher (14.18%) compared to a prior study, which reported a low extraction yield ratio of 3.6% in the aqueous extract of *S. mollis* collected in Al Jouf area (Amin and Musa, 2016). The % of a plant yield could be influenced by the polarity of the solvent and the used extraction method, as mentioned by (El Mannoubi, 2023). Our findings suggests that the extraction yield may be influenced by several other factors, including the seasonal growth cycle and the maturity of the plant parts, as well as proper drying and storage conditions to prevent decomposition. Furthermore, a high phenolic compound continent (19.30 mg GAE/g DW) has been observed in AES. This data aligns with previous study indicating that the TPC was 24.51 mg GAE/g DW in the 80% acetonic extract of *S. mollis* collected in Tunisia (Oueslati et al., 2012). Whereas a low concentration of polyphenols (2.28 mg GAE/g DW) were reported in the aqueous extract of the same plant collected in Al Jouf area (Amin and Musa, 2016). In addition, we found also a high level of flavonoids concentration (80.66 mg QE/g DW) compared to other study (Amin and Musa, 2016) which obtained an TFC of 7.43 mg QE/g DW. These findings indicated that the plant's biotope as well as the mineral composition and physical properties of soil may greatly influence the variations of polyphenols and flavonoids rates through metabolic changes and transcriptional control, which in turn, affects the plant's stress tolerance and nutritional value (Heimler et al., 2017; Messaoudi et al., 2022).

A various assays have been used to assess the antioxidant potential of plants, often relying on spectrophotometric methods that either measure free radical scavenging or quantify the products of reactions involving either a single electron or hydrogen atom transfer (Christodoulou et al., 2022). In this study, the antioxidant activity of AES was assessed using the FRAP, DPPH, and TAC assays. The AES demonstrated strong scavenging activity against the DPPH radical (IC50 = 0.39 mg/mL), which is significantly higher than the values reported by Oueslati et al. (Tunisia) and Amin et al. (Al jouf area) for the same plant collected from different regions (IC50 = 2.5 µg/mL and 2.44 µg/mL, respectively), (Amin and Musa, 2016; Oueslati et al., 2012). These differences may be explained by variation in extraction methods, the used solvents, or the plant’s

growing conditions in different geographical locations. In the FRAP assay, the EC50 value for the ferric reducing ability of AES was 434.65 µg/mL, considerably higher than the EC50 of 130 µg/mL reported in prior research using an 80% acetonic extract (Oueslati et al., 2012). The lower FRAP activity of our aqueous extract could be attributed to its reduced ability to solubilize some potent antioxidant compounds, which are more effectively extracted by organic solvents like acetone. This aligns with findings from other studies on medicinal plants, which demonstrated that the antioxidant activity of plant extracts is heavily influenced by the polarity of the solvent and its capacity to extract various antioxidant substances (Lahmar et al., 2023; Tourabi et al., 2023). Furthermore, the TAC assay revealed a concentration of 2.57 mg AAE/g DW in the AES, which is lower than the value (23.29 mg AAE/g DW) observed in the acetonic extract from the aerial-parts of Tunisian *S. mollis* (Oueslati et al., 2012). This disparity may be due to differences in the quantities of secondary metabolites extracted by different solvents, the utilized specific parts of the plant, as well as environmental factors like soil composition and growing conditions.

In the current study, diabetes was induced in rats via a single IP injection of STZ at a dose of 60 mg/kg, which caused various symptoms commonly associated to diabetes, such as polyuria, polydipsia, and polyphagia. Moreover, the rats in (STZ) group exhibited a statistically highly significant increase in blood sugar level throughout the entire experimental period. Normally, elevated plasma glucose levels stimulate pancreatic β-cells to secrete insulin in order to maintain glucose homeostasis (H. Guo et al., 2023). Our findings confirmed that the STZ-induced diabetes protocol, in which STZ was dissolved in distilled water to reach a final concentration of 20mg/mL, led to an irreversible destruction of β-cells in the Langerhans's islets, consistent with previous reports (Al-Hariri, 2012; Noorafshan et al., 2004). The daily oral intake of AES for two weeks did not show an obvious hypoglycemic effect in normal rats. However, AES significantly lowered the elevated blood glucose levels in the (STZ+AES) group compared to the (STZ). These outcomes demonstrated that *S. mollis* has a hypoglycemic effect in diabetic rats. Plants are natural antioxidants and potent sources of phytotherapy, mainly because they contain antidiabetic compounds (flavonoids, phenols, tannins, and alkaloids), which improve pancreatic function by either increasing insulin secretion or decreasing glucose absorption in the gut (Kooti et al., 2016) Previous phytochemical findings from AES, have established that *S. mollis* leaves possessed a range of secondary compounds, with a significant presence of polyphenols and flavonoids. These bioactive compounds improve pancreatic tissue efficiency by stimulating insulin secretion,

increasing glucose uptake in peripheral tissues such as adipose and muscles, or inhibiting hepatic gluconeogenesis (Jeeva S and Anlin Sheebha Y, 2014). To our knowledge, this is the first study to report the significant antidiabetic effect of *S. mollis* and its antioxidant properties in vivo, using an STZ-induced diabetic rat model.

In the present study, STZ-induced diabetes caused a considerable loss in body weight of rats in (STZ) group compared to control, which remained decreased despite the polyphagia until the end of the experimental period. Previous studies found a significant loss of body weight in STZ-induced diabetic rats due to uncontrolled glucose levels. Also, Muscle atrophy attributed to the catabolism of amino acids in muscle tissue, degradation of fat from adipose tissues, and degeneration of structural proteins, which are known to be a major contributor to body weight loss (Bencheikh et al., 2020; Eluehike and Onoagbe, 2018; Tebboub and Kechrid, 2021). Furthermore, the excessive food intake has not led to weight gain as a result of insulin deficiency, because the destruction of pancreatic cells has considerably reduced the insulin levels (Akhtar et al., 2023). Which has rendered the body cells unable to use glucose as an energy source, prompting compensatory utilization of muscle proteins and fats from adipose tissues for energy production (Riyahi et al., 2016; Singh et al., 2022). On the other hand, treatment with AES significantly inhibited weight loss in the (STZ+AES) group compared to the diabetic group. This result may be attributed to the potential of this plant to reduce insulin resistance and enhance anti-inflammatory effects. Similar results found that some plants (*Holarrhena pubescens*, *Spondias mombin* and *Cichorium intybus*) can increase body weight in diabetic rats via there antihyperglycemic effect by reducing the blood sugar level and improving insulin sensitivity in cells (Akhtar et al., 2023; Eluehike and Onoagbe, 2018; Saravanamuttu and Sudarsanam, 2012). Body weight gain indicates that the anabolic effects have taken precedence over the catabolic ones (Al-Attar and Alsalmi, 2019). Contrary, some antidiabetic plants such as *Bauhinia holophylla* has decreased the body weight of diabetic animals, possibly due to its toxic effect (Pinheiro et al., 2017). The results from relative weight of pancreas in this investigation showed a significant decrease in PRW of treated (STZ+AES) and non-treated diabetic rats compared to control, in accordance with many previous studies (Alsharif et al., 2023; Eluehike and Onoagbe, 2018; Shawky et al., 2020). They confirmed that β-cells in the pancreatic islets of Langerhans die after STZ-injection, suggesting that the decrease in pancreatic relative weight is related to the degradation and atrophy of the islets, as found later in our histological study. However, a study found that the PRW remained unchanged,

as the pancreatic weight appeared to decrease proportionally with the overall reduction in body weight, rather than being directly influenced by the diabetic condition. (Muhammed Zafar and Syed Naeem-ul-Hassan Naqvi, 2010). Whereas, oral administration of AES showed no significant effect of PRW in (AES) group.

It has been reported that various hematological parameters could be a useful indicator in assessing the harmful effects of drugs as well as medicinal plants, which may also vary during diabetes (Mahmoud, 2013). In this study, we found that STZ administration significantly reduced the WBC and LY while increased the level of MO and RBC. These results are in consonance with findings by earlier researches (Fagbohun et al., 2020; Rehman et al., 2023). The increased monocytes level might be due to high blood sugar level, which prompted the bone marrow to generate more monocyte progenitor cells, leading to monocytosis (Kanter et al., 2020). Additionally, the decrease in LY and WBC counts can be attributed to the body's stress response following the injection of STZ (Helal et al., 2005). Prolonged hyperglycemia can lead to an increase in RBC level and cause damage to the cytoskeleton of the RBC's membrane due to oxidative stress. This damage leads to a low-grade inflammation that is linked to many complications of diabetes (Simmons, 2010; Williams et al., 2023). However, following to AES administration in (STZ+AES) group, the number of RBC and MO were appreciably reduced to near normal, besides an abnormal decrease in PLT and Hb levels but an increase in the number of GR. In contrast, the aqueous extract of stem bark of the antidiabetic plant *Afzelia Africana* has increased LY, MO and PLT in diabetic rats (Oyedemi et al., 2011). Other studies showed that some antidiabetic plants can lead to reduced Hb and PLT level as a compensatory mechanism of antioxidant and anti-inflammatory effects of the plants (Esmail Al-Snafi et al., 2019; Yilmaz, 2020). Besides, in some contexts, the reduction in blood glucose level may correlate with lower hemoglobin levels particularly in the plants influence RBC production or its survival (Esmail Al-Snafi et al., 2019). The aqueous extract of *S. mollis* might normalize the RBC level by using vital nutrients of the plant, which support blood cell formation (hematopoiesis), protect the red cells from oxidative stress damage, and maintain their integrity and function (Cherrada et al., 2024). The significant increase in GR and the decrease in MO levels could be as result of the plant's potential to prevent diabetes complications and treat the inflammations and damages caused by STZ induction.

Impaired kidney function and increased protein catabolism are associated with higher creatinine and uric acid concentrations, while albumin and total protein levels can be influenced by changes

in protein synthesis and muscle loss caused by diabetes. In this study, STZ-induced diabetic rats showed an increased levels of: creatinine, uric acid, ASAT, ALAT, albumin, and total protein which indicated a renal dysfunction and metabolic disturbances in the liver. Studies have shown that the effects of diabetes on renal function, liver damage, as well as total metabolism, are significantly affected by these biochemical markers in diabetic models (Alq and Hussein, 2021; Ghanbari et al., 2015; L. Guo et al., 2021). It was notable that the treatment with AES reduced the hepatic markers ASAT and ALAT to normal besides albumin and total protein levels but increased the level of creatinine (to diabetic and normal rats) which is considered as a sign of renal failure or nephrotoxicity caused by the plant's extract. These outcomes concorded with those reported that the *Talinum triangulare* flavonoids extract and *Nigella sativa* oil were effective in reducing the increased serum uric acid and liver enzymes in STZ-induced diabetic rats (Al-Logmani and Zari, 2011; Oluba et al., 2019). Creatinine is a waste product of muscle metabolism that is filtered by the kidneys. When kidney function is impaired due to nephrotoxicity, creatinine accumulates in the blood, resulting in elevated serum creatinine levels (Kim and Moon, 2012). Some plants, such as *Aristolochia* and *Rhubarb,* have been associated with nephrotoxicity and may contribute to increased creatinine levels due to kidney damage (Pearson et al., 2022), which aligns with our findings.

Hyperglycemia promotes the generation ROS, leading to oxidative stress, which plays a major role in the pathogenesis of diabetes, particularly in STZ-induced models. Besides, it contributes to the complications linked to diabetes (Bhatti et al., 2022). In the current study, increased activities of SOD, GPx, CAT, GSH and MDA have been observed in the pancreatic homogenate of (STZ) group. Persistent hyperglycemia in diabetes leads to elevated production of oxygen free radicals, resulting in lipid peroxidation, which generates MDA and increases membrane fluidity and permeability. Antioxidant enzymes such as CAT, GPx, and SOD play crucial roles in protecting cells from oxidative damage (Kakkar et al., 1995). Kakkar et al. (1995) noted that, heightened GPx activity in diabetes may prevent SOD inactivation caused by excessive H_2O_2, thereby increasing SOD activity and providing further protection to CAT and GPx from inactivation by O_2 anion. Ultimately, this sequence of events would enhance both CAT and GPx activity (Kakkar et al., 1995) . The rise in CAT activity is attributed to increased generation of H_2O_2, as reduced insulin levels enhance fatty acyl CoA oxidase activity, which triggers the oxidation of fatty acids and H_2O_2 production (Kakkar et al., 1995). Studies have indicated that catalase plays a role in detoxification

by facilitating the decomposition of H_2O_2 into H_2O and O_2, thereby providing protective effects against oxidative damage (Bhatti et al., 2022; De duve and Baudhun, 1966). Additionally, elevated glucose levels contribute to increased oxidative stress in pancreatic β-cells. The overexpression of GPx boosts its activity and shields Langerhans's islets from harmful effects including the accumulation of H_2O_2 and lipid hydroperoxides by facilitating their breakdown with GSH as a co-substrate (Salazar-García and Corona, 2021). Higher levels of GSH may safeguard cellular proteins from oxidation via GSH redox cycle to neutralize reactive oxygen species generated by STZ induced diabetes (Soliman et al., 2015). Furthermore, GSH is recognized for its ability to neutralize hydrogen and lipid peroxides (Bhatti et al., 2022). On the other hand, administration of AES significantly restored the normal pancreatic SOD and GPx levels, but it also increased the level of MDA in the pancreas of the (STZ+AES) group more than in the (AES) group. Additionally, we noticed an elevation in GSH and CAT levels compared to control group. This could be due to the presence of effective phytochemicals in the aqueous extract of Suaeda mollis leaves. Researchers suggested that the bioactive compounds such as polyphenols, flavonoids and terpenoids present in antidiabetic plants could lower reactive oxygen species, boost the antioxidant enzymes activities and improve insulin sensitivity (Alam et al., 2022; Krawczyk et al., 2023). When MDA presents at elevated levels, it enhances glucose-stimulated insulin secretion in pancreatic islets by upregulating the expression of key genes like glucokinase, glucose transporter 2 (GLUT 2) and pancreatic duodenal homebox 1 (PDX1) (Wang et al., 2014). Researchers have indicated that following to STZ exposure, GLUT2 improves β-cell survival, while STZ reduces GLUT2 expression, impairing glucose-stimulated insulin secretion and leading to β-cell dysfunction. Although some β-cells may survive the initial STZ injury, their reduced functionality due to lower GLUT2 levels creates a negative feedback loop, worsening hyperglycemia and lowering β-cell activity (Hahn et al., 2020; Hosokawa et al., 2001). Moreover, MDA affects the intracellular ATP/ADP ratio and cytosolic calcium levels, which are essential for insulin secretion (Wang et al., 2014). A previous study proposed that malondialdehyde (MDA), a marker of oxidative stress and lipid peroxidation, serves as a possible therapeutic target for preserving pancreatic β--cell function, playing a role in diabetes-related complications (Angie et al., 2024). We hypothesize that although the two-week AES supplementation did not fully counteract the antioxidant imbalance and cellular damage induced by STZ, a prolonged study could potentially restore this balance. Additionally, the increased MDA concentration in the pancreas may contribute

to lowering glucose levels by enhancing insulin secretion from the surviving β-cells and promoting glucose uptake through the upregulation of GLUT 2 expression.

The results of histological study showed altered pathological changes in pancreas as a result of STZ injection. We observed a reduced β--cell mass, pyknotic nuclei, potential islets atrophy and increased fibrous tissue in (STZ) group compared to control group. This alteration contributed to impaired insulin production and glucose metabolism, characteristics of diabetes. These findings are similar with those observed by Indu et al. (2019) where diabetes was induced in rats by STZ and nicotinamide (Indu et al., 2019). Another study in Egypt also reported a shrunken in the islets of Langerhans, β-cells, generative and necrotic changes (Barakat et al., 2020). Whereas, our data showed that treating the diabetic rats with AES has restored the Langerhans islet's structure nearly to normal, but we observed a slight hypertrophy. The same results were found when using the Watermelon peels (20%) as a treatment to STZ induced diabetic rats (Rezq, 2017). Islet hypertrophy can occur in response to various physiological and metabolic changes, such as increased insulin secretion during hyperglycemia. This enlargement may result from β-cell proliferation (Simeone et al., 2006). Additionally, in diabetic states, islet hypertrophy may develop as a compensatory mechanism to maintain insulin production despite cellular stress or damage (Nugent et al., 2008).

Conclusion

Based on our research, the use of the aqueous extract from *S. mollis* leaves as a natural supplement for two-weeks in Wistar rats, enhance the antioxidant defense system in diabetic rats due to its high content of phytochemical compounds like flavonoids and polyphenols and showed positive effects on improving STZ-induced hyperglycemia. This extract appears to decrease the blood glucose level and improve the survival and function of insulin-secreting pancreatic β-cells. However, our findings indicate that AES may elevate the level of creatinine in the bloodstream, suggesting possible nephrotoxicity. This study deserves to be conducted over a longer period to confirm the plant's effect on the studied parameters. Further investigation is necessary to identify and characterize the active compounds responsible for these effects, indicating its potential as a valuable addition to diabetes management approaches.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data availability statement

The data is available in the manuscript. Additional data or information will be available on request.

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Author Contributions

Abrazi Yamina performed the experiments, conducted the visualization and analysis of data, writing – review and editing and Writing – original draft. Boufermes Radia contributed in writing – review and editing, supervision and conceptualized the study. Kadi Assia and Messarah Mahfoud managed the project administration, ensuring smooth coordination and progress. Chiheb Nadia provided essential resources and support for the phytochemical study. Houicha Haroun performed the FTIR analysis.

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Table 1. Extraction yield, total phenols and flavonoid contents in the aqueous extract of Suaeda mollis leaves.

Parameters	Values
Extraction yield (%)	14.18
Total phenols (mg GAE/g DW)	19.30±1.32
Flavonoids (mg QE/g DW)	80.66±1.34

Values are presented as mean±SEM (n=3). g DW: Gram of extract's dry weight, GAE: Gallic acid equivalent, QE: Quercetin equivalent.

Table 2. Antioxidant activities of the aqueous extract of Suaeda mollis leaves.

Parameters	Values
50% scavenging on DPPH radical (mg/mL)	0.39±0.05
FRAP test (EC50) (µg/mL)	434.65±0.09
Total antioxidant capacity (mg AAE/g DW)	2.57±0.28

Values are presented as mean±SEM (n=3).

Table 3. The effects of the aqueous extract of *S. mollis* leaves in body weight and relative pancreatic weight on normal and diabetic rats after two-weeks of treatment.

Parameters	Control	(STZ) (60mg/kg.BW)	(AES) (200mg/kg.BW)	(STZ+AES)
Initial body weight (g)	151.2±2.84	212±5.05	228.4±3.48	227±4.98
Final body weight (g)	220.6±1.61	176±7.45	269.8±3.99	241±5.42
Body weight change (%)	+46.18±4.35	-16.34±5.12$^{(c)}$	+18.11±1.53$^{(c)}$	+6.20±2.74$^{(f, c)}$
Relative weight (mg/100g BW)	0.48±0.02	0.29±0.04$^{(a)}$	0.44±0.02	0.26±0.03$^{(a)}$

Values are given as mean ±SEM for groups of 5 animals each. (C): the normal control group; (STZ): the diabetic rats; (AES): the normal rats + (200mg/kg) of AES; (STZ+AES): the diabetic rats + (200mg/kg) of AES. Significant difference: (a) $p<0.05$, (c) $p<0.001$ when compared to the control. (f) $p<0.001$ when compared to (STZ).

able 4. Effects of diabetes and AES supplementation on hematological parameters of control and treated (normal and diabetic) rats after two-weeks of treatment.

Parameters	Control	(STZ) (60mg/kg.BW)	(AES) (200mg/kg.BW)	(STZ+AES)
WBC (10^3 /µL)	8.48±1.21	6.38±0.91$^{(a)}$	7.18±0.75	7.12±0.76
LY (× 10^3 /µL)	6.62±0.52	3.94±0.82$^{(c)}$	5.21±0.91$^{(a)}$	4.0±0.78$^{(c)}$
MO (× 10^3 /µL)	0.66±0.23	1.14±0.46$^{(c)}$	0.59±0.33	0.8±0.31$^{(e)}$
GR (× 10^3 /µL)	1.22±0.52	1.26±0.55	1.96±0.76	5.38±0.85$^{(f, c)}$
RBC (× 10^6 /µL)	5.41±1.01	7.422±1.05$^{(c)}$	7.73±1.22	8.75±1.41$^{(a)}$
Hb (g/dL)	11.96±1.41	13.14±1.52	11.8±1.09	4.87±0.59$^{(f, c)}$
PLT (× 10^3 /µL)	368.8±8.68	293.2±7.74	506.4±9.57$^{(a)}$	204.2±3.99$^{(b)}$

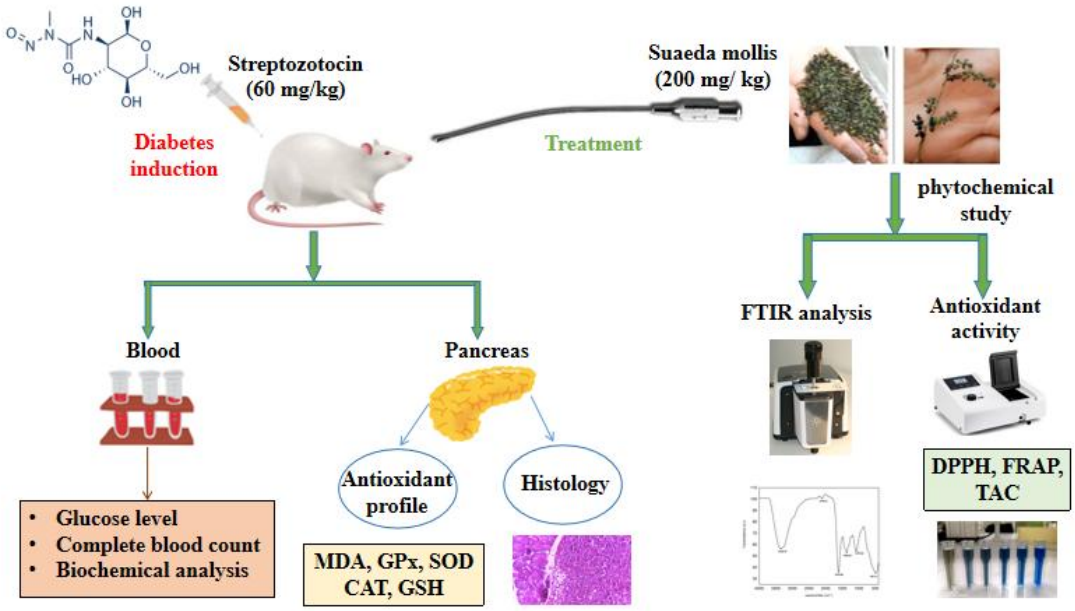
Values are presented as mean±SEM (n=5). White blood Cells (WBC); Lymphocytes (LY); Monocytes (MO); Granulocytes (GR); Red Blood Cells (RBC); Platelet (PLT); Hemoglobin (Hb). Letters in each column indicate significant differences as follows: (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ when compared to control. (e) $p<0.01$, (f) $p<0.001$ when compared to (STZ).

Table 5. The effects of AES supplementation on biochemical parameters in serum of normal and diabetic rats after two-weeks of treatment.

Parameters	Control	(STZ) (60mg/kg.BW)	(AES) (200mg/kg.BW)	(STZ+AES)
Creatinine (µmol/l)	22.4±1.4	43.8±3.08$^{(a)}$	65.8±3.61$^{(c)}$	67.6±3.51$^{(c)}$
Uric acid (µmol/l)	101.8±3.7	148.4±5.98$^{(a)}$	81.2±4.07	111.8±2.7
ASAT (U/L)	69.6±3.4	186±3.13$^{(c)}$	70.6±3.97	85.8±3.05$^{(f)}$
ALAT (U/L)	72.8±3	147±6.5$^{(b)}$	63.6±2.82	78.2±5.40$^{(e)}$
ALB (G/L)	30±1.73	39.4± 1.79$^{(c)}$	36.4±1.55$^{(b)}$	31±1.25$^{(f)}$
Prt tot (mg/ml)	101.8±3.67	145±5.90$^{(a)}$	54.46±2.71$^{(b)}$	52.83±2.80$^{(f, b)}$

Values are presented as mean±SEM (n=5 animals/group), ASAT: Aspartate aminotransferase; ALAT: Alanine aminotransferase; ALB: Albumin; Prt tot: Total protein. Letters in each column indicate significant differences as follows: (a) $p<0.05$, (b) $p<0.01$, (c) $p<0.001$ when compared to control. (e) $p<0.01$, (f) $p<0.001$ when compared to (STZ).

Graphical abstract



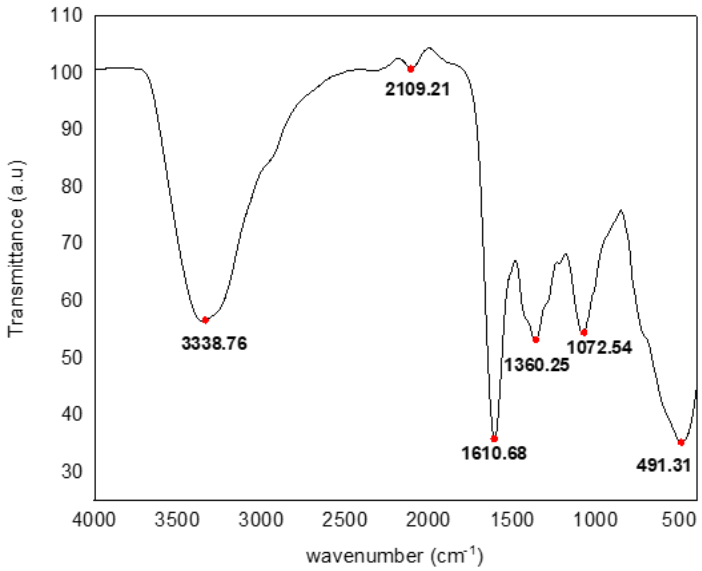


Figure 1. *FTIR spectra showing 5 bands of the bioactive compounds present in the aqueous extract of S. mollis leaves.*

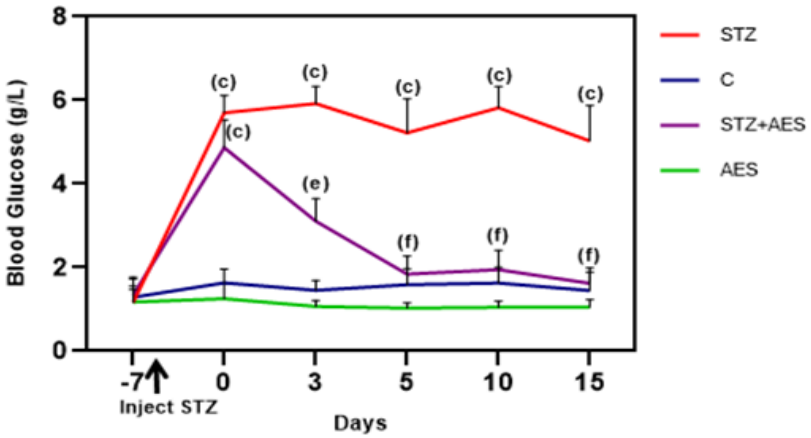


Figure 2. *Variations of blood glucose levels of control (C), Diabetic (STZ), Diabetic treated with aqueous extract of S. mollis (STZ + AES) and Normal treated with (200 mg/kg) of the aqueous extract of S. mollis (AES), before and after IP injection with STZ, during two-weeks of treatment. Note that diabetic rats started to show a relatively stable level of hyperglycemia approximately 48h after injection with STZ. Data are shown as mean±SEM. Letters in each point indicate significant differences as follows: (c) p<0.001 when compared to control. (e) p<0.01, (f) p<0.001 when compared to (STZ).*

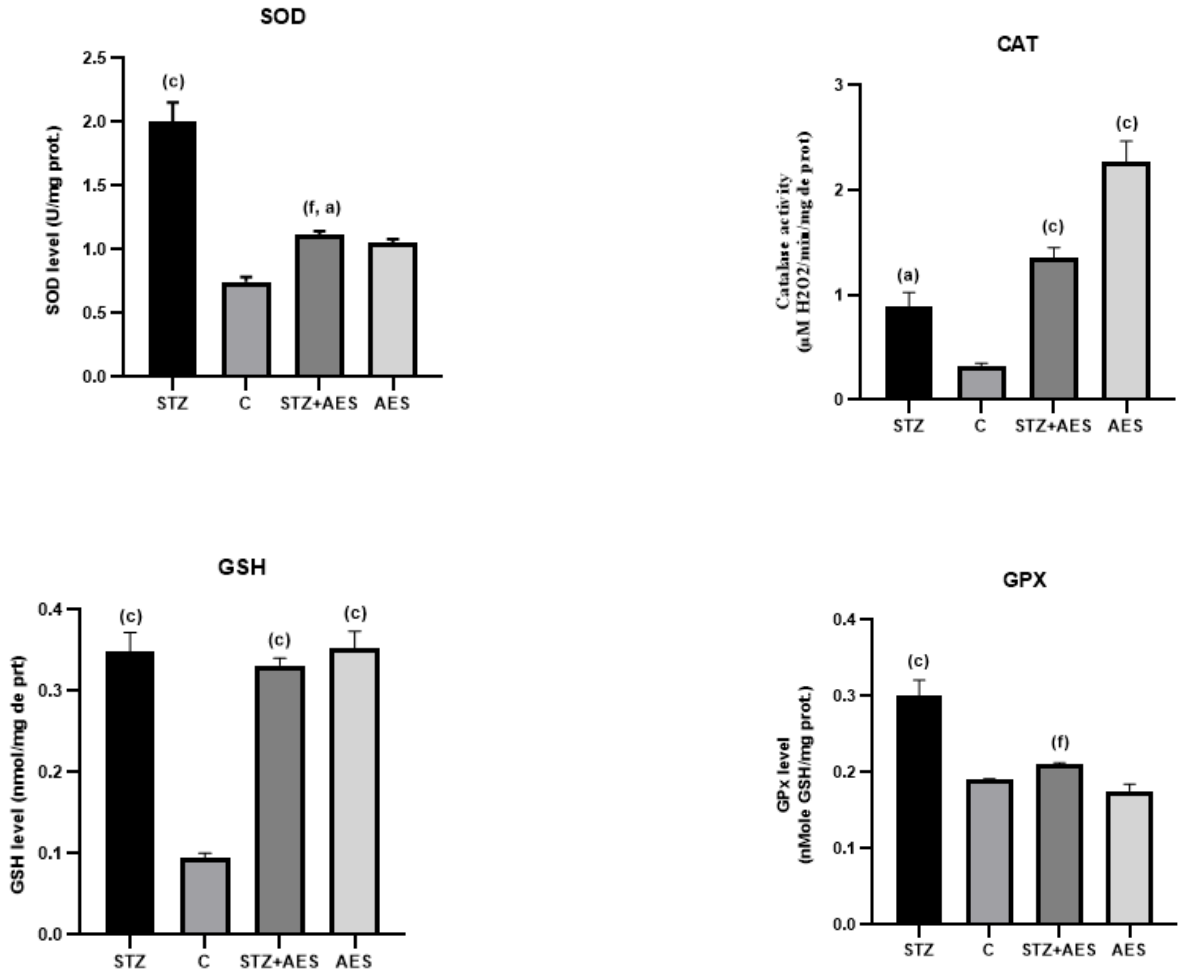
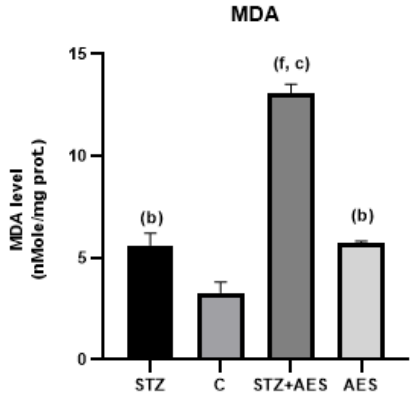


Figure 3. *Effects of STZ-induced diabetes and AES supplementation on oxidative stress*



biomarkers (the enzymatic and non-enzymatic antioxidants) in pancreas tissues of rats. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), and malondialdehyde (MDA) are represented as mean±SEM (n=5). (a) p<0.05, (b) p<0.01, (c) p<0.001 when compared to control. (d) p<0.05, (e) p<0.01, (f) p<0.001 when compared to (STZ).

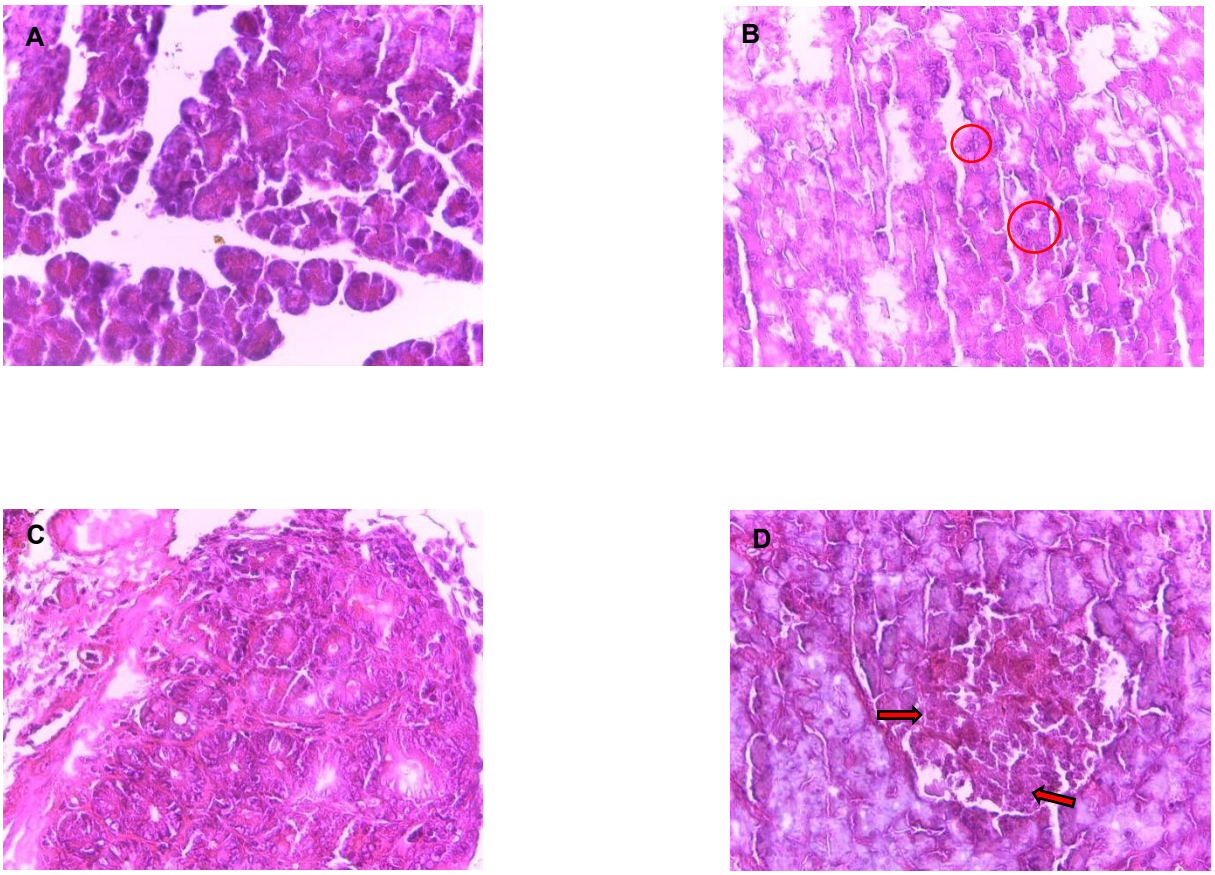


Figure 4. *Photomicrographs (A–D) demonstrates the histological sections of the pancreas tissues of different groups stained by hematoxylin and eosin [Magnification 40X]. A: control (C), B: Diabetic (STZ), C: Normal treated rats (AES) with (200 mg/kg) of the aqueous extract of S. mollis, D: Diabetic treated rats (STZ+AES) with the aqueous extract of S. mollis. Red cercles: pyknotic nuclei, red arrows: hypertrophy of islets.*

JICOA'22
The 5th International Days on Organic Chemistry of Annaba

LCOA and LSBO

BADJI MOKHTAR ANNABA UNIVERSITY
SCIENCES FACULTY
CHEMISTRY DEPARTMENT

CERTIFICATE

This certificate is awarded to **Ms. Yamina ABRAZI** for the participation in **"the 5th International Days on Organic Chemistry of Annaba"** -*JICOA'22*- with a *Poster* presentation entitled:

Étude phytochimique comparatif des extraits méthanolique et aqueux des feuilles de l'Atriplexhalimus de la Wilaya M'sila-Algérie.

Co-authors: Radia BOUFERMES, Lina KHANFER, Randa MERAIHIA, Mahfoud MESSARAH.

Topic: *Phytochemistry*

President of the session

Dr. Dalila Fedaoui

President of JICOA'22

Pr. Salah Eddine DJILANI

JICOA 22
4 et 5 Décembre 2022

People's Democratic Republic of Algeria, Ministry of High Education and Scientific Research
Badji Mokhtar University-Annaba, Faculty of Sciences - Department of Biochemistry
Laboratory of Biochemistry and Environmental Toxicology

LBTE

CERTIFICATE OF ATTENDENCE

ABRAZI Yamina

For attending : **Applied Research in Food Sciences, Health and Environment (1st IS-ARFSHE 23) December, 17-18th 2023, Annaba**

And Presenting an Poster Communication entitled :

Comparative phytochemical study between aqueous and methanolic extracts of *Suaeda mollis* leaves collected from Khenchela, Algeria

Authors : ABRAZI Yamina, Radia BOUFERMES, Nadia CHIHEB.

President of the Scientific Committee

Pr Boudjema SAMRAOUI

Head of Biochemistry Department

IS-ARFSHE 2023

People's Democratic Republic of Algeria
Ministry of Higher Education and Scientific Research
University Abbes Laghrour-Khenchela
Faculty of Nature and Life Sciences
Laboratory of Biotechnology, Water, Environment and Health

Biotechnologie, Eau, Environnement et Santé

CERTIFICATE OF PARTICIPATION

The president of the First International Webinar on:
Promotion and Exploitation of Plants of Ecological and Economic Interest
held between 15 and 16March 2023, certifies that:

ABRAZI YAMINA

Participated with an e-poster Communication

Entitled: **Etude phytochimique de l'extrait aqueux d'une plante du genre *Suaeda mollis* collectée dans la Wilaya de Khenchela - Algérie**

Co-authors: Boufermes Radia, Chiheb Nadia, Messarah Mahfoud.

Webinar chair	**Laboratory manager**	**Dean of the Faculty**
Dr. Djamel Bensizerara	*Pr. Kenza Kadi*	*Pr. Sofiane Hemmam Mounine*

ATTESTATION DE PARTICIPATION

Le comité scientifique du **1er Webinaire National Natural Products and Bioactive Compounds, an issue of sustainable development** atteste que :

ABRAZI Yamina

A participé au Webinaire, le 11 Mars 2023 et a présenté un e-poster intitulé :

Effet de l'extrait méthanoïque des feuilles de l'*Atriplex halimus* sur les paramètres biochimiques et hématologiques chez des rats rendus diabétiques par Sterptozotocine

Co-auteurs : BOUFERMES Radia, KHALLEF Nada, DJEROUROU Rayen, HOUAM Aya, MESSARAH Mahfoud.

Le Président du Comité Scientifique

Mme. BELARBI

La Doyenne de la Faculté SNV/STU

LE DOYEN
SOULIMANE Nassima Amal

République Algérienne Démocratique et Populaire
Ministère de l'Enseignement Supérieur et de la Recherche Scientifique
Université de Relizane

جامعة غليزان
RELIZANE UNIVERSITY

Attestation de participation

Le président du séminaire national (en ligne) ***Toxicologie et Phyto-Aromathérapie***organisé le 21 Février 2023par le département de Biologie / Faculté des sciences et de la technologie en partenariat avec le laboratoire de recherche *Environnement et Développement Durable* de l'université de Relizane et la participation de l'*ATRSSV*, atteste que :

ABRAZI Yamina

a participé au séminaire par une communication **affichée** intitulée

Effet de l'extrait aqueux des feuilles de l'Atriplex halimus sur Les paramètres biochimiques chez des rats rendus diabétiques par Streptozotocine.

Co-auteurs : **Boufermes R., Fetimi C., Boutarfa K., Messarah M.**

Président du séminaire

Dr. BRAHMI Mostapha

Université de Relizane
Webinaire National
21 février 2023
Toxicologie et Phyto-Aromathérapie

Doyen de la faculté des sciences et de la technologie

عميد كلية: العلوم والتكنولوجيا

Researcher Academy On Campus

Certificate of Attendance

ELSEVIER

This certifies that

Yamina ABRAZI

has attended the following

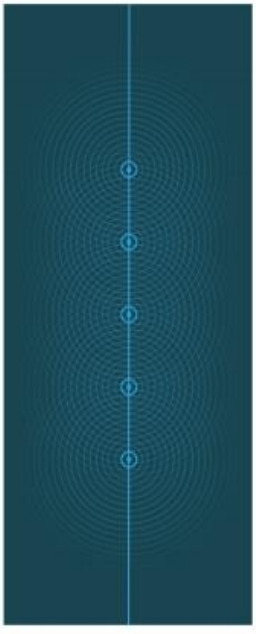
The Article Publishing Process: An Elsevier Author Workshop (120 minutes)

at Africa,
on Monday 01 June, 2020

Presented by Mary Ann Zimmerman, Senior Publisher, Theren Mohan, Solutions Sales Manager - eBooks

Suzanne BeDell
Managing Director, Education Reference & Continuity Books

Philippe Terheggen
Managing Director, Science, Technology & Medical Journals



Researcher Academy researcheracademy.com

Certificate of Completion

ELSEVIER

This certifies that

Yamina ABRAZI

has successfully completed the following module

From article to art: Creating visual abstracts - Part 4: Sketching the appropriate visual elements (13 minutes)

on Tuesday 14 November, 2023
Presented by Mark Belan

Suzanne BeDell
Managing Director, Education Reference & Continuity Books

Laura Hassink
Managing Director, Science, Technology & Medical Journals

ELSEVIER

Comparative Biochemistry and Physiology
- Part C: Toxicology & Pharmacology

Certificate of Reviewing

Awarded for 1 review in June 2025
presented to

YAMINA ABRAZI

in recognition of the review contributed to the journal

The Editors of Comparative Biochemistry and Physiology - Part C: Toxicology & Pharmacology

Elsevier Reviewer Recognition

CERTIFICATE Of PARTICIPATION

Abrazi Yamina

has participated in 3rd International Conference on Engineering and Applied Natural Sciences on 14-17 January in 2023 at Konya/Turkey.

PAPER TITLE	*Phytochemical study of Sanguisorba minor Scop and preventive effect of its aqueous extract on chemical carcinogenesis of the skin*
PRESENTATION TYPE	*Oral*

ICEANS 2023

ICEANS 2023 CONFERENCE CHAIRMAN
Asst. Prof. Dr. Umut ÖZKAYA

UNIVERSITE BADJI MOKHTAR-ANNABA
Faculté des Sciences, Département de Biochimie
Laboratoire de Recherche de Biochimie et de Toxicologie Environnementale

LBTE

Dimanche 1er juillet 2018 – Bibliothèque Centrale Sidi Amar

JOURNEE DE VULGARISATION SCIENTIFIQUE SUR L'IMMUNOLOGIE (JVSI)

Organisée par le Laboratoire de Biochimie et de Toxicologie Environnementale

Le Comité d'Organisation a le plaisir de délivrer cette attestation à :

Mlle Yamina ABRAZI

Pour sa participation effective à la Journée de Vulgarisation Scientifique sur l'Immunologie (JVSI), en qualité de membre du comité d'organisation.

Le Directeur du Laboratoire de Biochimie et de Toxicologie Environnementale

Pr. MESSARAH Mahfoud

Pour le Comité d'Organisation
Le Président

Professeur Amel BOUMENDJEL
Docteur en Immunologie

UNIVERSITE BADJI MOKHTAR-ANNABA
Faculté des Sciences, Département de Biochimie
Laboratoire de Recherche de Biochimie et de Toxicologie Environnementale

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Dimanche 1er juillet 2018 – Bibliothèque Centrale Sidi Amar

JOURNEE DE VULGARISATION SCIENTIFIQUE SUR L'IMMUNOLOGIE (JVSI)

Organisée par le Laboratoire de Biochimie et de Toxicologie Environnementale

Le Comité d'Organisation a le plaisir de délivrer cette attestation à :

Mme Abrazi Yamina

Pour sa participation effective à la Journée de Vulgarisation Scientifique sur l'Immunologie (JVSI), en présentant un poster et un dépliant infographiques portant sur :

Poster 1.3 : La réaction Ag-Ac

Le Directeur du Laboratoire de Biochimie et de Toxicologie Environnementale

Pr. MESSARAH Mahfoud

Pour le Comité d'Organisation
Le Président

Professeur Amel BOUMENDJEL
Docteur en Immunologie

LBTE
Laboratoire de Biochimie et Toxicologie Environnementale
مخبر الكيمياء الحيوية والتسمم البيئي

UNIVERSITE BADJI MOKHTAR – ANNABA
FACULTE DES SCIENCES. DEPARTEMENT DE BIOCHIMIE
LABORATOIRE DE BIOCHIMIE ET TOXICOLOGIE ENVIRONNEMENTALE

جامعة باجي مختار – عنابة
قسم الكيمياء الحيوية .كلية العلوم
مخبر الكيمياء الحيوية و التسمم البيئي

ATTESTATION DE STAGE

Nous soussignés, Professeur Mahfoud MESSARAH, Directeur du Laboratoire de Biochimie et de Toxicologie Environnementale, Faculté des Sciences, Université Badji Mokhtar d'Annaba, Algérie), et Professeure Assia KADI, Responsable de la spécialité de l'Offre de Formation Doctorale), attestons par la présente que :

Melle ABRAZI Yamina,

Doctorant(e) inscrit(e) au niveau du Département de Biochimie (Faculté des Sciences - UBMA), a effectué un stage pratique au sein du Laboratoire de Biochimie et de Toxicologie Environnementale, durant les quatre premières années de préparation de sa thèse de doctorat en sciences biologiques, et dont les résultats sont jugés scientifiquement exploitables et publiables.
La présente attestation est délivrée à l'intéressé(e) pour servir et valoir ce que de droit.

Fait à Annaba, le 16/10/2025

La Responsable de la spécialité de l'offre de formation doctorale

Dr. KADI-BIREM Assia
Maître de Conférences
Université Badji Mokhtar Annaba

Le Directeur du laboratoire

Pr. MESSARAH Mahfoud

Université Badji Mokhtar ANNABA – Directeur De Labo – Labo de Biochimie et Toxicologie Environnementale