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Topic

Phytochemical Study and Biological Activities of the Species *Salvia balansae* Noë ex Coss

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Abstract

Salvia balansae, an endemic perennial plant native to Algeria, particularly in the Mostaganem and Aures regions, exhibits significant medicinal potential. This study aims to explore the chemical composition and biological activities of *Salvia balansae* extracts obtained from different plant organs (leaves, flowers, and stems) collected from the Aures Mountains using various solvents (ethanol, methanol, and acetone). The maceration technique was employed to extract the chemical constituents, and the extracts were analysed for their total phenolic compounds, flavonoids, flavonols, condensed and hydrolysable tannin, triterpenoid, and ortho-diphenols content using the microplate reader technique. Advanced analytical techniques, such as liquid chromatography coupled with mass spectrometry (LC-MS), were used to identify the specific phenolic compounds.

The antioxidant activity of the extracts was assessed through multiple in vitro assays, including DPPH, ABTS, FIC, FRAP, Phenanthroline, CUPRAC, SNPAC, and Superoxide radical scavenging activity by alkaline DMSO assay. Additionally, the photoprotective properties were evaluated, given the increasing interest in natural sunscreen formulations. Principal Component Analysis (PCA) and Unweighted Pair-Group Method with Arithmetic Mean (UPGMA) were applied to discern the similarities and differences among the extracts concerning their chemical composition, secondary metabolite content, and biological activities.

Furthermore, the anti-inflammatory activity of the extracts was evaluated using the Bovine Serum Albumin (BSA) method, and the antidiabetic potential was assessed through the alpha-amylase inhibition assay. Results revealed that *S. balansae* extracts exhibit significant antioxidant, photoprotective, anti-inflammatory, and antidiabetic activities. This is attributed to their rich phenolic content. Moreover, the study identified several key phenolic compounds and demonstrated the impact of solvent type and plant organ on the efficacy of the extracts.

This research represents the first comprehensive investigation into the phytochemical and biological properties of *Salvia balansae* from the Aures Mountains, highlighting its potential as a source of natural antioxidants, photoprotective agents, anti-inflammatory, and antidiabetic agents.

Keywords: *Salvia balansae,* Endemic plant , LC-MS, phenolic compounds, biological activities**,** Triterpenoids.

Résumé

Salvia balansae, une plante vivace endémique de l'Algérie, en particulier des régions de Mostaganem et des Aurès, présente un potentiel médicinal significatif. Cette étude vise à explorer la composition chimique et les activités biologiques des extraits de *Salvia balansae* obtenus à partir de différents organes de la plante (feuilles, fleurs et tiges) collectés dans les montagnes des Aurès en utilisant divers solvants (éthanol, méthanol et acétone). La technique de macération a été utilisée pour extraire les constituants chimiques, et les extraits ont été analysés pour leur contenu en composés phénoliques totaux, flavonoïdes, flavonols, tanins condensés et hydrolysables, triterpènes et ortho-diphénols à l'aide d'une technique de lecteur de microplaques. La chromatographie liquide (LC-MS) a été utilisées pour identifier les composés phénoliques spécifiques.

L'activité antioxydante des extraits a été évaluée par plusieurs essais in vitro, y compris DPPH, ABTS, FIC, FRAP, Phenanthroline, CUPRAC, SNPAC et l'activité de piégeage des radicaux superoxydes par le test DMSO alcalin. De plus, les propriétés photoprotectrices ont été évaluées, étant donné l'intérêt croissant pour les formulations de crèmes solaires naturelles. L'analyse en composantes principales (ACP) et la méthode UPGMA (méthode de groupement non pondérée avec moyenne arithmétique) ont été appliquées pour discerner les similitudes et les différences entre les extraits en ce qui concerne leur composition chimique, le contenu en métabolites secondaires et les activités biologiques.

En outre, l'activité anti-inflammatoire des extraits a été évaluée en utilisant la méthode de l'albumine sérique bovine (BSA), et le potentiel antidiabétique a été évalué par le test d'inhibition de l'α-amylase. Les résultats ont révélé que les extraits de *S. balansae* présentent des activités antioxydantes, photoprotectrices, anti-inflammatoires et antidiabétiques significatives. Cela est attribué à leur richesse en composés phénoliques. De plus, l'étude a identifié plusieurs composés phénoliques clés et a démontré l'impact du type de solvant et de l'organe de la plante sur l'efficacité des extraits.

Cette recherche représente la première investigation complète des propriétés phytochimiques et biologiques de *Salvia balansae* des montagnes des Aurès, mettant en évidence son potentiel en tant que source d'antioxydants naturels, d'agents photoprotecteurs, anti-inflammatoires et antidiabétiques.

Mots-clés: *Salvia balansae,* Plante endémique, LC-MS, Composés phénoliques, Activités biologiques, Triterpénoïdes.

ملخص

يعتبر *Salvia balansae* نبات معمر مستوطن في الجزائر، خصوصًا في مناطق مستغانم والأوراس، و يتمتع بخصائص طبية كثيرة. تهدف هذه الدراسة إلى استكشاف التركيب الكيميائي والأنشطة البيولوجية لمستخلصات *Salvia balansae* المستخرجة من أجزاء مختلفة من النبات (الأوراق، الأزهار، والسيقان) المتحصل عليها من جبال الأوراس باستخدام مذيبات مختلفة (الإيثانول، الميثانول، والأسيتون). تم استخدام تقنية النقع لاستخراج المركبات الكيميائية، وتم تحليل المستخلصات لتحديد محتواها من المركبات الفينولية الكلية، الفلافونويدات، الفلافونولات، التانينات المكثفة والقابلة للتحلل، التريتربينويدات، والأرثو-دي فينولات باستخدام تقنية قارئ الألواح الدقيقة. تم استخدام تقنيات التحليل الكروماتوغرافي السائل المتصل بمطياف الكتلة (LC-MS) لتحديد المركبات الفينولية الخاصة بها.

تم تقييم النشاط المضاد للأكسدة للمستخلصات من خلال العديد من الاختبارات المخبرية، بما في ذلك DPPH ، ABTS، FIC، FRAP، Phenanthroline، CUPRAC، SNPAC، ونشاط إزالة الجذور المؤكسدة الفائقة باستخدام اختبار DMSO القلوي. بالإضافة إلى ذلك، تم تقييم الخصائص الواقية من الضوء نظرًا للاهتمام المتزايد بالتركيبات الطبيعية للمراهم الواقية للشمس. تم تطبيق تحليل المكونات الرئيسية (PCA) وطريقة UPGMA (طريقة التجميع غير الموزونة بمتوسط الحساب) لاكتشاف التشابهات والاختلافات بين المستخلصات فيما يتعلق بالتركيب الكيميائي، محتوى المستقلبات الثانوية، والأنشطة البيولوجية.

علاوة على ذلك، تم تقييم النشاط المضاد للالتهابات للمستخلصات باستخدام طريقة ألبومين مصل البقري (BSA) ، وتم تقييم الإمكانية المضادة للسكري من خلال اختبار تثبيط إنزيم ألفا-أميلاز. كشفت النتائج أن مستخلصات *S. balansae* ، خصوصًا تلك المستخرجة من جبال الأوراس، تظهر أنشطة مضادة للأكسدة، واقية من الضوء، مضادة للالتهابات، ومضادة للسكري بشكل كبير. يُعزى ذلك إلى غناها بالمركبات الفينولية والفلافونويدات. علاوة على ذلك، حددت الدراسة العديد من المركبات الفينولية الرئيسية وأظهرت تأثير نوع المذيب وجزء النبات على فعالية المستخلصات.

تمثل هذه الدراسة التحقيق الأول الشامل في الخصائص الكيميائية والبيولوجية *Salvia balansae* من جبال الأوراس، مما يبرز إمكاناتها كمصدر لمضادات الأكسدة الطبيعية، العوامل الواقية من الضوء، المضادة للالتهابات، والمضادة للسكري.

الكلمات المفتاحية: *Salvia balansae* ، نبات مستوطن ، LC-MS، مركبات فينولية، الأنشطة البيولوجية، التريتربينويدات.

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DEDICATION

I dedicate this work with deep love and gratitude

To my beloved parents, whose selfless sacrifices have paved the way for my success

To my precious family - my devoted husband and cherished children - for their unwavering patience and constant encouragement

To my dear sisters, whose love and support have been a source of strength and inspiration

To my extended family, whose boundless support and faith have been my pillars of strength

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LIST OF ABBREVIATIONS

ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

AC: Acetone

AChE: Acetylcholinesterase

$AlCl_3$: Aluminum chloride

BHA: Butylated hydroxyanisole

BHT: Butylated hydroxytoluene

COX: Cyclooxygenase

DMSO: Dimethyl sulfoxide

DPPH: 2,2-diphenyl-1-picrylhydrazyl

EDTA: Ethylenediaminetetraacetic acid

EtOH : Ethanol

$FeCl_3$: Ferric chloride

FRAP: Ferric reducing antioxidant power

H_2SO_4 : Sulfuric acid

HCl: Hydrochloric acid

IC_{50}: Half-maximal inhibitory concentration

LC-MS: Liquid Chromatography-Mass Spectrometry

LOX: Lipoxygenase

MeOH: Methanol

NaOH: Sodium hydroxide

NF-κB: Nuclear factor kappa B

PCA: Principal Component Analysis

Ppm: part per million

QE: Quercetin equivalents

ROS: Reactive oxygen species

SBCE: *Salvia balansae* crude extract

SOD: Superoxide dismutase

SPF: Sun protection factor

TAE: Tannic Acid Equivalents

TFC: Total flavonoid content

TFL: Total flavonol content

TNF-α: Tumor necrosis factor-alpha

TPC: Total phenolic content

UPGMA: Unweighted pair-group method with arithmetic mean

UV: Ultraviolet

UV-Vis: Ultraviolet-visible spectroscopy

General Introduction

Oxidative stress is a crucial concept in redox biology and medicine, it is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defences in the body **(Sies, 2015).** This imbalance can damage cells and tissues, contributing to diseases like diabetes mellitus, atherosclerosis, and cancer **(Ravichandran et al., 2023).**

Excessive reactive oxygen species (ROS) generated during oxidative metabolism can trigger inflammatory processes, synthesizing numerous inflammatory mediators. In turn, it can contribute to the development of various chronic diseases. The occurrence of diabetes and its consequences is significantly influenced by oxidative stress and inflammation. Excessive production of reactive oxygen species (ROS) in the body disrupts the equilibrium between internal oxidation and antioxidant actions, resulting in oxidative stress. This stress ultimately harms the macromolecules responsible for insulin secretion **(Han et al., 2023).**

Medicinal plants have long been a cornerstone in the quest for novel therapeutic agents, serving as a reservoir of bioactive compounds harnessed for their curative properties throughout human history **(Shi et al., 2022)**. These plants are a vital part of traditional medicine systems worldwide and have led to the development of many modern pharmaceuticals **(Balant et al., 2018).** The diverse array of secondary metabolites found in medicinal plants, such as alkaloids, flavonoids, tannins, and terpenoids, plays a crucial role in their therapeutic effects, offering antioxidant, anti-inflammatory, antimicrobial, and anticancer activities **(Ravichandran et al., 2023).** In fact, an estimated 25% of all prescribed drugs globally are derived from natural products, a testament to the immense potential within the plant kingdom **(Enyew et al., 2014).**

Among the variety of plant families recognised for their therapeutic properties, the Lamiaceae family is distinguished as a rich source of diverse phytochemicals and is well-known for its aundance of antioxidant-packed polyphenols **(Carović-Stanko et al., 2016).**

Within this phytochemically diverse family lies the genus *Salvia*, which stands out due to its rich phytochemical diversity and extensive use in traditional medicine. *Salvia*, commonly known as sage, encompasses over 900 species distributed globally, many of which are renowned for their medicinal and aromatic properties **(Kintzios, 2000)**. These species are noted for their significant pharmacological activities, including antioxidant, antimicrobial, and anti-inflammatory effects. The chemical complexity of *Salvia* species, attributed to their high content of essential oils, phenolic acids, and flavonoids, makes them valuable in both traditional and modern medicine **(Uysal et al., 2023).**

Salvia balansae, an understudied species within this genus, is endemic to the Aures Mountains and has not been extensively studied. Preliminary investigations suggest that it possesses a unique phytochemical profile with potential therapeutic benefits **(Mahdjoub et al., 2023; Mekki et al., 2023; Mokhtar et al., 2023)**. Given its limited exploration, *S. balansae* represents a promising candidate for further study, particularly in the context of discovering new bioactive compounds with pharmaceutical applications.

This research aims to fill the gap in knowledge about *Salvia balansae* by comprehensively studying, for the first time, the plant's phytochemical composition and biological activities from samples collected in the Aures Mountains region. By systematically investigating the leaves, flowers, and stems of *S. balansae* using different solvents, this study seeks to provide a comprehensive analysis of the phytochemical constituents present in the crude extracts. Additionally, it will evaluate the antioxidant, photoprotective, antidiabetic, and anti-inflammatory activities of these extracts, thereby elucidating the effects of solvents and plant organs on the chemical composition and biological properties of this endemic species.

Our research, reported in this manuscript, is divided into three parts.

1. The first part presents a bibliographic study of the Lamiaceae family, the *Salvia* genus, and the studied plant *Salvia balansae*.
2. The second part details the personal phytochemical works, including phytochemical screening, quantification methods, and LC-MS analysis employed in this study, as well as the in vitro biological activity evaluations, including antioxidant, photoprotective, antidiabetic, and anti-inflammatory activities.
3. The last part presents and discusses the results obtained from the various biological analyses performed on the different organic extracts of *S. balansae*, enabling a comprehensive understanding of the plant's phytochemical profile and associated biological activities.

Literature Review

I. General presentation of the Lamiaceae family

The Lamiaceae (Labiatae) is a very large and important plant family among the dicotyledons. **(Venkateshappa & Sreenath, 2013)** This family is considered one of the largest and most diverse plant families globally, comprising approximately 236 genera and more than 7000 species **(A. Abdelaty et al., 2021).** In the Algerian flora, the Lamiaceae family is represented by 28 genera and 146 species **(Quézel et al., 1962).** The main genera of the Lamiaceae family are *Salvia* (900), *Scutellaria* (360), *Thymus* (220), *Coleus* (325), *Teucrium* (250), *Plectranthus* (300), *Hyptis* (280), and *Nepeta* (200) **(Carović-Stanko et al., 2016).**

The name Lamiaceae originated from 'λάιμος' (laimos) in ancient Greek, which means 'jaws.' This name indicates the capacity of these plant flowers to trap and swallow small insects inside their corollas. On the other hand, Labiatae comes from "Labia", a Latin word that means "lip", indicating the distinct morphological features the species of this family share. The corolla is divided into an upper and lower lip, resembling lips **(Frezza et al., 2019).**

I.1 Taxonomy

The Lamiaceae family, often referred to as the mint family, is a diverse and ecologically important group of flowering plants. This botanical family falls within the Eudicots class of the Plantae kingdom and is categorized under the Lamiales order. Within the Lamiaceae family, there is a remarkable diversity of genera and species, each distinguished by its distinct botanical and chemical characteristics **(Uritu et al., 2018).** According to **Zhao et al. (2021),** the Lamiaceae family is systematically classified as follows.

Kingdom: Plants

Subkingdom: Tracheophytes

Phylum: Spermatophytes

Division: Angiosperms

Class: Magnoliopsida

Subclass: Asterids

Order: Lamiales

Family: Lamiaceae

I.2 Distribution

Lamiaceae species exhibit a global distribution, thriving in various natural environments with diverse growth patterns and habitat preferences. As shown in **Figure 1**, they are particularly abundant in the Mediterranean region. While some species within the family are endemic to specific areas, the overall adaptability of Lamiaceae is noteworthy **(Frezza et al., 2019).** Despite a general preference for warmer climates, these plants display versatility and adaptability, capable of thriving in areas with lower temperatures. This adaptability, coupled with their wide distribution, underscores the ecological resilience and versatility of Lamiaceae species **(Panda et al., 2022; Ramos Da Silva et al., 2021)**

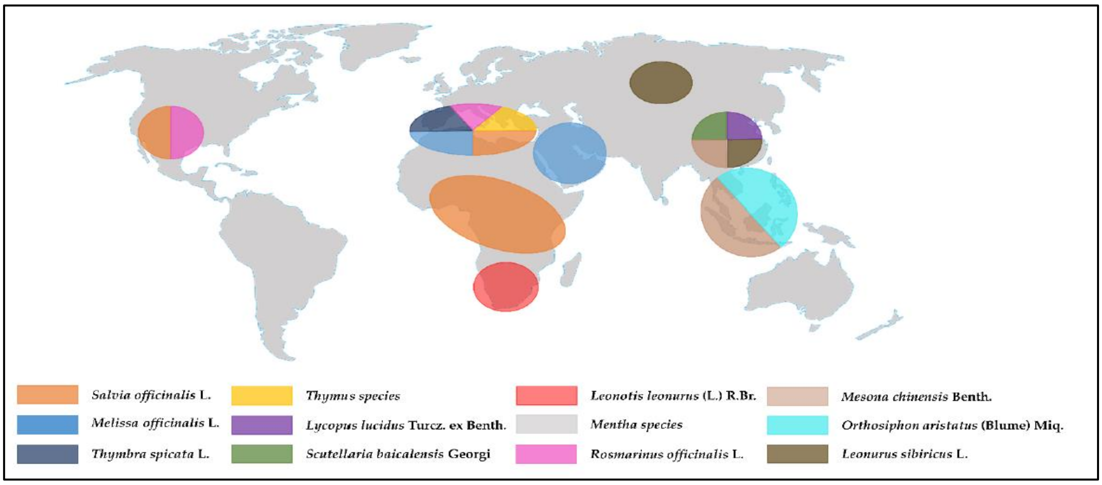


Figure 1. Lamiaceae family distribution around the world **(Diab et al., 2022)**

I.3 Botanical description of Lamiaceae

Lamiaceae plants are typically herbaceous, and they can be annual or perennial; some are aromatic subshrubs while they are rarely found as trees or vines **(Kokkini et al., 2003);** A notable characteristic of these plant species is that they possess stems with four distinct sides or edges, and their leaves are arranged directly across from each other on the stem in pairs, having a single, undivided leaf blade Their flowers are either hermaphrodite or functionally female (male-sterile) and are arranged in whorls, often forming spikes, heads, racemes, or cymes **(Carović-Stanko et al., 2016)**. The calyces of their flowers usually have five lobes and are two-lipped, although there are exceptions. Corollas are sympetalous and two-lipped in most cases, occasionally one-lipped or actinomorphic**(Kokkini et al., 2003).**

These plants typically have four stamens, sometimes reduced to two, with the upper pair being shorter. The ovary is superior, appearing four-lobed when mature, and the style is usually single, gynobasic, and briefly bifid above. The fruits contain four dry (rarely fleshy) nutlets, each containing one seed **(Ramos Da Silva et al., 2021).**

I.4 Phytochemistry

The complex phytochemistry of the Lamiaceae family arises from the variation in metabolites within the plant species, making precise determination in defining metabolites within Lamiaceae species a challenging task; the intricate phytochemistry of Lamiaceae arises from the coexistence of several groups and subgroups within the family, each possessing its distinct phytochemical characteristics and peculiarities **(Abdelaty et al., 2021).** The Lamiaceae family can be broadly categorised into two main groups: volatile terpenoids and non-volatile metabolites in the polar fraction, as shown in **Figure 2 (Frezza et al., 2019).**

The first group includes species known for producing volatile terpenoids commonly found in essential oils. Indeed, the essential oils derived from Lamiaceae are known for their high content of volatile terpenes, including monoterpenes, sesquiterpens, and diterpenes **(Frezza et al., 2019).**

Within the category of monoterpenes, the prominent compounds include 1,8-cineole, α-pinene, β-pinene, camphor, menthol, pulegone, limonene, borneol, γ-terpinene, linalool, thujanol, carvacrol and p-cymene **(Ramos Da Silva et al., 2021).**

As for the sesquiterpens, guaiol, spathulenol, germacrene D, α- copaene, 8-cedren-13-ol, Italicene epoxide, (Z)-α-trans-bergamotol and ß-caryophyllene were the dominant compounds **(Frezza et al., 2019).**

The second group consists mainly of species known for producing non-volatile metabolites in the polar fraction, often displaying reduced essential oil production capabilities. In general, the Lamiaceae family encompasses seven major classes of natural compounds: non-volatile terpenoids, lignans, flavonoids, iridoids, phenyl-ethanoid glycosides, caffeoyl-quinic acids, and phenolic acids **(Diab et al., 2022).**

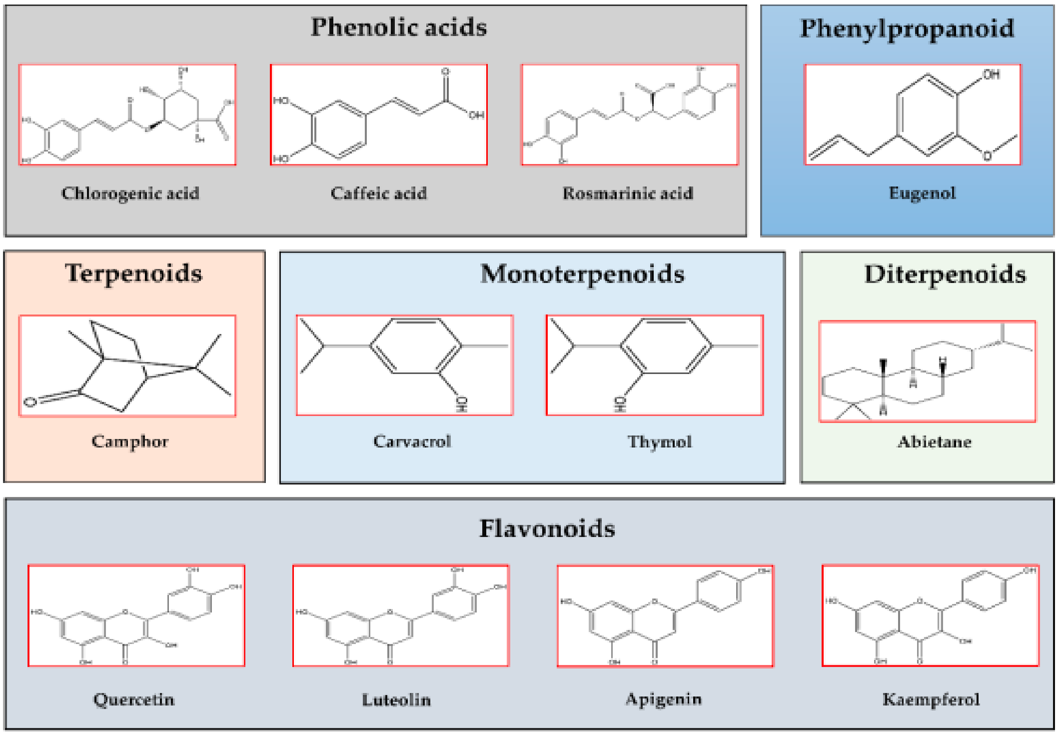


Figure 2. The chemical compositions of the prevalent and frequently encountered bioactive compounds identified in Lamiaceae plant species **(Diab et al., 2022)**

II. General presentation of the *Salvia* genus

The name *Salvia* reflects the substantial value and importance of the *Salvia* species **(Kamatou et al., 2008).** This name originates from the Latin term "Salvar," which signifies saving and healing, reflecting the belief in the healing and medicinal properties associated with this genus **(Wu et al., 2012).** *Salvia*'s historical use in traditional medicine and its diverse applications in culinary and therapeutic contexts further emphasise the appropriateness of its name.

Historically, the name *Salvia* was initially applied to the sage plants in the 1st century AD by the Roman naturalist Pliny the Elder. Over time, this name has transcended linguistic boundaries, finding its way into other European languages, including English. It has since become widely recognised as the common name for sage plants **(Kintzios, 2000).**

II.1 Taxonomy

The subfamily Nepetoideae stands out as the largest and most diverse within the Lamiaceae family, with a substantial 33 genera and about 3685 species **(Zhao et al., 2021).**

Furthermore, the genus *Salvia* emerges as the biggest and most diverse in this subfamily and the entire Lamiaceae family, with about 980 species **(Hu et al., 2018).**

Salvia, commonly identified as sage, is a diverse genus within the mint family, renowned for its extensive and varied taxonomy. Taxonomists have classified over 900 recognised species into four subgenera and twelve sections. The four subgenera of *Salvia* are *Salvia, Audibertia, Leonia,* and *Sclarea*, which represent distinct evolutionary lineages within the genus **(Mahdjoub et al., 2018).** Each subgenus exhibits a range of morphological and ecological traits that distinguish it from the others. For instance, the subgenus *Salvia* encompasses the most significant number of species and is characterised by its diverse floral morphology. In contrast, the subgenus Audibertia is known for its shrubby growth habit and white or pink flowers. **(Rose et al., 2021).**

These classifications are based on a range of characteristics, including floral morphology and genetic markers. This intricate taxonomy reflects the rich diversity and complexity within the *Salvia* genus.

II.1.1 Distribution

The genus *Salvia* displays a broad distribution, spanning various global regions such as tropical rainforests, arid and semi-arid zones, temperate forests, forest edges, meadows, and even degraded sites **(Clasenbockhoff, 2004)**. *Salvia* is absent mainly in northern regions and low-lying tropical areas, including the Amazon basins in central and west Africa. This distinctive distribution characterises *Salvia* as having a sub-cosmopolitan presence **(Wu et al., 2012).**

Members of *Salvia* present notable centres of diversity in various regions, including Central and South America, where approximately 580 species are found **(González-Gallegos et al., 2020).** Mexico stands out as a global hotspot for *Salvia* diversity, hosting around 300 species **(Wood, 2021)**. East Asia contributes approximately 100 *Salvia* species to this botanical tapestry. The Mediterranean and Central Asia regions together host around 250 *Salvia* species **(Hachem et al., 2020)**. Additionally, Iran harbours about 60 species, while Turkey is home to approximately 90 *Salvia* species.

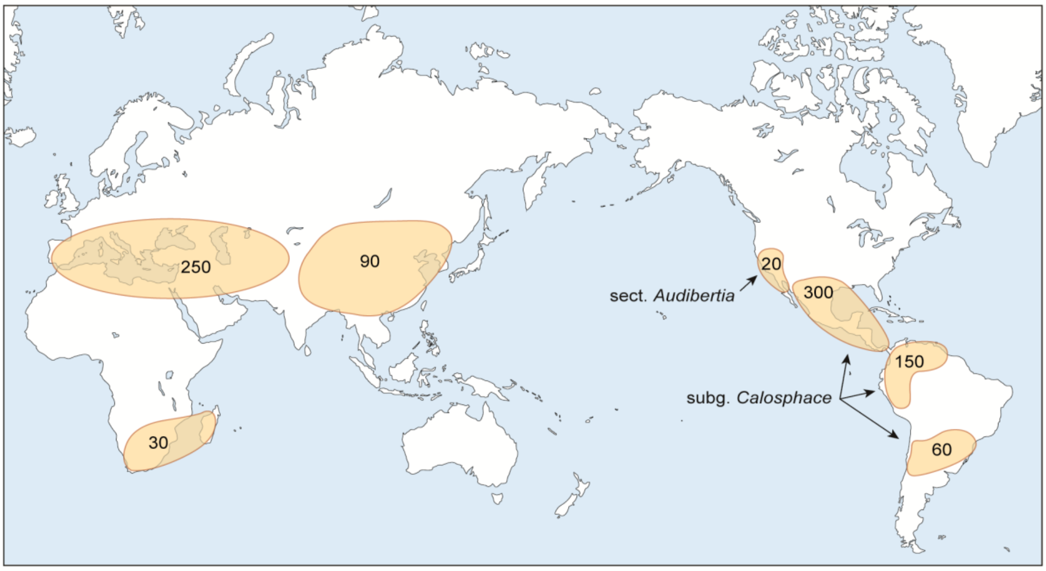


Figure 3. Regions with high concentrations of *Salvia* species **(Sun & Zheng, 2007)**

Africa contributes to the global richness of *Salvia* species with approximately 62 identified members. The most significant accumulation of *Salvia* species is observed in the northwestern and southern regions of the continent. However, it is noteworthy that these species are notably absent from much of the western and tropical regions of Africa **(Kamatou et al., 2008).**

Algeria boasts a remarkable botanical diversity housing 19 out of 36 *Salvia* species found in the Mediterranean region of North Africa, and 10 out of 19 Algerian *Salvia* species are endemic to Algeria **(Quézel et al., 1962).**

Algerian *Salvia* species grow in a variety of habitats, including grasslands, uncultivated fields, forests, hillsides, rocky areas, wadi banks, and scrubland; they thrive in diverse soil conditions and can be found in altitudes ranging from near sea levels up to 2000 meters **(Mahdjoub et al., 2018).**

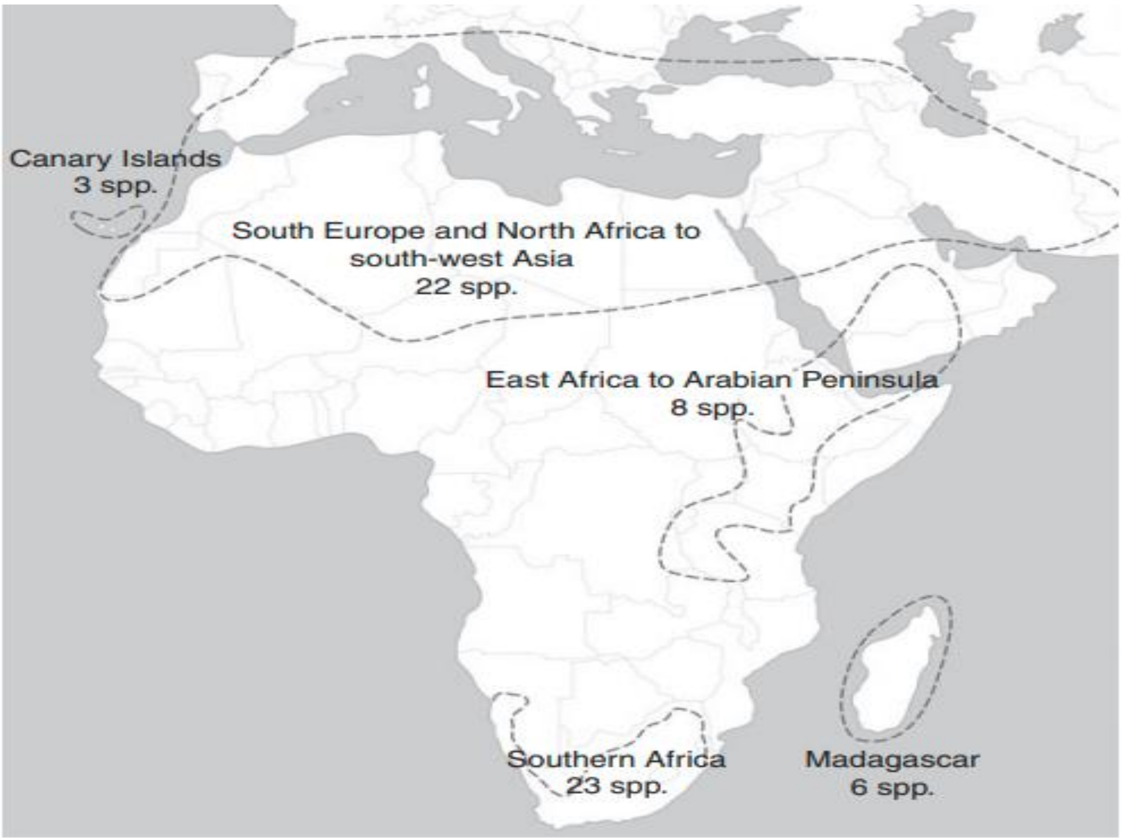


Figure 4. Dispersion of *Salvia s.l.* across the African continent **(Will & Claßen-Bockhoff, 2014)**

II.2 Botanical description

Salvia species exhibit a diverse range of growth forms, including perennial herbs, shrubs, and less commonly annual vines and trees **(Alziar, 1988; Clasenbockhoff, 2004).** Typically attaining heights ranging from 30 to 150 cm **(Jash et al., 2016).**

These plants are distinguished by their unique floral morphology characterised by tubular or bell-shaped calyces and corollas. The corolla features two lips: the upper lip is generally entire or possesses three teeth, while the lower lip typically bears two lobes. Notably, the stamens are reduced to two short structures with two anther cells, one fertile and the other sterile **(Quézel et al., 1962),** varying in sage from approximately 0.5 cm to 8-9 cm, these flowers display a wide spectrum of colours from white and yellow to red, pink, blue, and violet **(Uysal et al., 2023).**

These flowers house two stamens instead of four in most Lamiaceae, each stamen consisting of a short filament and a long connective with two unequal branches. The fruits are smooth ovoids or elongated nutlets; in many species, they have a gel-like coating. **(Clasenbockhoff, 2004)**.

Salvia plants produce dry schizocarp fruits containing four nutlets, which are botanically regarded as true fruits. These nutlets are oval to elongated, varying in size (1-5 mm) among species, and are indehiscent, lacking a natural splitting mechanism **(Jabeen et al., 2023)**. While some species have plain nutlets, many feature a mucilaginous coating aiding in adhesion for dispersal and germination. This coating, rich in polysaccharides, offers hydration and protection. The mucilage, along with nutlet characteristics, assists taxonomists in classifying *Salvia* species. In essence, *Salvia*'s schizocarp fruits house smooth nutlets, often coated in a sticky layer, contributing to their dispersal and protection **(Kılıç & Kiliç, 2021**).

The *Salvia* species are well known for their square stems and typically possess opposite, simple leaves that are often velvety or covered in fine hairs. These leaves exhibit various characteristics, such as being rugose, undivided, serrated, or lobed **(Kamatou et al., 2008)**

Sage plants manifest distinct trichomes across their foliage, stems, and flowers. These trichomes, categorised into glandular and non-glandular types, exhibit variability contingent upon environmental factors **(Alzawi et al., 2023)**. Glandular trichomes, characterised by metabolite-producing cells, notably synthesise aromatic essential oils that contribute to the plant's olfactory profile **(Giuliani et al., 2020).**

The density and morphology of these trichomes vary discernibly among species and are contingent upon specific growth conditions. Xeromorphic species, native to arid environments, notably exhibit heightened trichome numbers **(Giuliani et al., 2018)**. This morphological divergence assumes taxonomic and ecological significance, contributing to water conservation strategies and acting as a deterrent to herbivores and insects **(Eiji & Salmaki, 2016).**

II.3 Bioactive Compounds in *Salvia* Species

Salvia species have complex and diverse phytochemical profiles **(Sharifi-Rad et al., 2018)**, with over 773 polyphenolic compounds identified from 134 *Salvia* species as of 2011. The *Salvia* genus is an important source of phenolic acids, flavonoids, and other polyphenol-based secondary metabolites **(Wu et al., 2012).** These compounds significantly influence the plants' ecological relationships, medicinal properties, and overall biological importance **(Lopresti, 2017).**

Many phytochemical analyses of *Salvia* species have revealed various compounds, with terpenoids emerging as the main bioactive component **(Topçu, 2006).** Phenolic acids and flavonoids are prominently found, particularly in the aerial parts. Leaves and flowers are the main reservoirs for flavonoids, monoterpenoids, and triterpenoids, while roots are characterised by the presence of diterpenoids **(Kintzios, 2000; Lopresti, 2017; Topçu, 2006).**

II.3.1 Phenolic compounds

Polyphenols are a class of natural compounds characterised by their phenolic hydroxyl groups, which include phenolic acids, flavonoids, tannins, and stilbenes, that occurs in many *Salvia* species **(Wang et al., 2019).** *Salvia* plants can exhibit variations in the content, types, and amounts of specific polyphenols depending on environmental conditions, plant age, and species **(Dziadek et al., 2022).** The polyphenolic composition of a given *Salvia* species is influenced by factors such as growing climate, stage of maturity, and genetic differences between species. This can lead to differing profiles of phenolic acids, flavonoids, tannins, and other polyphenols across sage plants based on these parameters **(Wu et al., 2012).**

II.3.1.1 Phenolic acids

Phenolic acids, a class of secondary metabolites, are integral to the chemical composition of *Salvia* species **(Xu et al., 2018)**. In contrast, they are considered one of the major hydrophilic compounds found in the plants of this genus **(Min-hui et al., 2008).** These compounds are distinguished by having a phenolic ring (a benzene ring with one or more hydroxyl groups) and a carboxylic acid group. These compounds contribute to the distinctive features of *Salvia* **(Kumar & Goel, 2019).**

The core structure of phenolic acids in *Salvia* species is mainly caffeoyl depsidic glycoside **(Wang et al., 2019).** This means that caffeic acid serves as a fundamental building block in the structure of various phenolic acids **(Sharma et al., 2020).**

Depending on the extent of polymerisation, phenolic acids can be categorised into various forms, including monomers, dimers, trimers, tetramers, and larger multimers of caffeic acid. This classification reflects the number of caffeic acid units within their structures. Caffeic acid monomers, dimers, trimers, and tetramers are among the prominent forms observed, with trimers and tetramers being the most prevalent **(Wu et al., 2012).**

While oligomeric forms of caffeic acid dominate most *Salvia* species, the simpler monomeric serves as the foundational building block for various phenolic compounds, and its derivatives contribute to the plant's overall chemical diversity **(Silva et al., 2014)**. As the core phenolic acid building block, caffeic acid itself occurs modestly across the *Salvia* genus **(Sytar et al., 2022).**

The most widespread monomeric caffeic acid derivative is danshensu, scientifically known as 3-(3,4-dihydroxyphenyl)lactic acid **(Chen et al., 2014).** This compound is widely distributed across various *Salvia* plants, and it is particularly abundant in *Salvia miltiorrhiza*, a Chinese medicinal herb known for its diverse therapeutic applications **(Sharifi-Rad et al., 2018).**

Another common monomeric derivative is chlorogenic acid, formed by esterifying caffeic acid with quinic acid. Chlorogenic acid exhibits various beneficial activities, including antioxidant, anti-diabetic, antimicrobial, and neuroprotective properties. It has been identified in sage species from different regions **(Wang et al., 2022).**

Additionally, simple modifications like the methylation of caffeic acid give rise to other monomers found in *Salvia*. Examples include ferulic acid, isoferulic acid, mono-feruloyl-R,R-(+)-tartaric acid, syringic acid, and vanilic acid. While these monomeric derivatives may not be as bioactive as the more complex oligomers, they still contribute to the medicinal value of these species **(Lu & Yeap Foo, 2002).**

The prevalent dimer, rosmarinic acid, whose characterised by the presence of a phenolic group (OH) attached to a carboxylic group (COOH) **(Hajimehdipoor et al., 2012).** As a derivative of caffeic acid, it falls within the category of hydroxycinnamic acids, featuring a chemical structure that involves a caffeic moiety esterified with 3,4-dihydroxyphenyllactic acid **(Petersen, 2013).**

This compound is widely distributed in nature, mostly encountered in species of the Boraginaceae family and the Nepetoideae subfamily of Lamiaceae (mint) family **(Petersen & Simmonds, 2003).** It holds significance as a chemotaxonomic marker within the Nepetoideae subfamily **(Xu et al., 2018).**

This dimer holds significance as the major, most abundant, and biologically active compound in *Salvia* species, although its specific content can vary according to the particular species and environmental conditions **(Kamatou et al., 2012)**. For instance, it was found in high concentrations in *S. officinalis* but in lower amounts in *S. hypoleuca* **(Hajimehdipoor et al., 2012)**. A research investigation quantifying the amounts of rosmarinic acid and caffeic acid in different *Salvia* species using high-performance-thin-layer-chromatography (HPTLC), the results indicated that *S. compressa* exhibited the highest amounts of rosmarinic acid, while *S. mirzayanii* had the highest concentration of caffeic acid **(Kamatou et al., 2012).**

Other dimers of phenolic acids have been uncovered in *Salvia* species. One such example is prezwalskinic acid A from Tebetan sage *S. prezwalskii*, and salvianolic acid F in *S. miltiorrhiza* **(Lu & Yeap Foo, 2002).**

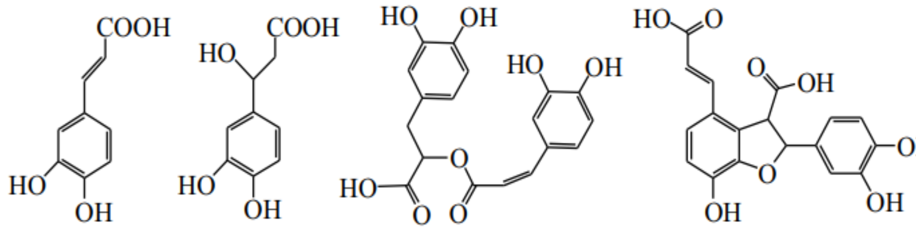
Key trimers contain three linked phenolic acid subunits, mainly caffeic acid. These compounds are considered the largest class of *Salvia* polyphenols identified **(Kumar & Goel, 2019).**

The trimeric phenolic acids found in *Salvia* species can vary among different species, contributing to the overall phytochemical composition. Notably, some commonly occurring trimers in *Salvia* species include lithospermic acid, found in several *Salvia* species such as *S. miltiorrhiza* a and *S. officinalis*, sage-coumarin, Yunnaneic acid E, C, D, and F, salvianolic acid J, H, I, and K **(Lu & Yeap Foo, 2002).**

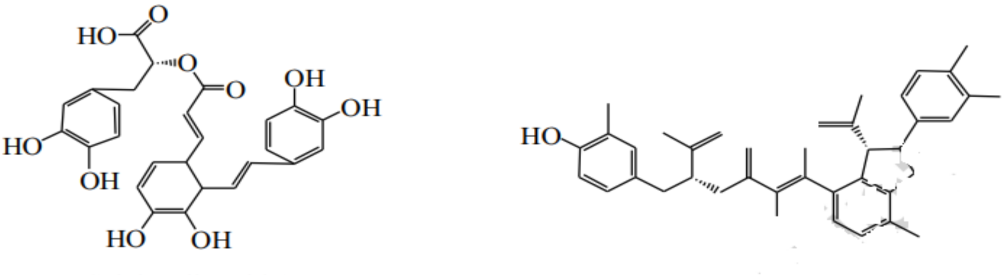
Caffeic acid tetramers comprising four subunits, typically caffeic acid they can be considered as dimerised rosmarinic acid, which means that they are structurally similar to rosmarinic acid **(Lu & Yeap Foo, 2002).**

Salvinolic acid B, E, and L, yunnaeic acid G, and H and sagerinic acid are some of the most well-known caffeic acid tetramers in Salvia species. Among them salvinolic acid B seems to hold a significant taxonomic importance Among them, salvinolic acid B holds significant taxonomic importance among *Salvia* species and is considered a prominent tetrameric form **(Wang et al., 2022).** It is also used as a quality control marker in *Salvia miltiorrhiza* **(Xu et al., 2018)**.

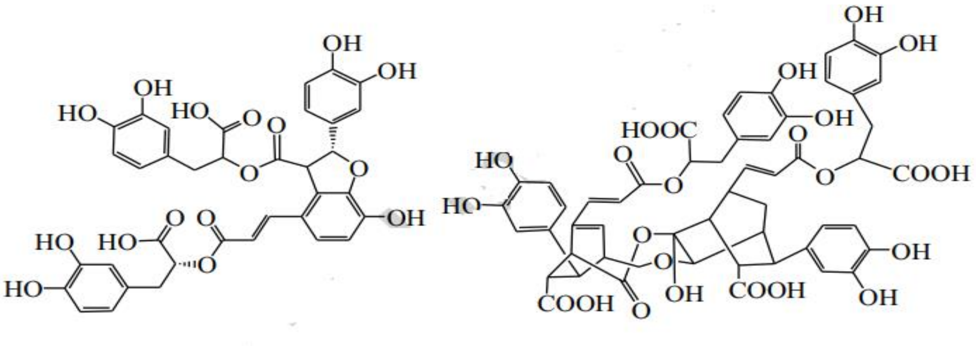
Caffeic acid multimers are a subclass of phenolic acids in *Salvia* plants composed of five or more interlinked caffeic acid subunits in an extended polymeric structure. Compared to the more widely studied dimeric, trimeric, and tetrameric forms, these higher-order caffeic acid oligomers have received less research attention so far. However, current evidence reveals their presence in certain *Salvia* species. Notable examples include yunnaneic acids A and B isolated from *Salvia yunnanensis*, which are unique cyclic hexamers formed from three sets of dimeric units **(Lu & Yeap Foo, 2002; Wu et al., 2012).**



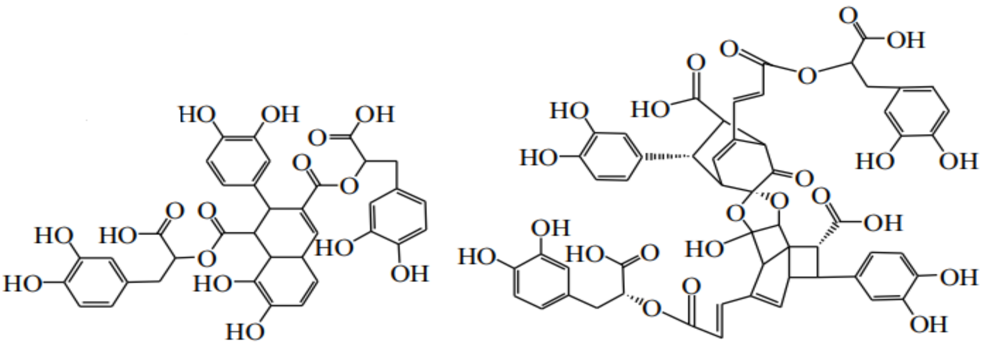
Danshensu Caffeic acid Rosmmarinic acid Przewalskinic acid A



Salvianolic acid A Lithospermic acid



Salvianolic acid B Yunnaneic acid A



Salvianolic acid L Yunnaneic acid B

Figure 5. Prevalent Phenolic Acid Structures in Plants of the *Salvia* Genus **(Xu et al., 2018)**

Table 1. Common phenolic acids in *Salvia* species.

NO	**Structures**	**Phenolic acid**	**Plant**	**Reference**
1	**Monomers**	(3,4-dihydroxycinnamic acid) Caffeic acid	*S. fruticosa.* *S. officinalis* *S. przewalskii*	(Koutsoulas et al., 2019) (Francik et al., 2020) (Ożarowski et al., 2017)
2		Ferulic acid	*S. officinalis*	(Francik et al., 2020)
3		Protocatechuic aldehyde	*S. yunnanensis* *S. miltiorrhiza*	(Y. Li et al., 2020) (Y. Pan et al., 2001)
4		3-(3,4 dihydroxyphenyl)lactic acid (danshensu)	*S. przewalskii* *S . pomifera.* *S.clandestina L.*	(Ożarowski et al., 2017) (Koutsoulas et al., 2019) (Nicolì et al., 2019)
5		3-methoxy-4-hydroxybenzoic acid (vanillic acid)	*S. officinalis* *S. ekimiana*	(Francik et al., 2020) (Orhan et al., 2012)
6	**Dimers**	Rosmarinic acid	*S.verticillata L* *S. miltiorrhiza*	(Katanić Stanković et al., 2020) (Chung et al., 2015)
7		Salvianolic acid F	*S.bulleyana*	(Grzegorczyk-Karolak et al., 2020)
8		Methyl rosmarinate	*S.palaestina*	(Sina Içen et al., 2021)
9		Sagerinic acid	*S. officinalis*	(Velamuri et al., 2020)
10		Przewalskinic acid A	*S. przewalskii*	(Ożarowski et al., 2017)
11	**Trimers**	Lithospermic acid	*S. miltiorrhiza*	(Zhu et al., 2023)
12		Sagecoumarin	*S. officinalis*	(Sharma et al., 2020)
13		Yunnaneic acid J	*S. Africana* *S. yunnanensis*	(Afonso et al., 2019) (Griffith et al., 2014)
14		Salvianolic acid K	*S.bulleyana*	(Grzegorczyk-Karolak et al., 2020)
15		Methyl salvianolate A	*S. yunnanensis*	(Z.-F. Zhang et al., 2008)
	Tetramers	Salvianolic acid B(lithospermic acid B)	*S. miltiorrhiza*	(Chung et al., 2015)

		Rabdosiin	*S. officinalis*	(Francik et al., 2020)
		Sagerinic acid	*S.verticillata L*	(Katanić Stanković et al., 2020)
		Yunnaneic acid G	*S. euphratica var. leiocalycina*	(Zengin et al., 2018)
		dimethyl lithospermate B	*S. miltiorrhiza*	(Kim et al., 2008)
	Multimers	Yunnaneic acids A	*S. yunnanensis*	(Griffith et al., 2014)
	Salts	magnesium lithospermate B	*S. miltiorrhiza*	(Chung et al., 2015)

II.3.1.2 Flavonoids

Flavonoids constitute a significant class of abundant compounds in *Salvia* species, along with phenolic acids and terpenes. They are the primary active components of this genus **(Wang et al., 2019),** essentially found in the aerial parts.

Flavonoids are a major class of polyphenolic compounds characterised by a benzo-γ-pyrone backbone. These compounds comprise 15 carbon atoms structurally organised into two aromatic ring systems interconnected through a three-carbon bridging unit **(Del Rio et al., 2013).**

They are categorised into several subgroups determined by the specific carbon position on the C ring, where the B ring is attached, and the degree of unsaturation and oxidation exhibited within it **(Panche et al., 2016).** The main **s**ubgroups are flavone, isoflavone, flavonols, flavanones, and flavan-3-ols. In contrast, most flavonoids are naturally found as glycosides rather than aglycones **(Del Rio et al., 2013).**

These compounds exhibit an impressive array of biochemical properties, from pigmentation and UV protection to plant-microbe signalling **(Panche et al., 2016).**

Different *Salvia* species contain distinct flavonoid profiles that influence their pharmacological activities. The most prevalent flavonoids are flavonols, flavone, and their glycoside forms **(Lu & Yeap Foo, 2002)**.

Additionally, substitutions on both the B ring and A ring along with oxygenation on the A ring at positions C6 and/or C6 plus C8 were identified in *Salvia* species. Notably, there was a frequent occurrence of mono-substituted (4`) and di-substitution (3`, 4`) B ring structure **(Kharazian, 2013).** Besides flavones and flavonols, some species contain flavanone, aurone, and other uncommon flavonoid types **(Lu & Yeap Foo, 2002)**.

Flavones are the predominant flavonoid subgroup in *Salvia*. They represent a prominent subcategory within the flavonoid family, widely found in the plant kingdom. Flavones are characterised by the presence of an unsaturated alkene linkage between the second and third carbons, a ketone group attached at Carbone 4, and the absence of oxygenation at C3 **(Panche et al., 2016; Picos-Salas et al., 2021).**

Flavones exhibit many possible substitutions, such as O-glycosylation, methylation, hydroxylation, C-glycosylation, and alkylation **(Del Rio et al., 2013).** In *Salvia* species, flavones that undergo 6-hydroxylation have been identified as having significant taxonomic importance, such as cirsiliol, cirsimartin, nepetin, and salvigenin **(Lu & Yeap Foo, 2002).** Salvigenin, in particular, is identified as a distinctive flavone in Anatolian sage and has also been isolated from most of the examined *Salvia* species growing in Turkey **(Topçu et al., 2017).** While substitution at positions 6 and 8 of flavone is commonly observed within the Lamiaceae family **(Valant-Vetschera et al., 2003),** the occurrence of 8 hydroxylated flavone is uncommon in *Salvia* species, and one of the rarest representatives is salvitin encountered in *S.plebeia* **(Lu & Yeap Foo, 2002).**

Regarding glycosylation, flavone aglycones are particularly plentiful. Methyl ether derivatives of flavones are extensively present, mostly in leaves or exudate from the aerial component of *Salvia* species **(Topçu et al., 2017).**

Luteolin, apigenin, and their derivatives seem to be the most common flavones encountered in the genus of *Salvia* **(Lopresti, 2017).** However, luteolin and its derivatives appear to be more ubiquitous and quantitatively abundant in most studied extracts of this genus than apigenin and its derivatives **(Topçu et al., 2017)**, although some *Salvia* species can show higher levels of apigenin. Still, luteolin emerges as the predominant flavone across *Salvia* species **(Nikolova et al., 2006).**

While flavones are the prevalent flavonoids in the *Salvia* genus, flavonols have also been observed in numerous *Salvia* species **(Lu & Yeap Foo, 2002).** Unlike flavones, flavonols contain an additional hydroxyl group attached at carbon 3 of their central ring structure, which is also subject to glycosylation. Flavonols display diverse methylation patterns **(Panche et al., 2016).**

The most frequent flavonols aglycone encountered in *Salvia* plants seems to be quercetin and kaempferol, along with their major glycosides rutin (quercetin-3-O- rutinoside) and kaempferol-3-O-glycoside **(Kharazian, 2013).** These major flavonols appear to be present in most studied *Salvia* plants such as *S.officinalis, S.fruticosa, and S.tomentosa* **(Nikolova et al., 2006).**

Flavonols aglycones less commonly found include isorhamnetin and herbacetin, along with their glycosides such as narcissin (isorhamnetin-3-O-rutinoside) **(Kharazian, 2013).** These compounds were extracted and identified in certain *Salvia* species, including *S.pomifera* and various Turkish sage varieties **(Topçu et al., 2017).**

Although many studies have reported that a variety of flavonol compounds have been identified across *Salvia* plants. However, the many different hydroxylation, methylation, and glycosylation positions on the flavone nucleus are much more limited with *Salvia* flavonols **(Kharazian, 2013).** As for 6-hydroxyflavonol position, this derivative is mainly represented by 6-hydroxykaempferol and its derivatives **(Lu & Yeap Foo, 2002).**

In *Salvia* plants, flavonol glycosides display a distinct pattern of substitution, whereas glycosidic bonds are mainly formed at the 3-hydroxyl position; bonding is exemplified by various Kaempferol 3-O-glycosides found in many *Salvia* sage plants. These glycosides vary, ranging from simpler forms like kaempferol3-O-glucosides in certain species to more complex triglycosides, such as astragalin, a triglycosides isolated from *S.cavaleriei* **(Kharazian, 2014)**. Similarly, quercetin glycosides prevalent in various *Salvia* plants, such as isoquercetin, mequielcanin, and quercetin 3-O-robinoside, also connect saccharides like glucose, gluconic acid, or robinose at the definitive 3-hydroxyl sites. Thus, the methylated forms of these quercetin 3-O-glycosides further diversify the pool of flavonol derivatives in select taxa like *S.blepharophylla* **(Kharazian, 2013)**.

While flavone and flavonols are the predominant subclasses of flavonoids in *Salvia*, other subclasses such as dihydroflavonols, flavanone, chalcones, anthocyanin, and isoflavonoids being infrequently encountered or found only in trace amounts in the studied *Salvia* species so far **(Kharazian, 2013, 2014)**.

Table 2. Major Flavonoid Types and Their Occurrence in *Salvia* Species

NO	Flavonoid Class	Compound	Plant	Reference
1	**Flavones**	Apigenin	*S. officinalis* *S. sclarea*	**(Uţă et al., 2021)**
2		Luteolin	*S. miltiorrhiza*	**(S. Lu, 2021)**
3		Chrysoeriol	*S. splendens*	**(Taher et al., 2021)**
4	**Flavonols**	Kaempferol	*S. cadmica*	**(Kocak et al., 2016)**
5		Quercetin	*S. hispanica*	**(Aslam et al., 2020)**
6		Myricetin	*S. fruticosa*	**(Tundis et al., 2017)**
7	**Flavanones**	Naringenin	*S. leucophylla*	**(Mocan et al., 2020)**
8		Hesperidin	*S. officinalis*	**(Özüpek et al., 2023)**
9	**Flavanols**	Catechin	*S. officinalis*	**(Draz et al., 2021)**
10	**Anthocyanidins**	Cyanidin	*S. splendens*	**(Faisal et al., 2022)**
11	**Isoflavones**	Genistein	*S. hispanica*	**(Ghafoor et al., 2020)**

II.3.2 Terpenoids

Terpenoids are a highly prevalent and structurally varied class of plant-derived natural compounds. They are derived biosynthetically from isoprene units and classified according to the number of isoprenes (C5) units they have, including monoterpenoids (10 carbon atoms), sesquiterpenoids (15 carbons), diterpenoids (20 carbons), sesterterpenes (25 carbons), and triterpenoids (30 carbons) **(Yang et al., 2020)**. Species belonging to the *Salvia* genus are renowned for their remarkable and immense terpenoid diversity, encompassing various structural classes and exhibiting unique carbon skeletons **(Wu et al., 2012).**

Monoterpenoids and sesquiterpenoids represent the primary constituents of the essential oils derived from *Salvia* species. These volatile terpenoids contribute significantly to the characteristic aromas associated with many *Salvia* plants **(Campos-Xolalpa et al., 2018)**. Common monoterpenoids found in *Salvia* essential oils include linalool, 1,8-cineole (eucalyptol), camphor, α-pinene, and β-pinene. Sesquiterpenoids, though relatively less abundant, have also been reported in *Salvia* species, with spathulenol being one of the most frequently encountered **(Topçu et al., 2017)**.

Diterpenoids, comprising 20 carbon atoms derived from four isoprene units, represent the largest, most diverse and abundant group of terpenoids found in *Salvia* species **(Bonito et al., 2011),** accounting for 545 out of the 791 *Salvia* constituents reported. These diterpenoids can be further classified into five distinct subgroups based on their structural features: abietane, clerodane, pimarane, labdane, and other diterpenoids **(Wu et al., 2012)**.

Abietane diterpenoids are the most abundant and diverse class of diterpenoids found in *Salvia* species, accounting for over 300 of the 545 diterpenoids isolated from the genus **(Wu et al., 2012)**. These tricyclic compounds are distinguished by the typical abietane skeleton, which can undergo various oxidative transformations and rearrangements, leading to an impressive array of structural diversity **(Bonito et al., 2011).** This structural type is particularly prevalent among the Anatolian *Salvia* taxa, which have yielded an impressive array of over 160 abietane diterpenoids, with approximately 120 newly discovered structures **(Topçu et al., 2017).**

Some of the most commonly encountered abietane diterpenoids include the bioactive compounds royleanone, 7-O-acetylhorminone, ferruginol, and horminone, which have demonstrated a broad spectrum of pharmacological activities **(Askari et al., 2021).**

While abietane diterpenoids dominate the *Salvia* genus overall, their distribution is concentrated in the European, North American, and Asian evolutionary branches, mainly in subgenera *Audibertia*, *Glutinaria*, *Rosmarinus*, as well as the clades encompassing *Salvia*, *Sclarea*, and *Salvia aegyptiaca* species. In contrast, abietanes are primarily absent from the Neotropical subgenus *Calosphace*, except for the early diverging lineages **(Ortiz-Mendoza et al., 2022)**.

Conversely, clerodane diterpenoids, characterised by their unique bicyclic skeleton, are comparatively less abundant in *Salvia* but show an inverse distribution pattern. These clerodanes are primarily restricted to the Neotropical Calosphace clade **(Ortiz-Mendoza et al., 2022)**

Salvia divinorum is renowned for containing clerodane diterpenoids like salvinorin A, divinatorin, and salvinicin A, with salvinorin A being a highly potent and selective kappa-opioid receptor agonist, exhibiting hallucinogenic, anti-inflammatory, antinociceptive, and antidiarrheal effects **(Zawilska & Wojcieszak, 2013)**.

Beyond *Salvia divinorum*, other *Salvia* species have also yielded clerodane diterpenoids, such as the cytotoxic salvileucalin B from *S. leucantha* and the antimicrobial splenolide A from *S. xalapensis* **(Esquivel et al., 2005)**.

While abietanes and clerodanes dominate the diterpenoid landscape in *Salvia*, the genus has also been found to produce diterpenoids with alternative ring systems, including pimaranes and labdanes **(Bonito et al., 2011).**

Pimarane diterpenoids, with their characteristic [4,4,1]-tricyclic skeleton, have been isolated and elucidated from several species within the *Salvia* genus, such as *S. wiedemannii,* which yielded the novel compound 14-oxo-pimaric acid. These pimarane derivatives have demonstrated diverse biological activities, ranging from antimicrobial to anti-inflammatory properties **(Wu et al., 2012)**.

In contrast, labdane diterpenoids, bearing the [4,4,6]-tricyclic framework, are less commonly reported in *Salvia,* but examples like the antimicrobial 8(17),12E,14-labdatrien-6,19-olide from *S. leriaefolia* have been identified **(Kintzios, 2000).**

While less diverse compared to the diterpenoids, *Salvia* species still display a notable array of triterpenoid structural classes. The most commonly encountered triterpenoids are of the oleanane and ursane skeletons, exemplified by the widespread occurrence of oleanolic and ursolic acids. Some *Salvia* species have also been found to contain triterpenoids with the less common lupane framework, such as betulinic acid **(Topçu, 2006).**

Certain *Salvia* species have yielded unique and highly functionalised triterpenoid structures, demonstrating the genus's capacity for producing rare and complex triterpenes. The roots of the endemic *S. kronenburgii,* for instance, afforded a series of novel tetrahydroxylated ursane and oleanane triterpenoids **(Çebi et al., 2019).**

Table 3. Prevalent Terpenoid Compounds in the *Salvia* Genus

NO	Structures	Compound	Plant	Reference
1	Monoterpenoid	α-Terpineol	*S. sclarea*	**(Kačániová et al., 2023)**
2		1,8-Cineole	*S. officinalis*	**(Craft et al., 2017)**
3		Linalool	*S. sclarea*	**(Rajabi et al., 2014)**
4	Sesquiterpenoid	spathulenol	*S. mirzayanii*	**(Ziaei et al., 2011)**
5		β-Caryophyllene	*S. multicaulis*	**(Talebi et al., 2021)**
6		salviadienol A	*S. chinensis*	**(Liu et al., 2019)**
7	Diterpenoid	Ferruginol	*S. miltiorrhiza*	**(Xu et al., 2018)**
8		Salvinorin A	*S. divinorum*	**(Selvaraj et al., 2023)**
9		iguestol	*S. broussonetii*	**(Fraga et al., 2014)**
10		Tanshinone I	*S. officinalis*	**(X. Wang et al., 2020)**
11	Triterpenoid	Oleanolic Acid	*S. miltiorrhiza*	**(Tung et al., 2017)**
12		Ursolic Acid	*S. officinalis*	**(Ghorbani & Esmaeilizadeh, 2017)**

II.4 Biological activities

The *Salvia* genus, comprising numerous herb and shrub species, has a rich history of traditional medicinal applications across diverse cultures worldwide **(Sharifi-Rad et al., 2018)**. For centuries, these plants have been valued for their medicinal virtues. In European traditional practices, various *Salvia* species were employed to address gastrointestinal disorders, respiratory ailments, excessive sweating, and skin inflammations**.** Similarly, in Asian and South American traditional medicine systems, these plants are found use in treating conditions like rheumatism, gout, ulcers, diarrhea, and hyperglycemia **(Ortiz-Mendoza et al., 2022; Xu et al., 2018)**.

In Africa and the Mediterranean region, *Salvia* plants have also played a significant role in traditional medicine. Several indigenous African *Salvia* species, such as *S. repens* and *S. runcinata*, have been used to treat various ailments, including skin conditions, respiratory issues, and bacterial infections. Similarly, in the Mediterranean region, species like *S. fruticosa* and *S. pomifera* have been traditionally used for their anti-inflammatory, antioxidant, and antimicrobial qualities **(Kamatou et al., 2008; Mervić et al., 2022).**

While *Salvia officinalis* is the most widely recognised representative, numerous other species, such as *S. fruticosa, S. lavandulifolia, S. sclarea,* and *S. tomentosa,* hold significance as sources of essential oils, culinary applications, pharmaceuticals, cosmetics, and antimicrobial agents **(Hao et al., 2015)**. Notably, *S. miltiorrhiza* and *S. hispanica* have been integral to traditional Chinese and South American medicine, respectively, for their applications in cardiovascular health and as nutraceuticals **(Kintzios, 2000)**.

II.4.1 Antioxidant activity

Numerous studies have unveiled the remarkable antioxidant potential of various *Salvia* species, underscoring their rich phytochemical diversity. Essential oils and extracts derived from species such as *S. syriaca, S. nemorosa, S. limbata, S. sclarea, S. reuterana, , S. miltiorrhiza, S. officinalis, S. lachnocalyx, S. sahendica, S. grossheimii, S. palaestina,* and *S. eremophila* have exhibited potent radical neutralizing abilities and inhibit lipid peroxidation **(Bonesi et al., 2017; Porres-Martínez et al., 2017; Tosun et al., 2009).**

The antioxidant capacities of *Salvia* species have been extensively studied, with many extracts and essential oils demonstrating exceptional free radical neutralising abilities and lipid peroxidation inhibition. Certain *Salvia* species, such *as S. euphratica, S. sclarea,* and *S. verticillata,* have emerged as particularly promising, exhibiting antioxidant activities that rival or even surpass synthetic antioxidants like BHA and BHT **(Gokdogan & Burun, 2022; Shojaeifard et al., 2023).** For instance, methanolic extracts from *S. reuterana, S. limbata,* and *S. sclarea* have demonstrated potent free radical scavenging ability against DPPH radicals, inhibition of oxidation in the β-carotene/linoleic acid system, and significant ferric reducing power comparable to or exceeding that of BHT **(Askari et al., 2021).** Similarly, essential oils from *S. palaestina* and *S. syriaca* have shown radical scavenging capacities on par with ascorbic acid **(Bahadori et al., 2017).** These findings underscore the rich phytochemical diversity of *Salvia* species and their tremendous potential as natural, plant-based sources of potent antioxidants.

These antioxidant effects can be ascribed to the presence of bioactive constituents, including phenolic compounds such as rosmarinic acid, salvianolic acids, and carnosic acid, flavonoid compounds like luteolin and apigenin glycosides, and terpenoids like spathulenol and abietane diterpenoids. Phenolic acids and flavonoids possess the ability to directly neutralise and stabilise highly reactive free radical species such as DPPH radicals, superoxide anions, and hydroxyl radicals by donating hydrogen atoms or electrons from their phenolic hydroxyl groups, thereby neutralising and stabilising the reactive species **(Bonesi et al., 2017)**. Additionally, they can chelate metal ions like iron and copper, inhibiting their involvement in Fenton-like redox reactions. that generate highly reactive hydroxyl radicals **(Zhumaliyeva et al., 2023).**

Terpenoids, exemplified by spathulenol in *S. syriaca*, exhibit antioxidant activities by inducing the upregulated expression of key antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, which play crucial roles in the cellular defence against oxidative stress **(Bonito et al., 2011; Topçu, 2006)**. Moreover, certain abietane diterpenoids, such as carnosic acid and rosmanol, can modulate signalling pathways like Nrf2 and NF-κB, regulating transcriptional activities of genes implicated in the cellular antioxidant response and inflammatory processes **(Zhumaliyeva et al., 2023).**

These molecular mechanisms, involving direct radical scavenging, metal chelation, enzyme induction, and signaling pathway modulation, contribute synergistically to the potent antioxidant capacity of *Salvia* species **(Tam et al., 2021).**

II.4.2 Anti-Inflammatory Activity

Salvia species have demonstrated remarkable anti-inflammatory properties, making them potential candidates for managing various inflammatory conditions. The active constituents present in these plants, such as tanshinones, salvianolic acids, and polysaccharides, have been found to modulate key inflammatory pathways and mediators **(Bonesi et al., 2017)**.

One notable example is the extract and compounds isolated from *Salvia miltiorrhiza*, which have shown promising effects in alleviating chronic hepatic inflammation **(Lu, 2021)**. These preparations can act on Kupffer cells, the resident macrophages in the liver, by downregulating the activity of the p38 MAPK-NF-κB65-c-fos pathway. By inhibiting this crucial signalling cascade, *Salvia miltiorrhiza* extracts and compounds can effectively suppress the activation of Kupffer cells and prevent the inflammatory response induced by creatine kinase **(Hao et al., 2015; Xu et al., 2018).**

Moreover, studies have shown that *Salvia* species can help reduce inflammation in various experimental models, including inhibition of enzymes like 5-lipoxygenase, COX-1, and COX-2. *Salvia* compounds can also reduce the levels of inflammatory mediators such as nitric oxide, prostaglandin E2, and cytokines like TNF-α and interleukins **(Lopresti, 2017; Puangpraphant et al., 2022)**. These mechanisms contribute to the ability of *Salvia* extracts and compounds to alleviate inflammatory conditions, ranging from hepatic injury to rheumatoid arthritis and neuroinflammation **(Bonesi et al., 2017; Brindisi et al., 2021)**.

II.4.3 Cytotoxic Activity

The cytotoxic capacity of *Salvia* species has been extensively studied, with various extracts and compounds exhibiting potential anticancer effects. The genus contains a wide variety of phytochemicals, particularly terpenes, including diterpenoids, triterpenoids, and sesterterpenes, that have exhibited remarkable cytotoxicity towards a wide range of malignancies **(Uysal et al., 2023)**.

Various terpenoids isolated from *Salvia* species have exhibited potent anticancer activities. Diterpenoids like taxodione, ferruginol, and hypargenins belonging to the abietane, clerodane, and labdane classes have shown significant cytotoxic properties over breast, lung, colon, and leukemia cancer cell lines at low micromolar concentrations **(Campos-Xolalpa et al., 2018).** Although less abundant, certain triterpenoids from *Salvia,* such as salvinemorol and highly oxygenated ursane-type triterpenes, have also demonstrated selective anticancer potential, targeting renal, lung carcinoma, and breast cancer cells **(Topçu, 2006; Tung et al., 2017)**. Notably, terpenoids extracted from *Salvia lachnocalyx*, including geranyl farnesol, sahandinone, and 4-dehydrosalvilimbinol, have demonstrated the ability to trigger apoptosis in MOLT-4 cancer cells, potentially through a mechanism involving topoisomerase I inhibition **(Mirzaei et al., 2020)**.

Furthermore, extracts from various *Salvia* species have displayed dose-dependent inhibition of cancer cell growth, with some exhibiting specificity towards certain cell types. For instance, extracts of *S. radula* and *S. africana-caerulea* exhibited notable anticancer activity, specifically targeting and inhibiting the growth of breast cancer cells (MCF-7) and brain (SF-268) cancer cells **(Formisano et al., 2016; Heerden et al., 2007)**. *S. lanceolata* extract was most potent against colon cancer cells (HT-29, IC_{50} 17.05 to 57.00 µg/mL) **(Kamatou et al., 2008)**.

Additionally, certain phytochemicals isolated from *Salvia* species have shown the ability to modulate key pathways involved in cancer progression, such as inducing apoptosis, inhibiting angiogenesis, and targeting hypoxia-inducible factors **(Askari et al., 2021; X. Wang et al., 2020)**. Notably, the cytotoxic effects of the bioactive molecule salvianolic acid B against U80 glioma cells were mediated through the generation of reactive oxygen species (ROS) following activation of the p38 signalling pathway, ultimately leading to apoptosis, while compounds like sibiriquinone A, cryptotanshinone, and dihydrotanshinone I from S.miltiorrhiza exhibited remarkable potency in suppressing the expression of luciferase induced by hypoxic conditions in gastric and hepatocellular carcinoma cell lines, with inhibitory concentrations as low as 0.28 µM **(Wang et al., 2019).**

II.4.4 Cognitive-enhancing effect

Growing research suggests that multiple *Salvia* species may enhance cognitive abilities, although the effects seem to depend on the specific species and preparation methods used **(Lopresti, 2017).**

Promising benefits like improved memory, attention, and neuroprotection have been consistently demonstrated for *S. officinalis* and *S. lavandulifolia* in human studies. Their terpenoids (α/β-pinene, 1,8-cineole), flavonoids (luteolin, quercetin), and phenolics (rosmarinic acid, carnosic acid) modulate neurotransmitters like acetylcholine by inhibiting acetylcholinesterase, reduce neuroinflammation via NF-κB suppression, promote BDNF/NGF-mediated neuronal survival and upregulate neuroplastic mediators. **(Guillemet et al., 2020; Salehi et al., 2019).** Their diverse phytochemicals, like terpenoids, flavonoids and phenolics, are thought to modulate neurotransmitters, reduce neuroinflammation and promote neuroplasticity. Intriguingly, *S. miltiorrhiza* has shown promise in mitigating cognitive deficits post-cerebrovascular events **(Tang et al., 2021)**.

However, not all species exhibit uniform effects across cognitive domains and neurobiological markers. Moreover, certain psychoactive species like *S. divinorum* contain compounds like salvinorin A with unexplored cognitive implications **(Pelot et al., 2017)**. While methodological limitations exist, the available data warrants further systematic investigation into isolating the active principles, elucidating mechanisms, and establishing the therapeutic potential of specific *Salvia* species and chemotypes for cognitive disorders through rigorous clinical research **(Lopresti, 2017).**

II.4.5 Other Activities

Salvia species possess a remarkable array of biological activities beyond their well-known antioxidant and anti-inflammatory effects. They have demonstrated potent antimicrobial properties against bacteria, fungi, and viruses **(Topçu et al., 2017)**, as well as promising antidiabetic **(Bahadori et al., 2017)**, antiangiogenic **(Zhumaliyeva et al., 2023)**, hepatoprotective **(Hao et al., 2015)**, and memory-enhancing effects **(Lopresti, 2017).** Several

Salvia plants exhibit significant antinociceptive properties **(Hwang et al., 2018)**. Moreover, some of these plants have displayed anticancer and cardiovascular protective properties **(Topçu et al., 2017)** and cholinesterase inhibitory activities **(Lopresti, 2017).** They have also shown enzyme inhibitory effects relevant to diabetes and obesity management. Additionally, some species have displayed antimalarial, antiviral, and anti-obesity potential. This vast array of biological activities, attributed to their diverse phytochemical constituents, highlights the immense therapeutic potential of the *Salvia* genus and underscores the importance of further research to fully explore and harness these versatile plants for various healthcare applications **(Sharifi-Rad et al., 2018).**

III. General presentation of *Salvia balansae* de Noë ex Coss

Salvia balansae Noë ex Coss. is an endemic medicinal plant species native to and confined within the geographic boundaries of Algeria **(Quézel et al., 1962).** Out of the 19 *Salvia* species found in Algeria, concentrated mainly in the northern regions, only *S. balansae* and *S. jaminiana* are restricted endemics protected by law **(Jora, 2012; Mahdjoub et al., 2018; Meddour et al., 2023; Mostari et al., 2020)**. *S. balansae* is further categorised as "rare" on the IUCN Red List **(Mostari et al., 2016)**.

This aromatic bushy sub-shrub grows 30-70 cm tall with woody stems, green linear leaves, and flowers featuring a calyx and corolla both divided into two lips exceeding 2 cm in length **(Quézel et al., 1962).** Remarkably, *S. balansae* populations are disjunctly distributed across over 500 km between the maritime northwest coastal region near Mostaganem with mild winters and the continental high-elevation Aures Mountains over 1000 m higher with colder winters **(Mokhtar et al., 2023; Mostari et al., 2020).** While sharing the semi-arid bioclimate, these populations differ in flower colour and leaf morphology. Consequently, the Aures taxon is considered a narrow locality endemic found solely in scrublands along the Oued Abdi valley, while the northwest typification is restricted to the Dahra and Pont du Cheliff area around Mostaganem **(Mostari et al., 2020; Seltzer et al., 1946).**

This disjunct distribution highlights *S. balansae* as a rare Algerian endemic exhibiting local adaptation across contrasting environments.

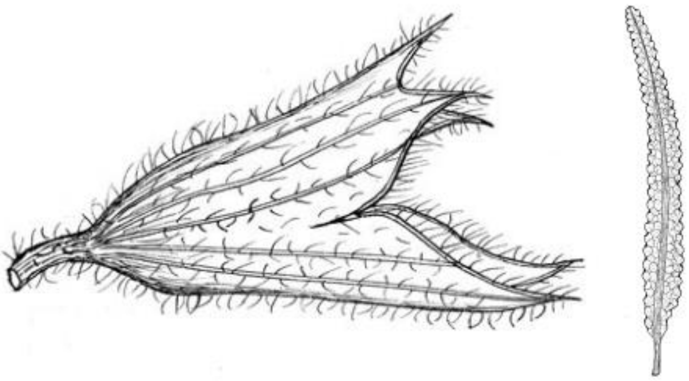


Figure 6. Botanical illustration of *Salvia balansae* de Noë ex Coss **(Quézel et al., 1962)**

III.1 Previous studies on *Salvia balansae* de Noë ex Coss

While many sage species are widespread and well-studied, endemic taxa, such as *Salvia balansae*, are poorly characterised regarding phytochemical content and pharmacological potential. The limited research conducted so far has exclusively targeted the population from the Mostaganem region in northwestern Algeria. Thus, only a few preliminary studies have provided insights into certain chemical features and biological activities of this localised population.

The first study **(Mekki et al., 2023)** examined the therapeutic potential of aqueous leaf extracts from Mostaganem *S. balansae* plants. The research findings demonstrated that these extracts possessed significant antioxidant and antidiabetic properties in vitro and could ameliorate metabolic disorders and testicular dysfunction associated with obesity in animal models.

Another investigation by **(Mahdjoub et al., 2023)** employed HPLC-DAD analysis to screen and profile the phenolic phytochemicals contained within leaf extracts of the Mostaganem *S. balansae* population. Significant amounts of total phenolics and flavonoids were detected. This analysis identified twelve individual phenolic constituents, with benzoic acid and tannic acid representing the major components. Notably, this study reported the presence of quercetin, benzoic acid, hydroxyflavone, myricetin, and ascorbic acid in *S. balansae* for the first time. When evaluated through multiple in vitro antioxidant assays, the leaf extracts exhibited potent antioxidant capacity, including DPPH and ABTS, chelating iron ions, and displaying reducing power properties, with the reducing potential increasing proportionally with extract concentration. Furthermore, a strong proportional correlation was observed between the extract's antioxidant activities and its phenolic and flavonoid content.

The most comprehensive phytochemical study so far is by **Mokhtar et al. (2023)** on the Mostaganem population. It provided the most comprehensive chemical profiling and bioactivity evaluation of this population to date. Using techniques like HPLC-DAD, HPLC-MS, GC-MS and ICP-MS, they identified phenolics (e.g. catechin, myricetin), fatty acids, and minerals in the aerial parts. Bioassays revealed potent antioxidant capacity and promising antimicrobial effects for the methanolic extract, though no significant enzyme inhibition.

However, despite these studies establishing the therapeutic value and phytochemical composition of the Mostaganem population, no research has been conducted yet on the distinct and morphologically different populations found in the remote Aures Mountains over 500 km away, which likely represents a separate endemic taxon. The phytochemistry and biological activities of this unstudied Aures mountain lineage remain entirely unexplored in terms of biology and chemistry.

Experimental part

Materials and Methods

I. Materials

I.1 Plant material

Aerial parts of *Salvia balansae* de Noë plant species were collected in June 2019 during its flowering stage. The collection site was Ichemoul, a region located 1350 meters above sea level in the Batna area of Algeria. The geographic coordinates of the site are 35.2721° N latitude and 6.4629° E longitude. This region has a supra-Mediterranean climate, with annual precipitation exceeding 450 mm. The taxonomic identification was authenticated by Dr Zeraib A., a lecturer at Abbes Laghrour University. A voucher specimen representing this collected plant material has been deposited in the Herbarium of the Biotechnology, Water, Environment and Health Laboratory at Abbes Laghrour University in Khenchela, Algeria, under the code ZA-SB-003-6-2019.

The fresh plant samples were thoroughly washed with water. Flowers, leaves, and stems were separated and air-dried in a well-ventilated room for three weeks at room temperature. The desiccated organs were individually powdered using dedicated mills to avoid cross-contamination. Powders were partitioned into opaque sachets by organ type, sealed, and stored under ambient, dark conditions until analysis, preserving their phytochemical composition.

Figure 7. *Salvia balansae* in bloom: Endemic sage of the Aures Mountains, Algeria

II. Methods

II.1 Extraction

50 g of the dried powder plant sample, each organ was individually subjected to maceration in 500 ml of various solvent systems: methanol-distilled water (8:2, v/v) (MW), ethanol-distilled water (7:3, v/v) (EW), and acetone-distilled water (6:4, v/v) (CW). This process was conducted at ambient temperature for 24 h with continuous mechanical stirring. The maceration procedure was repeated thrice to ensure comprehensive extraction of phytoconstituents. Subsequently, the resultant solutions underwent filtration, and The filtered maceration extracts were combined and concentrated via rotary evaporation under vacuum at 40°C. The resulting concentrated extracts were stored in amber bottles at 4°C for subsequent analysis

II.2 Yield calculation

The percentage yield of all the plant extracts was quantified employing the following formula:

Percentage Yield (%) = (Weight of dried crude extract (g) / Weight of initial dried plant material (g)) x 100

This equation allows for the calculation of extraction efficiency by determining the mass proportion of the recovered dried crude extract relative to the initial dry plant material used for extraction.

II.3 Phytochemical screening

The phytochemical composition of *Salvia balansae* extracts was preliminarily evaluated through qualitative phytochemical screening employing various standardised colourimetric and precipitate-based test protocols.

II.3.1 Flavonoids

Shinoda Test: This test was performed using the method described by **Kachkoul et al. (2018)**. Briefly, 1 mL aliquots of each extract were treated with concentrated hydrochloric acid, followed by the addition of magnesium ribbon fragments. The development of reddish-to-pinkish colouration indicated the potential presence of flavonoid moieties.

Ferric Chloride ($FeCl_3$) Test: The protocol outlined by **Archana et al. (2012)** was adopted. To each 1 mL aliquot of the extracts, a few drops of a ferric chloride solution were added. The formation of a blackish-red colour was registered as a positive result for flavonoid compounds.

Alkaline Reagent Test: This assay was conducted per the methodology delineated by **Pandey and Tripathi (2014)**. 2 mL of 2% sodium hydroxide (NaOH) solution was combined with 1 mL of each extract. The formation of a yellow colour indicated the presence of flavonoids.

II.3.2 Alkaloids

Dragendorff's Test: The detection of alkaloids was evaluated following the methodology reported by **Evans and Evans (2002)**. 3 mL of each extract was combined with 1% hydrochloric acid (5 mL) and heated in a water bath. Once the mixture had cooled, it was filtered, and a few drops of Dragendorff's reagent were added. The formation of a reddish-brown precipitate indicated a positive result for the presence of alkaloid compounds.

Mayer's Test: The Mayer test was conducted to confirm the presence of alkaloids, as per the protocol outlined by **Evans and Evans (2002)**. Plant extracts (3 mL) were treated with 1% hydrochloric acid (5 mL) and heated in a water bath. After cooling, the mixture was filtered, and a few drops of Mayer's reagent were added. The development of a yellowish-white precipitate was registered as a positive result for alkaloids within the respective extract.

II.3.3 Tannins

Ferric Chloride (FeCl3) Test: The detection of tannins was based on the method described by **Trease and Evans (1989)**. 2 mL of each plant extract was combined with 2 mL of a 5% $FeCl_3$ solution. The appearance of a greenish-black or dark-black colouration in the reaction mixture indicated a positive result, suggesting the presence of tannin compounds.

Alkaline Reagent Test: This test was conducted according to the protocol outlined by **De et al. (2010)**. 2 mL of each extract was mixed with 2 mL of 1N sodium hydroxide (NaOH) solution. The observation of yellow colouration in the mixture was registered as a positive result, confirming the presence of tannins within the respective extract.

II.3.4 Saponins

Saponins were detected in the tested extracts through the froth test, following the methodology described by **Harborne (1998)**. A 2 mL aliquot of each extract was diluted with 2 mL of distilled water and vigorously mixed by manually shaking the tubes lengthwise. After a 15-minute incubation period, the height of the persistent froth layer was measured. The results were interpreted based on the following criteria:

Froth layer < 1 cm: Absence of saponins

Froth layer = 1 cm: Poor presence of saponins

Froth layer > 1 cm: High presence of saponins

II.3.5 Terpenoids

The presence of terpenoids was evaluated following the procedure outlined by **Ismail et al. (2016).** 5 mL of each tested sample was mixed with 2 mL of chloroform. Subsequently, 3 mL of concentrated sulfuric acid was carefully layered onto the mixture. The appearance of a distinct reddish-brown ring at the interface between the two liquid layers indicated a positive result, confirming the presence of terpenoid compounds within the respective extract.

II.3.6 Sterols

The presence of sterols was evaluated through Salkowski's test, as per the methodology described by **Archana et al. (2012)**. Each tested extract (2 mL) was combined with chloroform (5 mL), and concentrated sulfuric acid (1 mL) was then cautiously added. The formation of a distinct reddish-brown-coloured layer indicated a positive result, confirming the presence of sterol moieties within the respective extract.

II.3.7 Steroids and Phytosteroids

The identification of steroids and phytosteroids was conducted using the method outlined by **Ali et al. (2018).** Each tested extract (1 mL) was combined with chloroform (1 mL), Then, a few drops of concentrated sulfuric acid were added with caution. The formation of a brown colour ring at the interface indicated a positive result for the presence of steroid compounds. Contrarily, the development of a bluish-brown ring signified the presence of phytosteroids within the respective extract.

II.3.8 Quinones

The presence of quinones was evaluated using the methodology described by **Ali et al. (2018).** A 1 mL sample from each plant extract was combined with 1 mL of concentrated sulfuric acid. The development of red colouration the reaction mixture indicated a positive result, confirming the presence of quinone moieties within the respective extract.

II.3.9 Anthraquinones

The presence of anthraquinones was investigated using the method outlined by **Harborne (1998).** Each tested crude sample (1 mL) was mixed with a few drops of 2% HCl. The formation of a red-coloured precipitate in the reaction mixture indicated a positive result, confirming the presence of anthraquinone compounds within the respective extract.

II.3.10 Coumarins

The presence of coumarins was conducted following the protocol reported by **Ali et al. (2018).** 1 mL of each tested extract was treated with 10% sodium hydroxide (NaOH) solution (1 mL). The development of a yellow colouration indicated a positive result, confirming the presence of coumarin moieties.

II.3.11 Cardiac glycosides

The presence of cardiac glycosides was investigated using the Keller-Killiani test, as per the methodology outlined by **Ismail et al. (2016).** Each plant extract (5 mL) was treated with a mixture comprising glacial acetic acid (2 mL) containing a single drop of ferric chloride solution and concentrated sulfuric acid (1 mL). The formation of a brown ring at the interface between the two layers was considered a positive indication of the presence of cardiac glycosides within the respective extract.

II.3.12 Phlobotannins

The presence of phlobatannins was assessed according to the method described by **Auwal et al. (2014)**. Each plant sample (2 mL) was mixed with a 1% HCl solution (2 mL), and the resulting mixture was boiled. The development of a red colour indicated a positive result for phlobatannins.

II.3.13 Anthocyanins and Betacyanins

The presence of anthocyanins and betacyanins was investigated following the protocol outlined by **Trease and Evans (1989).** Each plant sample (2 mL) was combined with a 2N sodium hydroxide (NaOH) solution (1 mL). After heating the mixture for 5 minutes at 100°C, the development of a bluish-green colour confirmed the presence of anthocyanins, while a yellow colour indicated the presence of betacyanins.

II.3.14 Diterpenes

The presence of diterpenes was evaluated by mixing 1 mL of each plant extract and 3-4 drops of copper acetate solution, following the method described by **Pandey and Tripathi (2014).** The development of an emerald green colouration indicated a positive result, confirming the presence of diterpene compounds.

II.3.15 Carbohydrates

The identification of Carbohydrates was evaluated through Molisch's test, as described by **Ismail et al. (2016)**. 3 mL of each extract was combined with a few drops of alcoholic α-naphthol solution and 0.2 mL of concentrated sulfuric acid. A violet ring at the interface between the acid and extract layer indicated the presence of carbohydrates in the respective plant extract.

II.3.16 Reducing Sugars

The detection of reducing sugars was investigated using Fehling's test, as per the methodology outlined by **Ismail et al. (2016)**. Each extract (1 mL) was mixed with Fehling's solutions A and B (1 mL each). After heating this mixture, the appearance of a reddish-brown precipitate indicated a positive result.

II.4 Quantitative analysis

II.4.1 Total phenolic Content

The total phenolic content of the tested extracts from *Salvia balansae* was quantified according to the Folin-Ciocalteu method, as outlined by **Singleton and Rossi (1965).**

This procedure relies on a redox reaction, where polyphenols reduce the yellow oxidised polyoxometalate complexes in the Folin-Ciocalteu reagent to blue-coloured molybdenum and tungsten oxides. The intensity of the resulting blue colouration, quantified spectrophotometrically at a wavelength of 765 nm, exhibits a direct proportionality to the concentration of polyphenolic constituents in the analysed sample.

20 µl of *Salvia balansae* crude extracts (0.5 mg/ml) was pipetted into individual wells of a 96-well microplate. To each well, 100 µL of Folin-Ciocalteu reagent solution, diluted ten times, and 75 µL of 7.5% sodium carbonate were subsequently added. The microplate was then incubated in the dark at ambient room temperature for 2 hours to allow the reaction to proceed.

After incubation, the absorbance was recorded at 765 nm using a 96-well microplate reader (Perkin Elmer En Spire, Singapore).

A calibration curve using gallic acid standards was constructed across the concentration range of 0-100 µg/mL. The total phenolic content present in the tested extracts was quantified by interpolation against this gallic acid calibration curve. Results were expressed as µg gallic acid equivalents (GAE) per mg of extract.

II.4.2 Total flavonoid Content

The aluminium chloride colourimetric technique described by **Mbaebie et al. (2012)** was employed. This technique relies on the generation of a coloured complex between Al^{3+} ions and the hydroxyl moieties of flavonoids, which can be measured spectrophotometrically.

For the analysis, 100 µL of a 2% aluminium chloride ($AlCl_3$) solution prepared in ethanol was mixed with 100 µL of each extract sample or standard and allowed to stand for 1 h at ambient temperature; the absorbance was then recorded at 420 nm. The total flavonoid contents were expressed as µg quercetin equivalent (µg EQ/mg extract).

II.4.3 Total flavonol Content

The quantification of total flavonol content in the crude extracts of *S. balansae* was conducted using the technique previously reported by **Benmeddour et al. (2013).**

For the assay, aliquots of 50 µL from the organic extracts or quercetin standard were treated with 50 µL of a 2% $AlCl_3$ solution and 150 µL of a 5% sodium acetate solution. Following that, the mixtures underwent incubation for 2.5 hours at room temperature, after which the absorbance was recorded at 440 nm. The flavonol content present in the extracts was quantified by interpolation against the quercetin calibration curve and expressed as µg of quercetin equivalents (µg QE) per mg.

II.4.4 Condensed Tannins Content

The condensed tannin content in the crude extracts of *S. balansae* was determined using the vanillin assay, as described by **Adedapo et al. (2008).** This assay is based on the ability of these compounds to react with vanillin in an acidic methanolic solution to produce a coloured chromophore. Briefly, to 25 µL of each crude extract, 150 µL of a 4% (w/v) vanillin solution prepared in methanol and 75 µL of concentrated hydrochloric acid were added. The mixture was allowed to stabilise at ambient temperature for 15 minutes. Then, the absorbance levels were recorded at 500 nm using a 96-well microplate reader. A calibration curve was plotted using catechin as the standard compound to determine the concentration of condensed tannins present in the crude extracts. The obtained results were represented as µg of catechin equivalents per mg of extract (µg EC/mg extract).

II.4.5 Hydrolysable tannins Content

The estimation of hydrolysable tannin content in the tested crude extracts was carried out using a ferric chloride-based assay as reported by **Mole and Waterman (1987)**. This method relies on the capacity of hydrolysable tannins to reduce $FeCl_3$ under acidic conditions, generating a coloured ferric-phenolic complex. In brief, 50 µl of each crude extract was combined with 175 µl of $FeCl_3$ solution (0.01 M of $FeCl_3$ in 0.001 M of HCl). After 15 seconds, the absorbance was read at 660 nm. The hydrolysable tannin amounts were represented as µg of tannic acid equivalents per mg of the crude extract (µg TAE/mg extract).

II.4.6 Ortho-diphenols Content

A rough estimation of ortho-diphenols content present in the crude extracts of *S.balansae* was evaluated using the colourimetric method described by **Martins-Gomes et al. (2018).** This technique relies on the development of a yellow-coloured molybdenum-diphenol complex under alkaline conditions. To 50 µL aliquots of the sample extracts, 200 µL of a 5% sodium molybdate solution was added. The absorbance values were recorded at a wavelength of 370 nm after allowing the mixture to incubate for 15 minutes at room temperature.

The results were expressed as µg of gallic acid equivalent (µg GAE/mg extract).

II.4.7 Total Triterpenoid Content

The Triterpenoid contents of the tested extracts were evaluated by the colourimetric vanillin assay as described by **Fan and He (2006)**. 10 µL of each crude extract was combined with 15 µL of a freshly prepared vanillin solution in glacial acetic acid and 50 µL of perchloric acid. This reaction mixture was then incubated at 60°C for a duration of 45 minutes to facilitate the reaction between the triterpenoid compounds present in the extract and the vanillin reagent.The mixture was left to cool down in an ice bath, and subsequently, 225 µL of glacial acetic acid was added. The spectrophotometric reading was recorded at 548 nm against a blank. The triterpenoid contents were expressed as µg of ursolic acid equivalents (UAE) per mg of the extract.

II.5 Liquid Chromatography-Mass (LC-MS)

The chemical profiling of *S. balansae* crude extracts was evaluated employing Liquid Chromatography-Mass (LC-MS). LC-MS tests were performed with a Shimadzu UFLC XR system consisting of a SIL-20AXR autosampler, CTO-20AC column oven, LC-20ADXR binary pump, and an LCMS-8040 triple quadrupole mass spectrometer.

The columns utilised were packed with 3 µm Inertsil ODS-4 C18 stationary phase (150 mm × 3.0 mm) and maintained at 40°C. The injection volume was set to 20 µL with a flow rate of 0.5 mL/min. Mobile phase A consisted of 0.2% acetic acid in 95% water and 5% methanol, while mobile phase B was 0.2% acetic acid in a 50:50 water acetonitrile mixture. The gradient elution program was used in the following form: 0-14 min, 10-20% B; 14-27 min, 20-55% B; 27-37 min, 55-100% B; 37-45 min, 100% B; 45-50 min, 10% B. Negative electrospray ionisation mode was used, and the following mass spectrometric parameters were optimised. Capillary voltage, −3.52 kV; nebulising gas 15 L/min; desolvation line temperature 280 °C; heat block 400 °C; and detection voltage, 1.35 V Mass spectra were acquired in full scan mode for deprotonated molecules [M-H]- using LabSolutions software.

The individual compounds present were identified and quantified by comparing their relative retention times and UV spectral data against those of authenticated reference standards, following the approach detailed by **Mahmoudi et al. (2021).**

II.6 Antioxidant assays

Several complementary in vitro antioxidant tests were employed to evaluate the antioxidant ability of the *S. balansae* crude extracts (SBCEs). The methods included DPPH, ABTS, FIC, FRAP, phenanthroline, Superoxide radical scavenging capacity by alkaline DMSO activity, Silver nanoparticles antioxidant capacity, and CUPRAC assays, appropriate blanks and controls were used. This assay panel aimed to explore the extracts’ antioxidant potential through different mechanisms, including radical scavenging, reducing capacity, and metal chelation.

II.6.1 DPPH radical scavenging activity

The capacity of S. balansae extracts to scavenge free radicals was assessed using the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay, adopting the test originally proposed by **Blois (1958)** and reported by **Burits and Bucar (2000)**, This method employs the ability of antioxidant species to neutralize the stable DPPH radical through donating a hydrogen atom or transferring an electron, culminating in forming a non-radical form. This redox reaction manifests visually as a discolouration of the DPPH solution, initially purple-hued to a pale yellow colouration. The colour change is quantifiable and correlates with the radical-scavenging capacity of the antioxidant **(Gulcin, 2020).**

Using a 96-well microplate reader, 160 µL of a 0.1 mM DPPH solution was mixed with 40 µL of the tested extracts at varying concentrations ranging from 6.25 to 400 µg/mL. The reaction mixtures were incubated at ambient temperature for 30 minutes in the dark. After incubation, the absorbance was read at 517 nm against a blank control. The assay included positive controls using butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), α-tocopherol, and ascorbic acid as standard antioxidant compounds.

The percentage of free radical scavenging capacity was calculated according to the equation below:

$$\text{The percentage of the free radicalair activity} = (A_c - A_s)/A_c \times 100$$

Where A_c represents the absorbance of the control reaction, and A_s is the absorbance of the sample reaction mixture.

The free radicalair capacity of the analysed extracts was determined as a percentage of inhibition (%). The results were expressed as the IC_{50}, which denotes the concentration of the extract required to scavenge or inhibit 50% of the DPPH radicals present in the reaction mixture, with the highest activity corresponding to the lowest IC_{50} value.

II.6.2 ABTS radical scavenging assay

The ABTS capacity relies on the capacity of antioxidant species to quench the stable blue-green coloured $ABTS^{\bullet+}$ radical cation, leading to the reduction of the characteristic blue-green colour that can then be detected spectrophotometrically **(Cano et al., 2023)**. The ABTS radical scavenging capacity of *S.balansae* tested samples was evaluated by employing the approach outlined by **Re et al. (1999).**

The $ABTS^{\bullet+}$ radical cation was generated by reacting the ABTS solution (7 mM) with potassium persulfate (2.45 mM). This mixture was incubated in obscurity at ambient temperature for 12-16 hours to ensure complete radical formation. Before the assay, the ABTS stock mixture underwent dilution to reach an absorbance of 0.700 ± 0.02 at 734 nm. In a 96-well microplate format, 160 µL of the diluted ABTS solution was mixed with 40 µL of each crude extract at varying concentrations ranging from 12.5 to 800 µg/mL. After incubating the reaction mixtures for 10 minutes at room temperature, the absorbance was read at 734 nm. The assay included positive controls using butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, and α-tocopherol as standard antioxidant compounds. The percentage inhibition of the ABTS radical cation by the crude extracts was calculated using the following equation:

$$\text{Percentage of inhibition} = [(A_c - A_s)/A_c] \times 100$$

Where A_c indicates the absorbance of the control reaction, and A_s is the absorbance of the sample reaction mixture.

Results were displayed as IC_{50} (µg/ml), denoting the concentration of the extract required to scavenge or inhibit 50% of the ABTS radical cations in the reaction system.

II.6.3 Cupric reducing antioxidant capacity (CUPRAC)

The ability of the tested S.balansae samples to reduce Cu(II) to Cu(I) through electron transfer mechanisms by the samples was exploited to indicate their potential to neutralize oxidants via redox reactions, using the technique reported by **Apak et al. (2004).**

In a 96-well microplate, a reaction mixture comprising 50 µL of a 7.5 mM neocuproine solution, 50 µL of a 10 mM copper(II) chloride solution, and 60 µL of a 1 M ammonium acetate buffer maintained at pH 7 was prepared. Subsequently, 40 µL aliquots of the extracts at concentrations ranging from 12.5 to 800 µg/mL were introduced into the respective wells. Following a 1-hour incubation period under dark conditions at room temperature, the optical density was read at 450 nm. The results were represented as $A_{0.5}$ (µg/mL), representing the extract concentration required to attain an absorbance of 0.5.

Reference standards included BHA, ascorbic acid, BHT, α-tocopherol and EDTA

II.6.4 Superoxide radical scavenging activity by alkaline DMSO assay

The alkaline DMSO test was adopted to assess the superoxide radical scavenging capacity of S.balansae extracts, as outlined by **Kunchandy and Rao (1990)** with slight modifications. Briefly, superoxide radicals were generated in a non-enzymatic system by combining NaOH with DMSO, promoting the alteration of NBT into red formazan dye, recorded at 560 nm **(Krishnaiah et al., 2011)**.

Briefly, 40 µl of each crude extract at various concentrations (12.5 to 800 µg/ml), 130 µl of alkaline DMSO (20 mg NaOH in 100 ml of DMSO), and 30 µl of NBT solution (1 mg/ml) were mixed in a 96-microplate reader. The absorbance levels were determined at 560 nm.

The percentage of the scavenging capacity of S.balansae was assessed according to the equation below:

$$\text{superoxide scavenging activity (\%)} = (A_c - A_s)/A_c \times 100$$

Where Ac represents the absorbance of the control reaction, and As denotes the absorbance of the extracted sample.

The results were represented as IC_{50} (µg/ml). BHT and ascorbic acid were used as standard references.

II.6.5 Ferrous ion chelating activity

The capability of the tested samples to chelate ferrous ions was evaluated through the ferrozine-based method as reported by **Decker and Welch (1990),** by employing the capacity of chelating agents present in the tested extracts to disrupt the formation of Fe^{+2}-ferrozine complex.

In brief, to 40 µl of each extract at various concentrations (12.5 to 800 µg/ml), 40 µl of methanol, 40 µl of 0.2 mM of ferrous chloride ($FeCl_2$) solution, and 80 µL of ferrozine reagent. The introduction of ferrozine initiated the reaction, which was subsequently allowed to proceed for 10 minutes before the spectrophotometric reading of absorbance at 593 nm against a blank.

The percentage of ferrous ions (Fe^{2+}) chelated by the extracts was quantified using the formula below:

$$Fe^{+2} \text{ chelating (\%)} = (A_c - A_s)/A_c \times 100$$

Where Ac indicates the absorbance of the control reaction, and As the absorbance of the extract sample.

Results were given as IC_{50} values (µg/mL), representing the extract concentration required to reach a 50% reduction in the initial ferrous ion concentration through chelation. The chelating efficacy of the tested samples was compared against ethylenediaminetetraacetic acid (EDTA) and α-tocopherol, which were used as standard reference compounds.

II.6.6 Reducing power assay

To assess the capacity of the *S. balansae* crude extracts to facilitate electron transfer reactions, the ferric reducing antioxidant power (FRAP) activity was employed, following the methodology originally outlined by **Oyaizu (1986)**. This spectrophotometric technique exploits the redox potential of antioxidant molecules to catalyze the transformation of the ferric-ferricyanide complex to its ferrous counterpart, as elucidated by **Ivanova et al. (2020)**.

Briefly, 10 µl of the crude extracts, spanning a concentration range of 3.125 to 200 µg/mL, were incubated with 40 µl of 0.2 M phosphate buffer (pH 6.6) and 50 µl of 1% potassium ferricyanide solution. Following a 20-minute incubation period at 50°C, the reactions were quenched by adding 50 µl of 10% trichloroacetic acid (TCA). Subsequently, 40 µl of distilled water and 10 µl of 0.1% ferric chloride ($FeCl_3$) solution were introduced. The absorbance of these complexes was then measured at 700 nm against a blank control.

The results were reported as $A_{0.5}$, indicating the tested extract concentration required to achieve an absorbance of 0.5. BHA, BHT, ascorbic acid, and α-tocopherol were used as standard references.

II.6.7 Phenanthroline assay

The assessment of the antioxidant potential of *S.balansae* crude extracts was carried out using the reduction capacity based on the phenanthroline technique, as described by **Szydłowska-Czerniak et al. (2008)**, this test relies on the capacity of chelating compounds contained in the tested extracts to interfere with the formation of the colored O-phenanthroline-Fe^{+2} complex by binding with Fe^{+2}, and thus preventing the complexation and decreasing the intensity of the orange-red color, which can be measured spectrophotometrically **(Ivanova et al., 2020).**

Briefly, the reaction mixture for the phenanthroline assay comprised 10 µL of each *S. balansae* extract at varying concentrations ranging from 3.125 to 200 µg/mL, 50 µL of ferric chloride solution 0.2%, 30 µL of 0.5% 1,10-phenanthroline reagent, and 110 µL of methanol. The mixture was incubated for 10 minutes at 20°C to facilitate the reaction. Subsequently, the absorbance was recorded at a wavelength of 510 nm against an appropriate blank solution.

The metal chelating capacity of the extracts was reported as $A_{0.5}$ values (µg/ml), which represents the concentration of the extract required to achieve an absorbance of 0.50.

Reference standards used were BHA (butylated hydroxyanisole), ascorbic acid, and BHT (butylated hydroxytoluene).

II.6.8 Sliver nanoparticles antioxidant capacity (SNPAC) assay

Silver nanoparticle antioxidant capability was applied to assess the S.balansae crude extracts' ability to reduce silver ions as developed by **Özyürek et al. (2012)**. The SNPAC exploits the possibility of Ag^+ ions reduction by phenolic compounds in the presence of citrate-stabilized silver to evaluate the antioxidant capacity by estimating the intensity of plasmon visible-absorbance at 423 nm **(Bedlovičová et al., 2020)**.

In a 96-well microplate, 20 µL aliquots of the samples at varying concentrations ranging from 3.25 to 400 µg/mL were mixed with 50 µL of distilled water and 130 µL SNP solution (1 mM silver nitrate, 1% sodium citrate). The resulting reaction mixture was incubated for 30 minutes at 25°C to facilitate the development of the chromophore. The absorbance was verified at a wavelength of 423 nm.

The results were reported as $A_{0.5}$ values (µg/mL), denoting the concentration of the sample required to achieve an absorbance of 0.50. Trolox and ascorbic acid were employed as standard reference compounds.

II.7 Photoprotective assay

The photoprotective capability of the studied samples was evaluated by evaluating their sun protective factor (SPF) using an in vitro method proposed by **Mansur et al. (1986)**. This approach relies on erythemal action spectrum and spectrophotometric analysis principles, considering the UV absorption characteristics of the tested extracts across UV-B (290-320 nm) and UV-A II (320-340 nm), the two main causative agents causing erythema and skin reddening **(L. Li et al., 2023)**.

Sample aliquots of *Salvia balansae* crude extracts were prepared, and the optical density readings were measured at 5 nm intervals over 290-320 nm. The SPF was then calculated by incorporating the absorbance data into the equation below:

$$\mathrm{SPF} = \mathrm{CF} \times \sum_{290}^{320} EE(\lambda) \times \mathrm{I}\ (\lambda) \times \mathrm{Abs}(\lambda)$$

CF: Correction factor (10);

EE (λ): Erythemogenic effect of radiation at wavelength λ;

I (λ): Solar intensity spectrum;

Abs(λ): Absorbance of samples;

EE(λ)×I(λ): constant values determined previously by **Sayre et al. (1979)** as shown in Table 4

Table 4. Correlation between Erythemogenic effect of radiation at wavelength (EE) and the solar intensity spectrum (I) at each wavelength **(Sayre et al., 1979)**

λ(nm)	**EE(λ) × I (λ)**
290	0.0150
295	0.0817
300	0.2874
305	0.3278
310	0.1864
315	0.0839
320	0.0180

II.8 Anti-inflammatory activity

The in vitro anti-inflammatory capability of S.balansae crude extracts was assessed through the BSA (bovine serum albumin) protein denaturation test, as reported by **Karthik et al. (2013)**.

Briefly, 0.5 mL of a 0.2% bovine serum albumin (BSA) solution prepared in Tris-buffered saline (pH 6.8) was mixed with 0.5 mL of either. After incubation at 37 °C for 15 minutes, the mixtures were subjected to heat for five minutes at 72 °C. Upon cooling for 10 minutes, the turbidity was determined spectrophotometrically at 660 nm.

The inhibition percentage of precipitation, serving as a protein denaturation indicator, was calculated as follows:

$$\textbf{Percentage of Inhibition} = \left(\frac{\textbf{Absorbance of control} - \textbf{Absorbance of extract}}{\textbf{Absorbance of control}}\right) \times \mathbf{100}$$

II.9 α-Amylase enzyme inhibition activity

The antidiabetic potential of *S.balansae* tested extracts was analyzed in vitro with the α-amylase inhibition assay as described by **Zengin and Aktumsek (2014).** In brief, 25 µl of the sample or the standard (acarbose) at varying concentrations, and 50 µl of α-amylase solution

(1 Unit) prepared in sodium phosphate buffer (pH 6.9 with 6 mM NaCl) were preincubated at 37 °C for 10 minutes. Then 50 µl of 1 % starch solution was introduced to initiate the reaction, followed by further incubation for 20 minutes at 37°C. Subsequently, 25 µl of 1 M HCl and 100 µl of iodine-potassium iodide solution were added. A blank control was similarly prepared by mixing the sample solution with all the reagents without α-amylase. The absorbance was then determined at 630 nm. The α-amylase inhibitory capacity was evaluated using the equation below:

$$\alpha\text{-amylase \% inhibition} = 1 - [(Ac - Ae) - (As - Ab)/(Ac - Ae)]$$

Ac: Absorbance of the starch solution + IKI + HCl + MeOH + phosphate buffer solutions.

Ae: Absorbance of the mixture of α-amylase + starch + IKI + HCL+ MeOH solutions.

As: Absorbance of the mixture of α-amylase + extract + starch + IKI + HCl solutions.

Ab: Absorbance of the mixture of the extract + IKI + phosphate buffer solutions.

II.10 Statistical Analysis

The experimental results were reported as mean ± standard deviation (SD) values, obtained from three independent and parallel replicates. One-way analysis of variance (ANOVA) was conducted, and significant differences between mean values were identified by performing Tukey's honest significant difference (HSD) post-hoc multiple comparison test using STATISTICA 10.0 software (StatSoft Inc., USA). The level of statistical significance was established at $p<0.05$. Multivariate analyses, including principal component analysis (PCA) and unweighted pair group method with arithmetic mean (UPGMA), were employed to evaluate the similarities among the *Salvia balansae* leaf extracts based on their phenolic profiles and biological activities. Furthermore, the interrelationships between these parameters were determined by computing Pearson's correlation coefficients at a 95.0% confidence interval.

Results and Discussion

I. Extraction yield

The extraction of phenolic compounds from the endemic Algerian species *Salvia balansae* was investigated using three different solvent systems: methanol, ethanol, and acetone on the leaves, flowers, and stems of the plant. The extraction yields exhibited significant variations based on the solvent polarity and the plant part utilized **(Table 5).**

Table 5. Extraction Yields of *Salvia balansae* crude extracts

	MeOH 80%	***Et OH 70%***	***Acetone 60%***
Leaves	20.05	25.53	23.15
Flowers	29.99	39.19	33.48
Steams	12.34	11.76	12. 06

The floral tissues demonstrated the highest abundance of extractable phenolic constituents, with yields of 29.99 % for methanol, 39.19 % for ethanol, and 33.48 % for acetone. This was followed by leaf extracts with yields ranging from 20.05 % (methanol) to 25.53 % (ethanol). The stem extracts showed the lowest yields (with yields of 11.76 % for ethanol, 12.34 % for methanol, and 12.06 % for acetone), with methanol being the most efficient solvent at 12.34 %.

Among the leaf and floral extracts, ethanol was the most effective solvent system, yielding 25.53 % and 39.19 % for leaves and flowers, respectively. This outperformed the extraction capabilities of acetone and methanol for these plant parts. Conversely, methanol facilitated the highest extraction yield for stems at 12.34 %.

These observations highlight the critical influence of solvent polarity on the extraction process and the selectivity towards diverse phenolic compounds present in each plant part. The superior yields from floral tissues can be attributed to their higher accumulation of phenolic metabolites in flowers, serving as an evolutionary adaptation to attract pollinators through visual cues **(Chew et al., 2009).** Furthermore, the aqueous mixtures of organic solvents employed in this study have been demonstrated to enhance extraction efficiency by promoting molecular diffusion through increased mass transfer and cellular porosity **(Andersen and Markham, 2006)**

The nature and polarity of the solvent used in plant extraction processes are critical factors that significantly influence the yield and chemical composition of the extracts. Studies have shown that solvent polarity is a primary variable affecting the extraction process, with higher polarity solvents generally leading to increased extraction yields and altered chemical profiles **(Hussain et al., 2024; Jacques et al., 2007; Nawaz et al., 2020)**. For instance, the use of water, a highly polar solvent, resulted in the highest global extraction yield for pitanga leaves, while non-polar solvents like supercritical CO_2 yielded lower amounts of extract **(Hussain et al., 2024)**. Similarly, ethanol, a polar solvent, was found to be the most effective in extracting curcuminoid content from Curcuma xanthorriza **(Nawaz et al., 2019).**

II. Phytochemical analysis

II.1 Qualitative analysis

The qualitative phytochemical screening tests performed on various extracts derived from *Salvia balansae* revealed the presence of multiple major groups of plant secondary metabolites, as represented in **Table 6**.

Notable phytochemical groups detected across the extracts included flavonoids, tannins, saponins, terpenoids, quinones, cardiac glycosides, sterols, phytosterols, coumarins, betacyanins, diterpenes, carbohydrates, and reducing sugars. These findings corroborate previous studies on species belonging to the *Salvia* genus, which consistently reported a rich diversity of secondary metabolites, with flavonoids and terpenoids particularly abundant **(Kintzios, 2000; Walker et al., 2004)**. The detection of such a wide array of phytochemicals in *S. balansae* extracts is significant, as many of these compound classes are known to contribute to the medicinal and pharmacological properties attributed to plants from this genus **(Moshari-Nasirkandi et al., 2023; Xu et al., 2018).**

The identified phytochemical groups in *Salvia balansae* are known to exhibit potential biological activities, including antioxidant, anti-inflammatory, antimicrobial, and cytotoxic properties **(Campos-Xolalpa et al., 2018; Puangpraphant et al., 2022)**. For example, flavonoids and tannins are well-recognized for their antioxidant properties **(Andersen and Markham, 2006; Das et al., 2020)**, while terpenoids and quinones have demonstrated antimicrobial and cytotoxic effects **(Bisio et al., 2019; Yang et al., 2020).** Additionally, saponins have been studied for their potential anticancer and immunomodulatory activities **(Landa-Cansigno et al., 2023).**

Table 6. Qualitative Phytochemical Profile of *Salvia balansae* Extracts

	MeOH			EtOH			AC		
	L	F	S	L	F	S	L	F	S
1- Flavonoids									
- Shinoda test	+	+	+	+	+	+	+	+	+
- FeCl3 test	+	+	+	+	+	+	+	+	+
- Alkaline reagent test	+	+	+	+	+	+	+	+	+
2- Alkaloids									
- Dragendorff's test	-	-	-	-	-	-	-	-	-
- Mayer's test	-	-	-	-	-	-	-	-	-
3- Tannins									
- FeCl$_3$ test	+	+	+	+	+	+	+	+	+
- Alkaline reagent test	+	+	+	+	+	+	+	+	+
4- Saponins	+	+	+	+	+	+	+	+	+
5- Terpenoids	+	+	+	+	+	+	+	+	+
6- Quinones	+	+	+	+	+	+	+	+	+
7- Anthraquinones	-	-	-	-	-	-	-	-	-
8- Cardiac glycosides	+	+	+	+	+	+	+	+	+
9- Sterols	+	+	+	+	+	+	+	+	+
10- Steroids	-	-	-	-	-	-	-	-	-
11- Phytosteroids	+	+	+	+	+	+	+	+	+
12- Coumarins	+	+	+	+	+	+	+	+	+
1 3- Anthocyanins	-	-	-	-	-	-	-	-	-
14- Betacyanins	+	+	+	+	+	+	+	+	+
15- Phlobotannins	-	-	-	-	-	-	-	-	-
16- Diterpenes	+	+	+	+	+	+	+	+	+
17- Carbohydrates	+	+	+	+	+	+	+	+	+
18- Reducing sugars	+	+	+	+	+	+	+	+	+

MeOH, methanol; EtOH, ethanol; Ac, acetone; L, leaves; F, flowers; S, stems. (+) Presence ; (-) Absence

Notably, certain phytochemical groups, such as alkaloids, anthraquinones, steroids, anthocyanins, and phlobatannins, were not detected in the studied extracts, which was supported by other studies **(Bursal et al., 2019; Gad et al., 2022).**

The absence of these compounds may be specific to the plant species or influenced by the extraction conditions employed. However, the absence of alkaloids could be beneficial, as some alkaloids are known to exhibit toxicity **(Adibah et al., 2019).**

The findings of this phytochemical screening indicate that *Salvia balansae* is a promising source of bioactive compounds with potential therapeutic applications.

II.2 Quantitative analysis

II.2.1 Total Phenolic Content (TPC)

The total phenolic content (TPC) is a crucial parameter for evaluating the potential bioactivity and therapeutic applications of plant extracts. Phenolic compounds are renowned for their antioxidant properties, which are primarily attributed to the presence, position, and molecular size of hydroxyl groups in their chemical structures **(Kheniche et al., 2022; Pandey &Tripathi, 2014)**. This study investigated the TPC of crude extracts obtained from different parts (flowers, leaves, stems) of the aromatic plant *Salvia balansae* using various extraction solvents (methanol, ethanol, acetone), as evidenced by the results presented in **Table 7.**

The TPC values exhibited significant variations, ranging from 147.86 to 99.85 (µg GAE/mg) for flower extracts, 83.55 to 60.79 mg GAE/g for leaf extracts, and 134.19 to 114.30 µg GAE/mg for stem extracts. These variations were governed by several critical factors, including the extraction solvent's polarity, solvent-to-solute ratio, plant species, drying method, extraction method, and water-solvent ratio **(Assefa & Keum, 2017; Chew et al., 2009; Iloki-Assanga et al., 2015; Lezoul et al., 2020; Park et al., 2014).**

Methanol and acetone proved to be more selective for extracting phenolic compounds from *S. balansae*, with the methanolic extract of flowers (147.83 µg GAE/mg) and the acetonic extract of stems (134.19 µg GAE/mg) exhibiting the highest TPC values. These results align with prior studies which highlighted the efficacy of these solvents for extracting a diverse range of phenolic compounds from various plant matrices **(Benchikh et al., 2023; Mohammedi & Atik, 2011; Wijekoon et al., 2011).** The high TPC values observed in these extracts can be attributed to the ability of methanol and acetone to solubilise both polar and non-polar phenolic compounds, facilitated by their intermediate polarity and hydrogen-bonding capabilities **(Alara et al., 2021; Lama-Muñoz & Contreras, 2022).**

Furthermore, the combination of water and organic solvents, such as methanol or acetone, has been reported to enhance the extraction of phenolic compounds due to increased polarity and improved molecular diffusion through cellular porosity **(Assefa & Keum, 2017; Zardo et al., 2021)**. This phenomenon may contribute to the higher TPC values observed in the methanolic and acetonic extracts compared to the ethanolic extracts, which exhibited lower TPC levels across all plant parts

Table 7. Phytochemical Composition of Crude Extracts from *Salvia balansae* (SBCE)

SBCE		TPC (µg GAE/mg)	TFC (µg QE/mg)	FOL (µg QE/mg)	CT (µg CE/mg)	HT (µg TAE/mg)	TT (µg UAE/mg)	ODP (µgGAE/mg)
Solvents	**Organs**							
MeOH	***Leaves***	113.12±0.38^{d}	60.22±0.40^{b}	30.93±0.33^{b}	46.73±0.91^{c}	8.15±0.51^{f}	392.33±0.03^{a}	158.57±0.76^{d}
	Flowers	147.87±0.21^{a}	55.47±0.24^{c}	21.19±0.29^{d}	10.06±0.52^{fj}	3.56 ± 0.64^{j}	124.83±0.02^{d}	287.9±0.50^{a}
	Stems	99.85±0.10^{e}	17.23±0.06^{f}	14.80±0.41^{e}	11.27±0.45^{f}	7.63± 0.56^{f}	231.5± 0.01^{c}	97.87±0.53^{f}
EtOH	***Leaves***	82.61±0.38^{f}	61.79±0.63^{b}	35.28±0.05^{a}	14.91±0.79^{e}	16.44± 0.38^{e}	347.27±0.07^{ab}	143±0.58^{e}
	Flowers	83.56±0.10^{f}	34.70±0.06^{e}	13.94±0.16^{e}	27.94±0.26^{d}	17.85±0.55^{de}	312.76± 0.02^{b}	57.53±0.59^{h}
	Stems	60.80±0.42^{j}	17.58±0.35^{f}	15.12±0.19^{e}	7.03±0.26^{j}	20.67± 0.68^{d}	342.53±0.01^{ab}	25.63±0.56^{i}
AC	***Leaves***	129.89±0.27^{c}	72.17±0.12^{a}	33.77±0.21^{a}	69.15±0.52^{b}	30.82± 0.71^{b}	189.64± 0.05^{c}	257.5±0.32^{b}
	Flowers	114.31±0.49^{d}	36.80±0.60^{d}	24.04±0.57^{c}	11.88±0.26^{a}	68.96±0.67^{a}	194.09±0.05^{c}	173.87±0.53^{c}
	Stems	134.2±0.96^{b}	16.67±0.20^{f}	9.42± 0.14^{f}	67.64±0.79^{b}	27.26±0.71^{c}	238.53± 0.12^{c}	87.47±0.34^{j}

Mean values within a column marked with the same superscript letter are not significantly different ($P \geq 0.05$). In contrast, values with different superscript letters indicate significant differences ($P < 0.05$) based on Tukey's HSD post-hoc test.

SBCE, *Salvia balansae* crude extracts; **TPC**, total phenolic content (**GAE**, gallic acid equivalents); **TFC**, total flavonoid content (**QE**, quercetin equivalents); **FOL**, flavonol content (QE); **CT**, condensed tannins (CE, catechin equivalent); **HT**, hydrolysable tannins (**TAE**, tannic acid equivalent); **TT**, triterpenoid content (**UAE**, ursolic acid equivalent); **ODP**, ortho diphenol content (GAE).

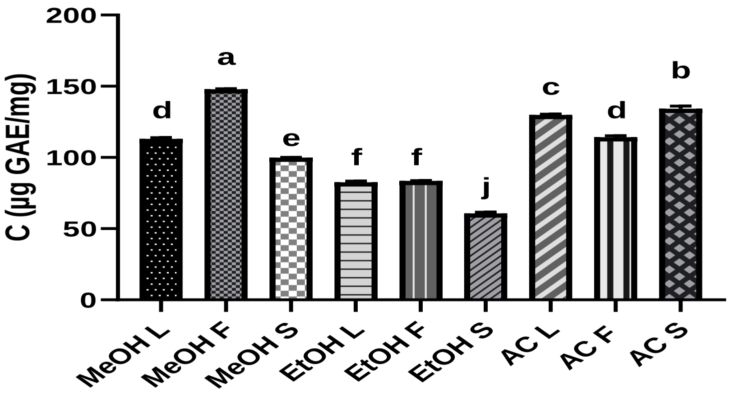


Figure 8. Polyphenol content in *Salvia balansae*

Interestingly, the distribution of TPC among the different plant parts varied depending on the extraction solvent employed, as indicated in **Figure 8**. For methanol and ethanol extracts, the TPC levels followed the order: flowers > leaves > stems, while for acetone extracts, the order was stems > leaves > flowers. These differences can be related to the differential synthesis, storage, and distribution of phenolic compounds among plant organs, which are influenced by various factors, including gene expression, biosynthesis/degradation processes, transport mechanisms, and inter-organ interactions **(Iloki-Assanga et al., 2015; Lahmadi et al., 2022; Riahi et al., 2013).**

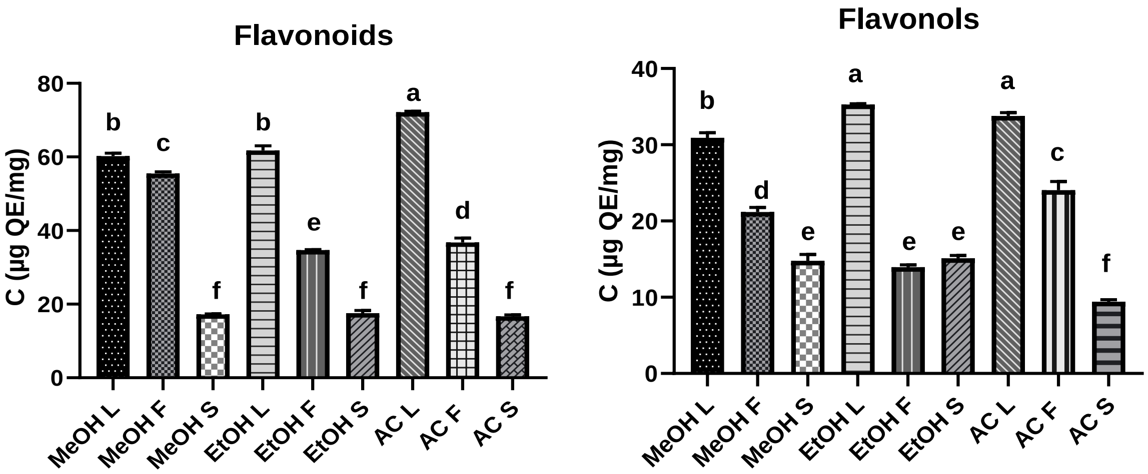
The distribution and accumulation of phenolic compounds throughout different plant parts can be influenced by various factors, including soil properties, climate conditions, biotic and abiotic stresses, and the plant's developmental stage **(Iloki-Assanga et al., 2015; Khiya et al., 2021; Lahmadi et al., 2022)**. These results underline the significance of considering internal and external factors while investigating the phytochemical composition of plant extracts.

While the present study demonstrated that flowers are richer in polyphenols compared to leaves and stems, which is in accordance with previous reports on other plant species **(Eom et al., 2022; Maoulainine et al., 2012; Park et al., 2014)**, it is essential to acknowledge that some researchers have reported contradictory results, with leaves exhibiting the highest TPC levels **(Lezoul et al., 2020; Riahi et al., 2013; Stankovic et al., 2011).** These discrepancies highlight the complexity of phytochemical distribution within plants and emphasise the need for comprehensive investigations across various plant species, cultivars, and environmental conditions.

II.2.2 Total flavonoids (TFC) and total flavonols (FOL) Content

Flavonoids and flavonols, prominent subclasses of phenolic compounds, are secondary metabolites of significant importance in plants due to their remarkable chemical and biological properties, particularly their potent radical scavenging capabilities **(Alara et al., 2021; Pucker & Selmar, 2022; Tooski et al., 2016)**. Flavonoids and flavonols were quantified in the crude extracts obtained from *Salvia balansae*. The results are presented in **Table 7.**

Our results demonstrated that acetone exhibited the highest extraction efficiency for both total flavonoids and flavonols across all plant parts compared to methanol and ethanol, with the highest concentration observed in leaf extracts (72.17-35.28 µg QE/mg for flavonoids and flavonols, respectively). These results align with prior studies that have demonstrated the suitability of acetone, particularly in combination with water, for efficient extraction of flavonoids and flavonols **(Jimoh et al., 2010; Stankovic et al., 2011; Wijekoon et al., 2011; Zengin & Aktumsek, 2014)**. The lipophilic and hydrophilic characteristics of flavonoids contribute to their solubility in water-acetone mixtures, where acetone enhances the solubility of lipophilic components, and water facilitates the solubilisation of hydrophilic components **(Andersen & Markham, 2006; Chebil et al., 2007; Tooski et al., 2016).**


Flavonoids

Flavonols

Figure 9. Flavonoids and Flavonols Content in *Salvia balansae*

Furthermore, the distribution of flavonoids and flavonols among plant parts followed the order: leaves > flowers > stems, with leaves exhibiting the highest concentrations as shown in **Figure 9**. This observation aligns with previous studies **(Mohammedi & Atik, 2011; Riahi et al., 2013; Stankovic et al., 2011**) and can be explained by the important physiological properties of flavonoids and flavonols in leaves, which are considered highly active tissues that play a crucial role in photosynthesis, secondary metabolism, and defence mechanisms **(Andersen & Markham, 2006; Brunetti et al., 2013; Gad et al., 2022; Pucker & Selmar, 2022)**.

II.2.3 Condensed tannins (CT) and Hydrolysable tannins (HT) Content

Tannins, a diverse group of compounds classified as hydrolysable (ellagitannins) and condensed (proanthocyanidins), are renowned for their antioxidant properties and associated health benefits **(Tong et al., 2022)**. Thus, by analysing both hydrolysable and condensed tannins, we aim to gain a comprehensive understanding of the tannin profile in *S.balansae* and determine the potential variations among plant organs using different solvent systems. The results are displayed in **Table 7.**

The results revealed that acetone exhibited superior extraction efficiency for both CT and HT compared to methanol and ethanol, with the highest concentrations observed in flower extracts (111.87 µg CE/mg for CT and 34.48 µg TAE/mg for HT). This indicates that the concentration of CT and HT is highly influenced by the type of solvent used. The order of the used solvents according to their extraction efficiency was recorded as follows: acetone > ethanol > methanol.

These findings are consistent with previous studies that have identified acetone, particularly in combination with water, as a suitable solvent for tannin extraction **(Das et al., 2020; Khan et al., 2023; Rifna & Dwivedi, 2022).** The varying polarities of acetone and water allow for the selective extraction of diverse tannin types, facilitating efficient recovery while preventing degradation and oxidation **(Bouterfas et al., 2014; Hagerman, 1988).**

The analysis of different plant organs revealed that flowers and leaves exhibited the highest concentrations of (CT) and (HT). The condensed tannin content ranged from 7.03 to 69.15 µg CE/mg, with the acetonic extract of leaves displaying the highest concentration at 69.15 ± 0.52 µg CE/mg. On the other hand, the hydrolysable tannin content ranged from 3.56 to 68.96 µg TAE/mg, with the acetonic extract of flowers displaying the highest concentration at 68.96 ± 0.67 µg TAE/mg. Stems also exhibited significant amounts of hydrolysable tannins, with the acetonic extract recording the highest concentration at 27.26 ± 0.71 µg TAE/mg. These findings further substantiate the observation that flowers and leaves are the predominant sites for tannin accumulation, with condensed tannins being the predominant class, suggesting their pivotal role in the defence mechanisms and physiological functions of *S. balansae*.

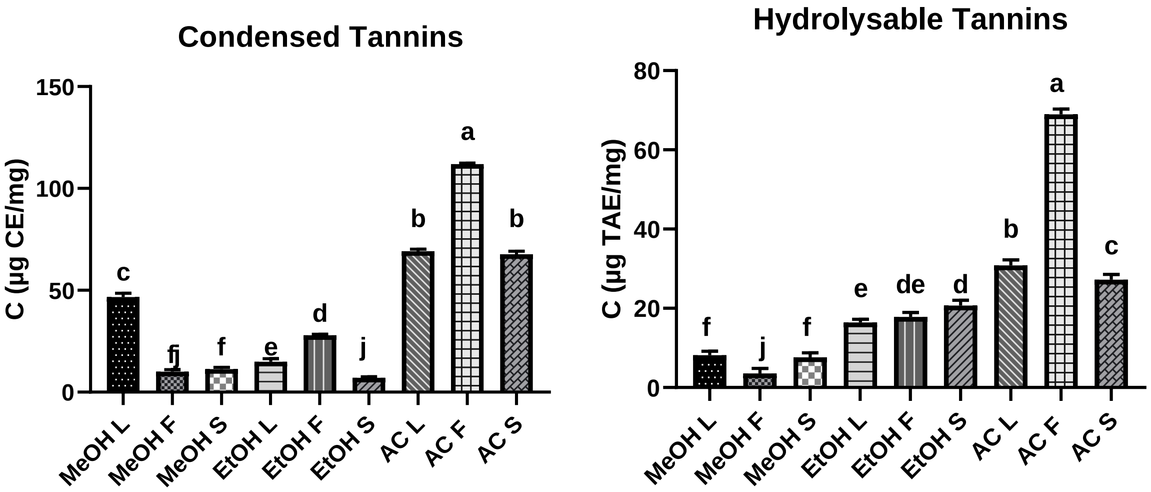


Figure 10. Condensed and Hydrolysable tannins Content in *Salvia balansae*

Notably, the distribution of tannins among plant parts revealed that flowers and leaves exhibited the highest concentrations of both CT and HT, as indicated in Figure 10. The predominance of CT over HT suggests a more significant role of CT in the defence mechanisms and physiological functions of *S. balansae.*

This observation aligns with the established protective functions of tannins against herbivores, pathogens, and environmental stressors **(Maisetta et al., 2019; Peter Constabel et al., 2014; Rauf et al., 2019).**

The variability in tannins concentration and composition among plant parts can be attributed to various physiological and ecological factors, such as growth stage, temperature, light availability, and nutrient availability **(Gebrehiwot et al., 2002; Tong et al., 2022).** These factors regulate tannin biosynthesis and accumulation, leading to distinct tannin profiles in different plant organs.

While leaves are commonly recognised as the predominant site of tannins accumulation **(Boumaza et al., 2022; Guglani et al., 2020; Rana et al., 2006)**, our study revealed that flowers of *S. balansae* exhibited particularly high tannins content, comparable to that of leaves. This observation highlights the importance of tannins in protecting reproductive organs and potentially attracting pollinators, thereby enhancing reproductive success **(Gebrehiwot et al., 2002; Laouini & Ouahrani, 2017; Ouerghemmi et al., 2017).**

II.2.4 Total Triterpenoids Content (TTC)

Many species in the *Salvia* genus are acknowledged for their capacity to synthesise and accumulate triterpenoids, considered one of the most diverse groups of secondary metabolites **(Tung et al., 2017).** Triterpenoids fulfil an essential role in plant life and possess a wide range of biological activities; therefore, given their substantial importance, we opted to quantify these metabolites in the different extracts of the studied plant **(Fan et al., 2023)**.

The results displayed in **Table 7**. expressed as (µg UAE/mg) reveals that the methanolic (MeOH) extract of leaves retained the highest triterpenoid (TT) content at 392.33 ± 0.03 µg UAE/mg compared to the other solvent extracts, followed by the ethanolic (EtOH) extract of leaves at 347.27 ± 0.07 µg UAE/mg, then the acetone (AC) extract of leaves at 189.64 ± 0.05 µg UAE/mg. Within the range of solvents examined for the different plant components, the EtOH and AC extracts exhibited the highest TTC, with the highest value of 347.27 ± 0.07 µg UAE/mg found in the EtOH extract of leaves. However, the lowest TT content was recorded in the MeOH extract of flowers at 124.83±0.02 µg UAE/mg.

These findings indicate that triterpenoids' extraction efficiency depends on the polarity of the solvent used and the inherent chemical properties of the compounds being extracted. The superior performance of ethanol and acetone in retrieving triterpenoids aligns with previous research, which has validated their effectiveness for this purpose **(Attar & Ghane, 2019, 2021; Bellumori et al., 2016; Zhang et al., 2020)**. Nevertheless, it is important to admit that variability in results could be ascribed to various components, including the extraction method employed, the plant species under investigation, and various extrinsic and intrinsic elements **(Azmir et al., 2013; Ghane et al., 2018).**

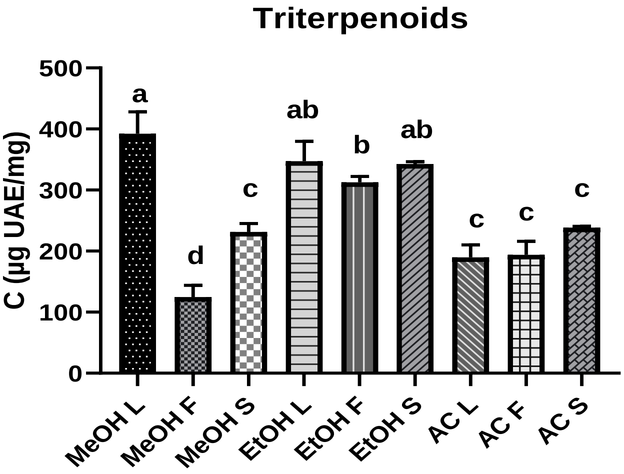


Figure 11. Triterpenoid Contents in *Salvia balansae*

Notably, the study revealed that the leaves of *Salvia balansae* generally exhibited the highest TTC compared to other plant parts, as shown in **Figure 11**, with the TTC in leaves ranging from 392.33±0.03 µg UAE/mg for the methanolic extract, 347.27±0.07 µg UAE/mg for the ethanolic extract, and 189.64 ± 0.05 µg UAE/mg for the acetone extract. The concentration followed the order: leaves > stems > flowers, indicating that the vegetative parts of the plant contained higher triterpenoid levels than the reproductive parts. This observation can be attributed to the fact that leaves are often considered significant reservoirs of triterpenoids, with glandular trichomes serving as common sites for their synthesis and storage **(Singh & Sharma, 2015)**. Additionally, triterpenoids play crucial roles in the defence responses of vegetative organs against biotic and abiotic stresses **(Singh & Sharma, 2015),** particularly after herbivore damage, where they are involved in direct and indirect defence mechanisms against herbivores and microbial pathogens **(Chen et al., 2014; Cheng et al., 2007)**. These findings are consistent with previous studies conducted on Avera Lanata.L **(Yamunadevi et al., 2011)** and align with the observations of **Tosun et al. (2009).**

II.2.5 Ortho-diphenol (ODP)Content

Ortho-diphenols, a subgroup of phenolic compounds characterised by the presence of two hydroxyl groups in adjacent positions on an aromatic ring, are recognised for their potent antioxidant properties conferred by their unique catechol structure **(Giuliani et al., 2018)**. The results are displayed in a **Table 7**.

The quantification of ODP in the crude extracts of *Salvia balansae* revealed intriguing insights into the phytochemical composition of *Salvia balansae*. These specialised metabolites exhibited remarkable variations in their accumulation across the different crude extracts obtained from diverse plant organs and solvents. The ortho-diphenol content spanned a wide range from 287.9 ± 0.5 to 25.63 ± 0.56 µg GAE/mg.

Notably, the foliar organs emerged as the predominant repositories of these bioactive compounds, surpassing the accumulation levels observed in other plant parts. This trend was consistent for the ethanolic and acetone extracts, with the order of abundance being leaves > flowers > stems. However, a contrasting pattern was observed for the methanolic extracts, where the floral organs harbored the highest ortho-diphenol concentrations, followed by leaves and stems. The methanolic extract of flowers stood out as the richest source, boasting an ortho-diphenol content of 287.9 ± 0.5 µg GAE/mg, while the ethanolic extract of stems exhibited the lowest accumulation at 25.63 ± 0.56 µg GAE/mg.

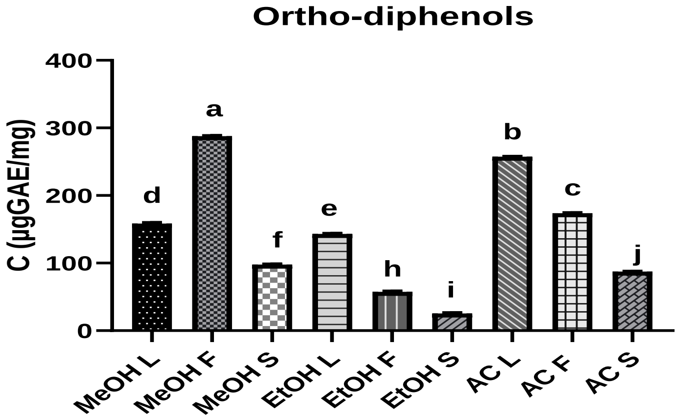


Figure 12. Ortho-diphenols content in *Salvia balansae*

Based on our current understanding, this study is the first to analyse the ortho-diphenol content in the Algerian endemic species *Salvia balansae*. However, our findings resonate with a recent investigation conducted by **Babaie et al. (2023)** on the related species *Salvia tebesana*. Their research revealed methanol as a more effective solvent than water and ethanol for extracting ortho-diphenols while also identifying leaves as the plant organ with the highest concentration of these compounds compared to stems.

This differential distribution of ortho-diphenols across plant organs and solvent systems could be attributed to several factors, including the inherent chemical properties of the compounds, their biosynthetic pathways, and the extraction efficiencies of the various solvents. The substantial quantities of these redox-regulating compounds detected across various extracts may be attributed to the plant's adaptive response to the harsh environmental conditions prevalent in the Aures mountain range, where abiotic stressors such as intense UV radiation and limited precipitation may stimulate an enhanced biosynthesis of these photoprotective and antioxidant molecules as a defence mechanism (Hashim et al., 2020; Ibrahim et al., 2022; Uddin, 2019)**.**

III. Liquid chromatography-mass spectrometry

The comprehensive profiling of phenolic constituents in *Salvia balansae* crude extracts (SBCEs) through liquid chromatography-mass spectrometry (LC-MS) analysis unveiled a remarkable diversity of these specialised metabolites. The study identified 18 distinct phenolic compounds, encompassing 8 phenolic acids and 10 flavonoids, highlighting the biosynthetic prowess of this endemic species native to the Aures mountain range.

Quinic acid emerged as the predominant phenolic acid, with concentrations ranging between 5.051 ppm in acetonic leaf extract to a substantial 69.69 ppm in the ethanolic extract of stems. Concurrently, rosmarinic acid, a characteristic marker compound in the *Salvia* genus **(Katanić Stanković et al., 2020; Remok et al., 2023)**, presented a concentration spectrum varying between (2.881-32.914 ppm) in the ethanolic flower extract and the methanolic flower extract respectively, underscoring its ubiquitous presence across various plant organs.

Table 8. Phenolic Compound Profiling in *S. balansae* Crude Extracts Using LC/MS

	Phenolic compounds	**Chemical class**	**Phenolic compounds quantity (ppm)**								
			MeOH extracts			**EtOH extracts**			**Ac extracts**		
			L	***F***	***S***	***L***	***F***	***S***	***L***	***F***	***S***
1	***Quinic acid***	Phenolic acid	40,122	40,313	59,394	16,927	47,509	69,69	5,051	19,55	22,498
2	***Gallic acid***	Phenolic acid	0,115	0,02	0,083	0,114	0,031	0,07	0,037	0,045	0,018
3	***Protocachuic acid***	Phenolic acid	1,026	0,27	ND	1,057	0,637	ND	0,597	1,126	0,568
4	***Caffeic acid***	Phenolic acid	1,231	1,563	1,873	1,085	2,508	1,876	0,772	2,945	2,42
5	***Syringic acid***	Phenolic acid	ND	ND	ND	ND	ND	ND	ND	ND	1,15
6	***p-coumaric acid***	Phenolic acid	0,348	0,267	0,087	0,39	0,099	0,127	0,644	0,48	0,312
7	***Trans frulic acid***	Phenolic acid	0,146	0,571	0,078	0,161	1,656	0,047	0,252	2,068	0,134
8	***Rosmarinic acid***	Phenolic acid	18,741	32,914	26,614	3,389	2,881	6,39	3,907	6,61	14,712
9	***Naringenin***	Flavonone	0,305	ND	ND	0,109	ND	0,172	0,409	ND	ND
10	***Naringin***	Flavanone	3,839	2,248	ND	2,697	2,098	1,23	2,109	2,55	2,052
11	***Apegenin-7-O-glucoside***	Flavonol	6,592	46,672	6,943	4,956	49,549	3,751	4,538	68,507	9,225
12	***Hyperoside (quercetin-3-O-galactoside***	Flavonol	0,586	0,307	ND	0,504	0,344	0,408	0,365	0,507	0,635
13	***Quercetin***	Flavonol	ND	ND	ND	ND	ND	0,068	ND	0,054	0,094
14	***Luteolin-7-O-glucoside***	Flavone	14,328	40,985	13,683	11,96	29,641	7,802	8,822	44,917	13,501
15	***Apegenin***	Flavone	0,445	6,416	0,565	0,72	3,142	0,73	0,858	5,565	0,946
16	***Cirsiliol***	Flavone	2,378	3,81	8,362	2,081	2,828	10,575	4,6	3,285	15,608
17	***Cirsilineol***	Flavone	0,381	ND	ND	0,38	ND	ND	0,353	ND	ND
18	***Acacetin***	Flavone	0,767	0,497	0,229	0,712	0,705	0,176	1,226	0,242	0,199

MeOH, Methanol; **EtOH**, Ethanol; **Ac**, Acetone; **L**, Leaves; **F**, Flowers; **S**, Stems.

Among the flavonoid repertoire, three compounds stood out as the major constituents: luteolin-7-O-glucoside, cirsiliol, and apigenin-7-O-glucoside. These compounds are commonly present in the *Salvia* genus, as reported in previous studies **(Farhat et al., 2013; Martins et al., 2015; Tohma et al., 2016).** Luteolin-7-O-glucoside exhibited a considerable concentration range, with the lowest levels observed in the ethanolic stem extract and the highest concentration attained in the acetone flower extract. Apigenin-7-O-glucoside displayed a comparable trend, with the lowest concentration recorded in the ethanolic extract of stems, while the highest levels were detected in the acetonic flower extract. Cirsiliol, another prominent flavonoid, demonstrated a similar variation, with the lowest concentration in the ethanolic leaf extract and the highest in the acetonic stem extract.

These findings underscore the intricate interplay between plant organs, solvent systems, and the inherent chemical properties of the phenolic compounds, influencing their extraction efficiency and accumulation patterns **(Dent et al., 2013; Jakovljević et al., 2019)**. The observed variability in phenolic composition among *S. balansae* and other *Salvia* species, such as *S. lavandulifolia, S. officinalis, S. verticillata L.,* and *S. bicolor,* is attributed to the complex chemical profiles exhibited by this genus, as well as the unique environmental adaptations and genetic characteristics of each species **(Carvalho et al., 2011; Ghorbani & Esmaeilizadeh, 2017; Jedidi et al., 2020; Katanić Stanković et al., 2020; Tohma et al., 2016).**

Comparison with previous studies on *Salvia balansae* from Mostaganem **(Mahdjoub et al., 2023; Mokhtar et al., 2023)** showed variations in the types and quantities of phenolic compounds, suggesting differences between the species or populations studied. The observed variability in the phenolic composition is expected, as different *Salvia* species are known to possess intricate and diverse chemical profiles. This complexity arises from the ability of each species to adapt and tailor its biochemistry to suit the specific environmental conditions and genetic makeup it has evolved under, as supported by numerous studies in the existing literature **(Carvalho et al., 2011; Tohma et al., 2016; Tosun et al., 2009).**

Principal Component Analysis (PCA) revealed three distinct groups of extracts based on their phenolic compound content **Figure 13**.

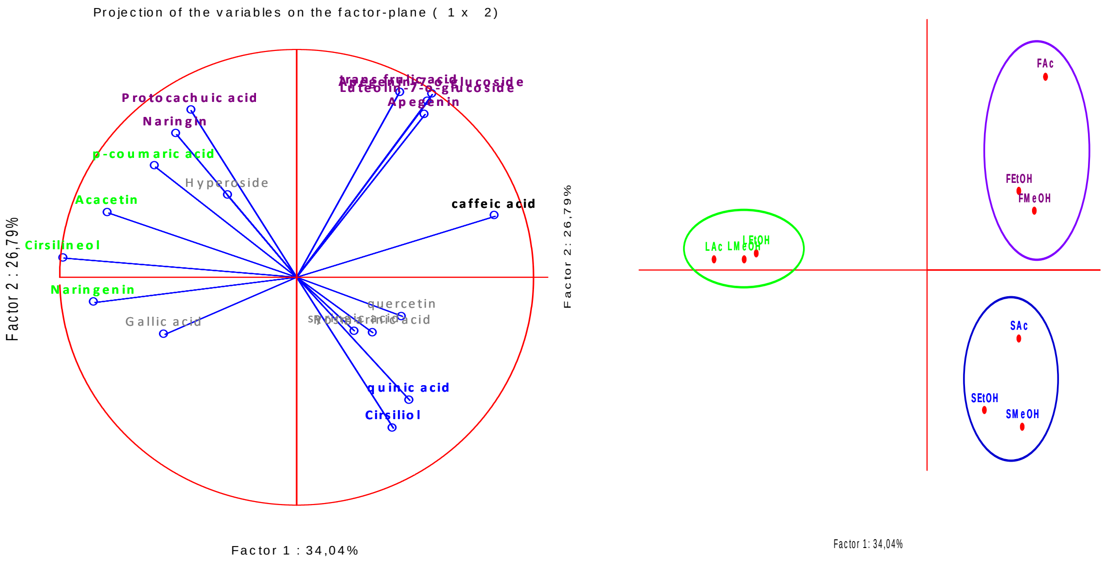


Figure 13. Phenolic compound diversity in *Salvia balansae* extracts by PCA

The first group consisted of flower extracts rich in luteolin-7-o-glucoside, apigenin, and apigenin-7-o-glucoside. Stem extracts high in quinic acid and cirsiliol made up the second group, and leaf extracts high in cirsilineol, acacetin, protocatechuic acid, naringenin, and p-coumaric acid made up the third.

The variation in phenolic compound composition and concentration among different plant organs was attributed to factors such as gene expression, biosynthesis/degradation processes, transport mechanisms, and environmental conditions like climate, soil, and biotic/abiotic stresses, as reported in various studies **(Iloki-Assanga et al., 2015; Khiya et al., 2021; Lahmadi et al., 2022; Maoulainine et al., 2012; Riahi et al., 2013)**

IV. Biological activities

IV.1 Antioxidant activity

To evaluate the antioxidant potential of a plant sample accurately, it is crucial to employ multiple analytical methods rather than relying on a single technique. Different antioxidant assays provide insights into various aspects of antioxidant activity. Consequently, to assess the efficacy of *Salvia balansae* crude extracts (SBCEs), several analytical tests were conducted to gain a comprehensive understanding of the antioxidant properties of the compounds present. The results of these multiple assays are presented as mean ± standard error of the mean in Table 9, providing a comprehensive overview of the antioxidant potential of the SBCEs.

Table 9. Antioxidant activities of *Salvia balansae* crude extracts (SBCE)

SBCE		DPPH radical scavenging assay (IC_{50} µg/ml)	ABTS radical scavenging (IC_{50} µg/ml)	Fe^{2+} chelating assay (IC_{50} µg/ml)	CUPRAC capacity ($A_{0.5}$ µg/ml)	Reducing power assay ($A_{0.5}$ µg/ml)	O-Phenantroline assay ($A_{0.5}$ µg/ml)	SNPAC ($A_{0.5}$ µg/ml)	DMSO (IC_{50} µg/ml)
Solvents	**Organs**								
MeOH	**Leaves**	83.54 ±1.04	54.88 ± 0.85	44.45 ± 0.98	58.72 ± 0.52	58.72 ± 0.75	28.69 ± 0.51	210.13 ± 1.81	394.73 ± 1.43
	Flowers	22.53 ± 0.33	33.69 ± 0.86	90.24 ± 0.92	39.72 ± 1.38	73.06 ± 0.34	17.71 ± 0.80	93.22 ± 0.89	108.40 ± 0.23
	Stems	42.25 ± 0.88	58.39 ± 1.06	44.42 ± 1.17	61.14 ± 1.29	86.97 ± 0.28	21.35 ± 0.74	329.08 ± 0.38	289,.5 ± 0.54
EtOH	**Leaves**	264.10 ± 1.76	55.08 ± 0.85	122.50 ± 1.41	70.98 ± 1.45	114.08 ± 0.60	47.02 ± 1.15	> 400	> 800
	Flowers	120.96 ± 0.71	46.26 ± 0.51	43.95 ± 0.87	69.96 ± 1.26	66.18 ± 0.95	43.01 ± 1.36	183.44 ± 1.29	165.88 ± 0.42
	Stems	59.61 ± 0.64	59.61 ± 0.64	132,30 ± 0,55	91.34 ± 0.64	76.09 ± 0.94	60.13 ± 0.89	> 400	411.56 ± 0.96
AC	**Leaves**	66.15 ± 0.74	39.60 ± 1.16	275.66 ± 1.56	38.18 ± 0.42	95.84 ± 0.50	20.81 ± 0.11	384.63 ± 1.65	> 800
	Flowers	50.28 ± 0.84	52.39 ± 1.84	260.68 ± 1.22	39.72 ± 1.38	82.30 ± 0.50	46.66 ± 0.52	352.33 ± 0,72	> 800
	Stems	51.23 ± 0.76	49.58 ± 0.42	64.36 ± 0.78	64.42 ± 0.33	105.37 ± 0.81	49.59 ± 0.77	390.48 ± 0.32	> 800
Standard compounds	**BHA**	4.79 ± 0.05	1.86 ± 0.03	NT	5.21 ± 0.37	8.21 ± 0.43	1.09 ± 0.29	NT	NT
	BHT	17.41 ± 0.41	2.59 ± 0.14	NT	9.11 ± 0.16	39.86 ± 0.70	11.49 ± 0.97	NT	23.73 ± 1.11
	α-tocopherol	12.95 ± 0.19	8.31 ± 0.49	31.51 ± 0.78	20.25 ± 0.37	4.89 ± 004	NT	NT	NT
	Ascorbic acid	13.14 ± 0.12	3.25 ± 0.51	NT	10.66 ± 0.45	6.41 ± 0.24	9.04 ± 0.90	8.74 ± 0.67	NT
	EDTA	NT	NT	8.14±0.64	1.86 ± 0.03	NT	NT	NT	NT

Mean values that share the same superscript letters in the specified column are not significantly different, whereas those with different superscript letters are significantly ($P < 0.05$) different as judged by Tukey's HSD post-hoc test. SBCE, *Salvia balansae* crude extracts

BHT: Butyl Hydroxyl Toluene, **BHA**: Butyl Hydroxyl Anisole, **EDTA**: Ethylenediaminetetraacetic acid, **NT**: Not Tested,

IV.1.1 DPPH radical scavenging assay

The DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay is widely employed to evaluate the ability of antioxidants to neutralise free radicals, which is a crucial mechanism in preventing oxidative stress-related diseases **(Tatarczak-Michalewska & Flieger, 2022)**. The DPPH radical is a stable organic nitrogen radical with a deep purple colour that becomes colourless or pale yellow upon reduction by antioxidants through the donation of hydrogen atoms or electrons **(Alam et al., 2013; Molyneux, 2004)**.

The DPPH radical scavenging assay results revealed diverse antioxidant capacities among the different SBCEs, as demonstrated in **Table 9**. The flower extracts obtained using methanol and acetone as solvents exhibited the most potent radical scavenging abilities, with IC_{50} values of 22.53 and 50.28 µg/mL, respectively. These findings are consistent with previous studies that have reported superior antioxidant activities in flower extracts compared to other plant organs **(Chlif et al., 2021; Ouerghemmi et al., 2017)**. This variation in antioxidant distribution among plant parts can be attributed to the diverse metabolic pathways and accumulation patterns of phytochemicals in different organs **(Chlif et al., 2021).**

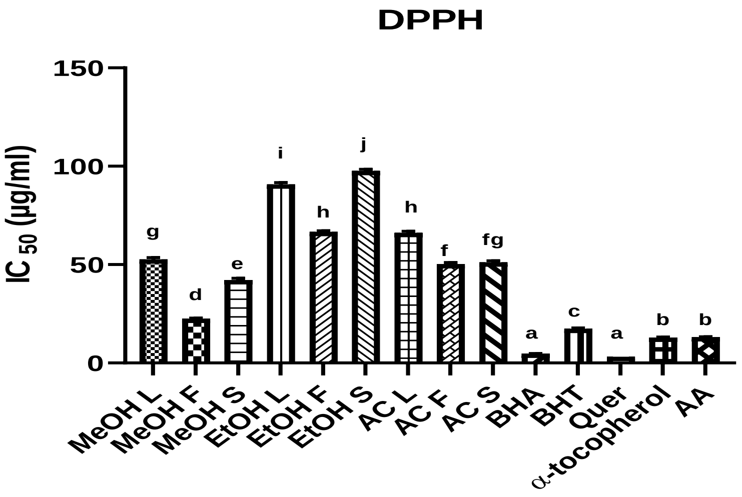


Figure 14. Antiradicalair capacity of *Salvia balansae* crude extracts

The superior capacity of the acetone and methanol flower extracts to scavenge DPPH radicals as indicated in **Figure 14**. can be related to their rich composition of phytochemical constituents, particularly the abundance of phenolic compounds, flavonoids, and tannins **(Iloki-Assanga et al., 2015; Park et al., 2014; Zengin & Aktumsek, 2014)**. These compounds are known to possess redox properties and can act as hydrogen or electron donors, contributing to their radical scavenging capabilities **(Chlif et al., 2021; Kobus-Cisowska et al., 2020; Maoulainine et al., 2012)**.

Notably, the ethanol extracts, particularly the leaf extracts, exhibited the lowest DPPH radical scavenging activity (IC_{50} = 97.72 µg/ml). This discrepancy in antioxidant activity among different solvent extracts can be attributed to the varying polarities of the solvents used for extraction, which selectively solubilize different classes of phytochemicals **(Ounis et al., 2023; Rani et al., 2023).**

While the SBCEs exhibited lower potency in scavenging DPPH radicals compared to the reference standards quercetin, ascorbic acid, α-tocopherol, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), their efficacy can still be considered significant **(Chlif et al., 2021)**. It is crucial to acknowledge that the SBCEs consist of a complex mixture of compounds, unlike the pure standards.

IV.1.2 ABTS radical scavenging assay

In evaluating the antioxidant potential of natural products, it is crucial to employ multiple analytical methods to understand their radical scavenging capabilities. the ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) assay was employed, in addition to the widely utilised DPPH assay, to assess the free radical quenching capacity of *Salvia balansae* crude extracts (SBCEs). The ABTS assay measures the ability of a substance to neutralise the ABTS radical cation generated through oxidation, and it can detect the antioxidant potential of both hydrophobic and hydrophilic compounds across a broad pH spectrum **(Rahim et al., 2021)**.

The results indicated in **Table 9** revealed varying radical scavenging activities among the different SBCEs in the ABTS assay, with IC_{50} values ranging from 33.68 to 59.61 µg/mL. Notably, the methanol flower extract exhibited the highest radical quenching efficiency, followed by the acetone leaf extract and the ethanol flower extract. In contrast, the stem extracts displayed the lowest scavenging activity compared to other extracts. These findings corroborate previous studies that have highlighted the efficacy of methanol in extracting antioxidant compounds capable of neutralising free radicals **(Nistor et al., 2021; Rahim et al., 2021; Saha et al., 2021).**

Regarding the quenching potential among different plant parts, the flowers exhibited the highest scavenging efficiency as highlited in **Figure 15**. Particularly, the methanol flower extract showed an IC50 of 33.68 µg/mL, suggesting the presence of compounds that can effectively counteract oxidative stress. These findings align with previous studies **(Elfalleh, 2012)** that have reported superior antioxidant activities in flower extracts compared to other plant organs.

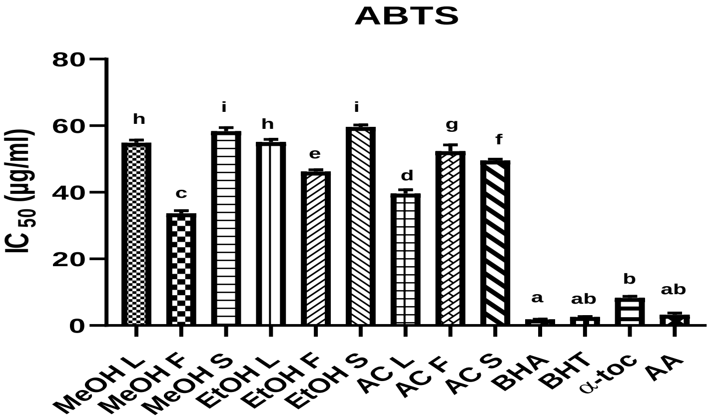


Figure 15. ABTS free radical scavenging of *Salvia balansae* crude extracts

Interestingly, the IC_{50} values obtained in the ABTS assay were lower than those observed in the DPPH assay, suggesting that the SBCEs had a higher affinity for neutralising ABTS radicals compared to DPPH radicals. This observation aligns with previous research and can be attributed to the fundamental differences between the two assays **(Aissani et al., 2022; Kusumorini et al., 2022; Rafińska et al., 2019)**. While the ABTS assay can detect the antioxidant potential of both hydrophobic and hydrophilic substances across a wide pH range, the DPPH assay primarily detects hydrophobic antioxidants **(Cano et al., 2023; Rafińska et al., 2019)**. Additionally, factors such as stoichiometry, stereoselectivity, solubility, chemical structure, and reactivity of the antioxidant compounds may contribute to the differences in their radical scavenging efficiencies between the two assays **(Wang et al., 1999)**.

IV.1.3 Cupric reducing antioxidant capacity (CUPRAC)

The CUPRAC (Cupric Reducing Antioxidant Capacity) assay emerged as a valuable tool in evaluating the antioxidant potential of the *Salvia balansae* crude extracts (SBCEs). This assay relies on the ability of antioxidants present in plant extracts to reduce Cu(II) to Cu(I), utilising the copper(II)-neocuproine reagent as the chromogenic oxidant. The resulting Cu(I)-neocuproine complex exhibits maximum absorption at 450 nm, allowing for quantitative measurement of the reducing capacity **(Munteanu & Apetrei, 2021).**

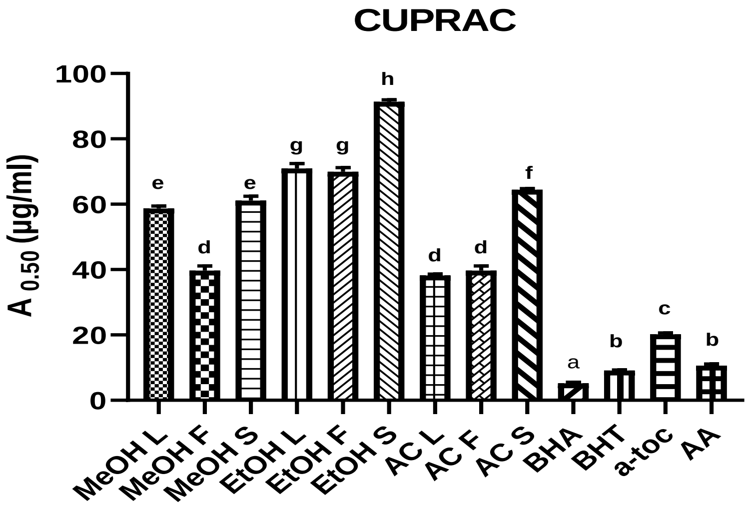


Figure 16. Cupric reducing antioxidant capacity of *Salvia balansae* crude extracts

The CUPRAC assay results unveiled intriguing insights into the antioxidant capacities of the SBCEs. Notably, the acetone extracts demonstrated the highest antioxidant activity, closely followed by the methanol extracts, while the ethanol extracts appeared to be the least effective.

This observation aligns with previous studies **(Boeing et al., 2014; Elham Sadeqzadeh, 2015)** that have reported a lack of significant differences between the antioxidant profiles and stability of methanol and acetone extracts, potentially due to shared redox mechanisms detected by the assay **(Lü et al., 2010; Özyürek et al., 2011)**, overlapping solvent properties enabling similar extraction of antioxidants, and the inherent experimental variability **(Apak et al., 2007)**.

The effectiveness of methanol and acetone as optimal solvents for conducting the CUPRAC assay corroborates findings from prior research. **Zengin and Aktumsek (2014)** reported that acetone and methanol extracts of *Asphodeline anatolica* exhibited the highest cupric reducing capacity, while **Georgiev and Pavlov, (2017) and Zhang et al. (2020)** revealed the efficiency of methanol extracts in reducing Cu(II) ions. **George et al. (2022) and Rimkiene et al. (2015)** also found that acetone extracts recorded the best antioxidant capacity in the CUPRAC assay.

Regarding the antioxidant potential among different plant parts, the CUPRAC assay results indicated that the flower extracts recorded the best antioxidant activity, along with the leaf extracts. Interestingly, there was no significant difference between the reducing power of the acetonic leaf extracts and the methanol flower extracts. While some studies **(Başyiğit et al.,**

2020; Eroglu et al., 2023) have reported that flowers exhibit the highest reducing power, others **(Jabbar et al., 2022; Sarikurkcu & Zengin, 2020)** have indicated that leaves demonstrate the best antioxidant capacity. These discrepancies highlight the potential influence of the extraction solvent on the antioxidant potency of different plant organs, as suggested by **Pudziuvelyte et al. (2020)**.

Notably, the CUPRAC assay demonstrated relatively high antioxidant values when compared to the DPPH and ABTS assays, which are also based on electron transfer mechanisms. This trend aligns with findings from previous research **(Çelik et al., 2010; Stojkovic et al., 2014),** suggesting that the CUPRAC assay may be more sensitive in detecting the reducing capacities of the SBCEs or that the specific antioxidant compounds present in these extracts exhibit a higher affinity for the CUPRAC reaction environment.

IV.1.4 Reducing power assay

The FRAP (Ferric Reducing Antioxidant Power) assay is a widely employed method for assessing the antioxidant capacity of plant polyphenols. This assay is based on the ability of antioxidants to reduce the ferric (Fe^{3+}) form of iron to the ferrous (Fe^{2+}) state, resulting in the formation of a blue-coloured complex known as Perl's Prussian blue, which exhibits maximum absorption at 700 nm **(Skroza et al., 2022).**

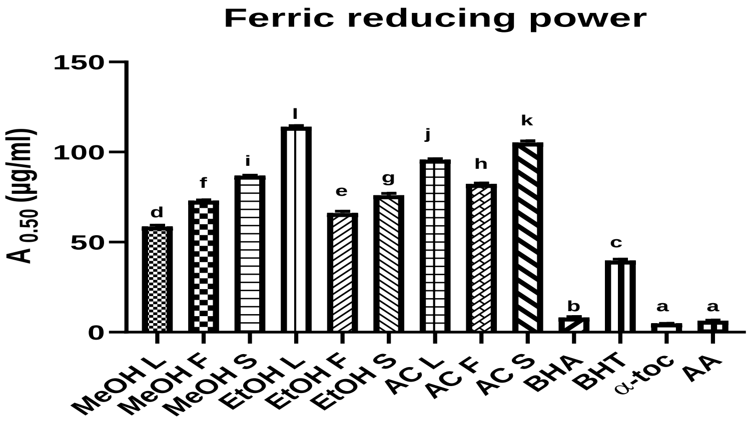


Figure 17. Ferric reducing antioxidant power of *Salvia balansae*

In the present study, the FRAP assay results were expressed as $A_{0.5}$, representing the concentration (µg/mL) at which the absorbance reaches 0.5. The data presented in **Table 9** revealed that the methanol extracts exhibited the highest reducing power among the different solvents used, followed by the ethanol and acetone extracts. This trend suggests that the methanol extracts possess a superior ability to reduce ferric ions, which can indicate their antioxidant potential, as reported by **Benali et al. (2020)**. Furthermore, this observation aligns with the phenolic content of the extracts, as phenolic compounds are known to contribute significantly to the reducing power of plant extracts **(Das et al., 2020).**

Numerous previous studies **(Abedin et al., 2022; Murugan et al., 2020; Nguyen & Scarlett, 2016; Yılar et al., 2020)** have highlighted the efficiency of methanol in extracting antioxidants capable of reducing the Fe^{3+}-ferricyanide complex, corroborating the findings of the present study.

Regarding the antioxidant potential among different plant parts, the results indicated that the leaf and flower extracts exhibited the highest ferric-reducing power, as highlighted in **Figure 17**. In contrast, the stem extracts demonstrated the lowest reductive capabilities. The $A_{0.5}$ values followed the order: methanolic leaf extracts > ethanolic flower extracts > acetonic flower extracts, suggesting variations in the reducing power among different plant organs.

These findings suggest the presence of electron-donating components, or reductants, in the different organs of *Salvia balansae,* which are capable of forming stable compounds by neutralising free radicals. The efficiency of leaf extracts in reducing Fe^{3+}-ferricyanide has been previously reported **(Chlif et al., 2021; Tabaraki & Ghadiri, 2013)**, while other studies have demonstrated the efficacy of flower extracts **(Amri et al., 2017; Nabavi et al., 2012)**.

It is important to note that while the choice of extraction solvent and its concentration significantly influence the presence and concentration of antioxidants and their activity, variations can also occur within the samples themselves **(Shirin & Jamuna, 2010),** potentially contributing to the observed differences in reducing power among the different plant organs.

IV.1.5 Phenanthroline assay

The O-Phenanthroline chelating assay is an important analytical technique used to evaluate the antioxidant potential of natural products. This assay relies on using $FeCl_3$ as a source of ferric (Fe^{3+}) ions and ortho-phenanthroline as a chelating agent for iron **(Szydłowska-Czerniak et al., 2008).** The underlying principle involves the oxidation of antioxidant compounds by the Fe^{3+} ions generated from $FeCl_3$, reducing Fe^{3+} to the ferrous (Fe^{2+}) state. The resulting Fe^{2+} ions form an orange-red complex with o-phenanthroline, which can be quantitatively measured through spectrophotometric analysis **(Dalimunthe et al., 2023)**.

The data displayed in **Table 9**. the methanolic extracts showed the highest ability to reduce ferric (Fe^{3+}) ions to the ferrous (Fe^{2+}) state, followed by the acetonic extracts. On the other hand, the ethanolic extracts exhibited the weakest antioxidant activity. Notably, the methanolic flower extract recorded the highest A $_{0.5}$ value of 17.71 µg/mL, indicating its potent reducing ability, while the ethanolic stem extract showed the lowest A $_{0.5}$ value of 60.13 µg/mL.

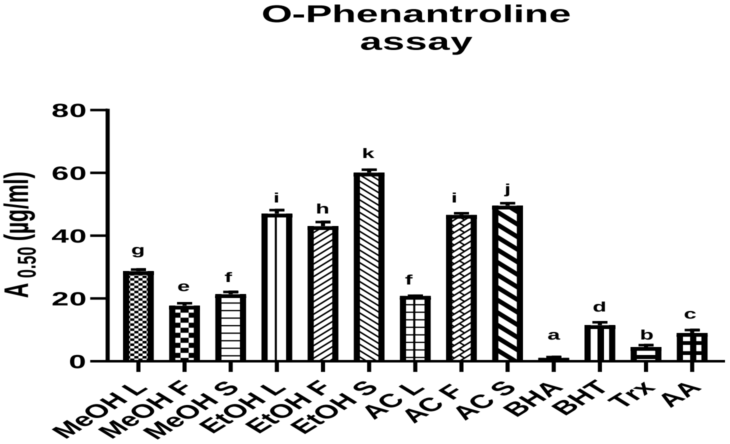


Figure 18. O-Phenanthroline chelating assay of *Salvia balansae* crude extracts

These findings are in agreement with previous studies that have reported the efficiency of methanol **(Bakhouche et al., 2021)** and acetone **(Bendjedid et al., 2021)** in extracting antioxidant compounds capable of reducing iron, as assessed by the phenanthroline assay. Furthermore, the A $_{0.5}$ values of the methanolic extracts (ranging from 17.71 to 28.69 µg/mL) were comparable to those reported for methanolic extracts of *Salvia aegyptiaca* (A $_{0.5}$ of 18.71 µg/mL) and *Salvia verbenaca* (A $_{0.5}$ of 27.03 µg/mL) by **Mamache et al. (2020).**

The observed differences in reducing power towards the Fe^{2+}-phenanthroline complex can be attributed to the reducing capacity of polyphenolic antioxidants, which relies on the degree of hydroxylation and conjugation of the phenolic compounds **(Mamache et al., 2020; Szydłowska-Czerniak et al., 2008)**. Specifically, for flavonoids, the presence of additional hydroxyl groups and the conjugation of the aromatic ring system can enhance their ability to donate electrons and reduce Fe^{3+} to Fe^{2+}, thereby contributing to their antioxidant activity **(Bendjedid et al., 2021; Mamache et al., 2020).**

IV.1.6 Ferrous ion chelating activity

In biological systems, ferrous iron (Fe^{2+}) can catalyse the generation of reactive oxygen species (ROS), leading to oxidative stress. Compounds capable of chelating iron can exhibit antioxidant properties by binding to and reducing the reactivity of iron ions. This chelation process is particularly significant for ferrous ions, as they participate in metal-catalysed oxidation reactions **(Ying et al., 2021).** By mitigating these reactions, chelating agents have the potential to prevent oxidative damage and promote cellular health **(Guglani et al., 2020).**

The ferrous ion chelating assay evaluates the capability of a compound to sequester and inactivate ferrous ions (Fe $^{2+}$), determining its potential to serve as a chelating agent and reduce iron oxidative processes **(Alam et al., 2013)**.

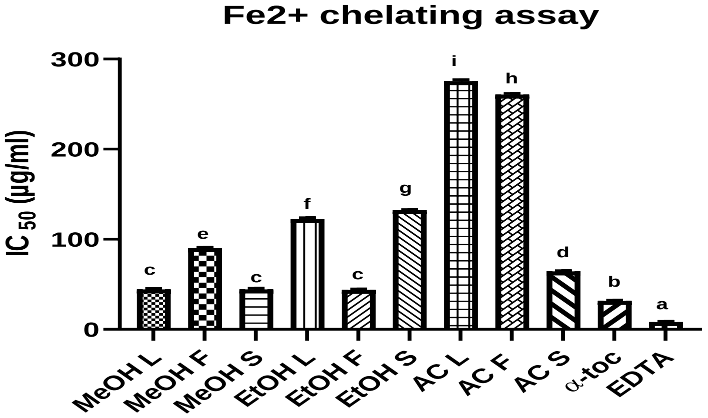


Figure 19. Iron(II) chelation capacity of *Salvia balansae* crude extracts

The results of the ferrous (Fe^{2+}) ion chelating capacity of the tested extracts from *Salvia balansae* are displayed in the **table 9**, and the chelating capacity is expressed as IC$_{50}$ values, which ranged from 44.41 to 275.66 µg/ml. Among the solvents used, methanol demonstrated a great chelating capacity with an IC$_{50}$ ranging from 44.41 to 90.24 µg/ml, indicating that the methanol extracts contain high amounts of antioxidants capable of inhibiting the formation of the ferrozine-iron complex. In contrast, the acetone extracts were the least potent in chelating ferrous ions.

These findings align with previous studies by **Chavan et al. (2013) and Jaiswal et al. (2012)**, who demonstrated the superior potency of methanol over ethanol and acetone in extracting chelating compounds.

It is noteworthy that the methanolic leaf extracts of *S. balansae* demonstrated a superior ferrous ion chelating ability when compared to the methanolic extracts of *Salvia aegyptiaca*, which had a chelating capacity value of 67.99, and *Salvia verbenaca*, with a value of 70.39, as reported in the study by **Mamache et al. (2020).**

The findings indicate that the ability of the *S. balansae* extracts to chelate metal ions is influenced by the solvent used for extraction. Concerning the different plant parts (leaves, flowers, stems), the data did not reveal a consistent trend regarding their effectiveness in chelating ferrous ions. This variability could be attributed to potential differences in the types and quantities of chelating compounds present in each plant organ and variations in their overall chemical composition.

The obtained results demonstrate that the extracts derived from *S. balansae* possess the capability to confer a protective effect against oxidative damage stemming from metal-catalysed Fenton reactions. The presence of iron ions can promote lipid degradation through a series of reactions, including the Haber-Weiss and Fenton pathways, which generate highly reactive hydroxyl radicals that can inflict harm on lipid molecules **(Ying et al., 2021)**. Ferrous ions, commonly encountered in food systems and recognised for their pro-oxidant properties, can amplify oxidative damage by initiating these detrimental reactions. Consequently, this oxidative stress and the ensuing lipid deterioration can have adverse implications for food quality and shelf-life stability. These findings highlight the importance of regulating and minimizing the presence of ferrous ions in food products to ensure effective preservation and maintain their integrity during storage and distribution **(Siddhuraju et al., 2014).**

IV.1.7 Sliver nanoparticles antioxidant capacity (SNPAC) assay

The SNPAC assay was employed to evaluate the total antioxidant capacity (TAC) of polyphenols and other antioxidants. This spectrophotometric method is based on the reduction of silver ions (Ag+) by antioxidants in the presence of citrate-stabilised silver seeds, leading to the formation of silver nanoparticles (SNPs). The growth of these SNPs results in an intense surface plasmon resonance (SPR) absorption band at 423 nm, which is directly proportional to the antioxidant capacity of the compounds under investigation **(Bedlovičová et al., 2020).**

Based on the provided results in **Table 9**, the *Salvia balansae* crude extracts exhibited varying antioxidant capacity levels as measured by the silver nanoparticle antioxidant capacity (SNPAC) assay. The SNPAC activity was expressed as $A_{0.5}$ (µg/mL), representing the extract concentration required to achieve an absorbance of 0.50 at 423 nm. Lower $A_{0.5}$ values indicate higher antioxidant capacity, as less extract is needed to achieve the desired absorption level.

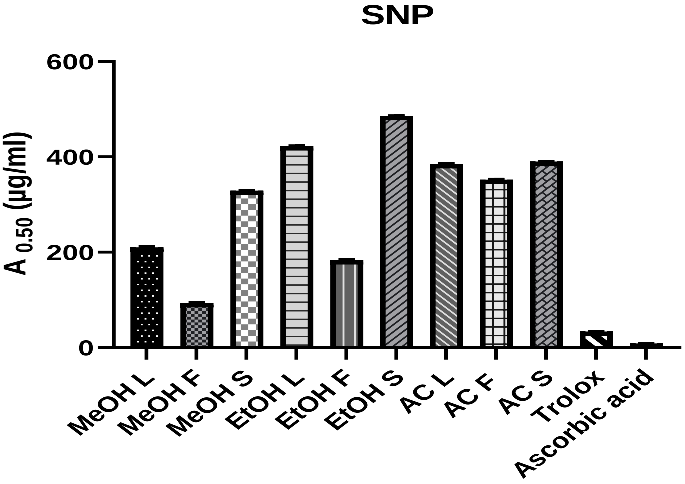


Figure 20. Silver nanoparticle antioxidant capacity of *Salvia balansae* crude extracts

Among the different solvent extracts, the methanol extract of flowers showed the highest SNPAC activity with an $A_{0.5}$ value of 93.22 ±0.89 µg/mL, indicating a potent antioxidant capacity. This was followed by the ethanol extract of flowers ($A_{0.5}$ = 183.44 ±1.29µg/mL) and the methanol extract of leaves ($A_{0.5}$ = 210.13 ±1.81µg/mL). The ethanol extracts of leaves and stems exhibited relatively lower SNPAC activity, with $A_{0.5}$ values greater than 400 µg/mL.

Among the methanol extracts, the flowers displayed the highest SNPAC activity (93.22 ± 0.89), followed by the leaves (210.13 ± 1.81) and stems (329.08 ± 0.38). Similarly, for the ethanol extracts, the flowers showed the highest SNPAC activity (183.44 ± 1.29), while the leaves and stems exhibited significantly lower activities (> 400). The acetone extracts followed a similar trend, with the flowers having the highest SNPAC activity (352.33 ± 0.72), followed by the leaves (384.63 ± 1.65) and stems (390.48 ± 0.32).

The choice of solvent significantly impacts silver nanoparticle synthesis from natural extracts, their size/morphology, as well as their catalytic activity for reduction reactions by modulating factors like extraction efficiency and the chemical environment around the nanoparticles **(Azizinezhad et al., 2014; Lomonosov et al., 2022).**

The varying efficiencies of these solvents in extracting compounds with silver-reducing capacity can be attributed to their differences in polarity and ability to solubilise specific types of antioxidant compounds **(Osorio-Tobón, 2020)**. Methanol, a polar protic solvent, is effective in extracting a wide range of polar antioxidant compounds, such as phenolic acids, flavonoids, and tannins **(Jaiswal et al., 2012)**. Ethanol, although polar, may not be as effective in extracting certain antioxidant compounds due to its specific solubility properties **(Yesufu et al., 2022)**.

Acetone, with its intermediate polarity, can extract both polar and moderately non-polar antioxidant compounds, leading to comparable SNPAC activities across different plant organs **(Lefebvre et al., 2021).**

The superior silver-reducing capacity of the flower extracts compared to the leaf and stem extracts is likely due to the higher accumulation of antioxidant compounds in the floral organs **(Faisal et al., 2022)**. Several studies have reported similar findings, where flower extracts exhibited higher antioxidant activities than other plant parts. For example, **Elemike et al. (2018)** demonstrated that flower extract has superior silver-reducing capacity compared to leaves, which they attributed to the higher levels of amides, essential oils, and aldehyde functional groups present in the extracts.

It is important to note that the SNPAC assay specifically measures the ability of antioxidants to reduce silver ions (Ag^+) and generate silver nanoparticles, which may not necessarily correlate with other antioxidant assays that measure different mechanisms of action. However, the observed trends are generally consistent with the literature on the influence of solvent polarity and plant organs on the extraction of antioxidant compounds **(Akbal et al., 2016; Pilaquinga et al., 2021).**

IV.1.8 Superoxide radical scavenging activity by alkaline DMSO assay

Based on the results in **Table 9**. from the alkaline DMSO assay, it is evident that the solvent used for extraction and the plant organ significantly influenced the superoxide radical scavenging activity of the *Salvia balansae* crude extracts (SBCE).

The methanol extracts exhibited the highest activity, with IC_{50} values ranging from 108.40 ± 0.23 µg/mL for the flower extract to 394.73 ± 1.43 µg/mL for the leaf extract. The solvent efficiency followed the order: methanol > ethanol > acetone. These findings suggest that methanol is an efficient solvent for extracting compounds with superoxide radical scavenging activity from *Salvia balansae*.

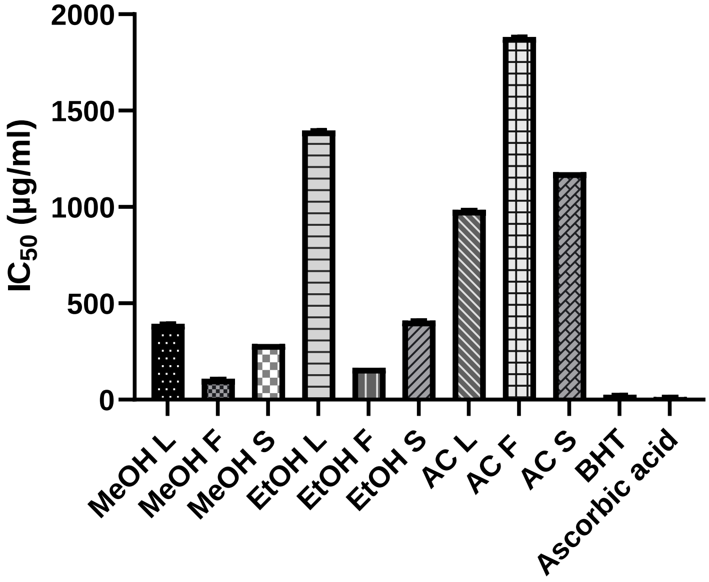


Figure 21. Superoxide radical scavenging activity of *Salvia balansae* crude extracts

The superoxide anion radical is known to play a crucial role in generating various other harmful free radicals, such as peroxyl, alkoxyl, hydroxyl, and nitric oxide, through Fenton reactions and lipid or nitric oxide oxidation **(Andrés et al., 2023; Lewis & Martic, 2022)**.

The observed superoxide anion scavenging activity of the SBCE could be attributed to the presence of phenolic compounds with free hydroxyl groups, whereas the presence of free hydroxyl groups facilitates proton-coupled electron transfer **(Nakayama & Uno, 2015).**

Across all three solvents, the flower extracts exhibited the highest superoxide radical scavenging activity, with IC_{50} values of 108.40 ± 0.23 µg/mL (methanol), 165.88 ± 0.42 µg/mL (ethanol), and >800 µg/mL (acetone). This indicates that the flowers of *Salvia balansae* are a rich source of antioxidant compounds capable of neutralising superoxide radicals. The stem extracts displayed moderate activity, while the leaf extracts generally exhibited lower superoxide radical scavenging activity compared to the flower and stem extracts.

These findings are consistent with previous studies reporting variations in antioxidant activity among different plant organs, attributed to the differential accumulation and distribution of antioxidant compounds, and indicating the superoxide radical scavenging capacity of flowers **(Faisal et al., 2022; Shareef et al., 2014).**

The alkaline DMSO assay evaluates the direct superoxide scavenging ability of the plant extracts in a non-enzymatic system, independent of enzymatic mechanisms such as superoxide dismutase **(Mehlous et al., 2022; Shareef et al., 2014)**. The observed scavenging activity suggests that the *Salvia balansae* extracts, particularly the methanol extract from the flowers, possess potent superoxide scavenging compounds capable of neutralising these highly toxic radicals.

IV.1.9 Correlation of phenolic compounds in SBCE with Antioxidant Activity

The phytochemical investigation of *Salvia balansae* crude extracts (SBCE) has provided a comprehensive understanding of the antioxidant potential of various secondary metabolites present in the extracts. The correlation analysis between the identified compounds and the antioxidant activity assays reveals important insights into the bioactivity of these compounds, highlighting their potential therapeutic applications.

Ortho-diphenols (ODP) exhibit robust negative correlations with several antioxidant assays, including ABTS (r = -0.748), CUPRAC (r = -0.876), and phenanthroline (r = -0.718). This inverse relationship signifies that higher concentrations of ODP correlate with enhanced antioxidant activity, as lower $IC_{50}/A_{0.5}$ values indicate stronger antioxidant capacity. These findings align with the well-established notion that phenolic compounds, particularly those with multiple hydroxyl groups, are potent radical scavengers due to their ability to donate hydrogen atoms or electrons to neutralise free radicals **(Farhat et al., 2013; Kontogianni et al., 2013).**

Moreover, ODP positively correlates with total phenolic content (TPC) (r = 0.764, P = 0.017) and total flavonoid content (TFC) (r = 0.761, P = 0.017), underscoring the interplay between different classes of phenolics in contributing to the overall antioxidant potential of the extracts. TPC itself shows significant negative correlations with ABTS (r = -0.718, P = 0.029), CUPRAC (r = -0.83, P = 0.006), and DPPH (r = -0.808, P = 0.008) assays, reinforcing the role of phenolic content as a critical determinant of antioxidant efficacy **(Jaiswal et al., 2012; Lu & Yeap Foo, 2002).**

Rosmarinic acid, a major phenolic compound in *Salvia* species, demonstrates a strong negative correlation with the DPPH assay (r = -0.796, P = 0.01). This relationship can be attributed to the chemical structure of rosmarinic acid, which contains two catechol moieties, each with ortho-hydroxyl groups on the phenolic rings. These structural features facilitate the neutralisation of DPPH radicals, thereby reducing absorbance values and indicating higher antioxidant activity **(Khojasteh et al., 2020).** This finding is consistent with previous studies that have highlighted the superior radical scavenging abilities of rosmarinic acid due to its multiple hydroxyl groups **(Petersen, 2013; Truong et al., 2022; Wang et al., 1999).**

Apigenin-7-O-glucoside, a flavonoid derivative, exhibits a moderate negative correlation with the ABTS assay (r = -0.625, P = 0.017). The presence of a glycosidic linkage in apigenin-7-O-glucoside may influence its interaction with the ABTS radical cation, affecting its antioxidant capacity **(Kashyap et al., 2022).**

The observed negative correlations between these compounds and antioxidant assays provide valuable insights into the antioxidant potential of *Salvia balansae* extracts. The inverse relationships suggest that phenolic compounds, particularly TPC and ODP, significantly contribute to antioxidant activity. It is crucial to consider the synergistic effects of these metabolites, as well as their structural features, to comprehend their bioactivity and potential therapeutic applications fully. Previous research has shown that the combined effects of different phenolic compounds can enhance antioxidant activity beyond what would be expected from their contributions **(Ouerghemmi et al., 2017; Riahi et al., 2013).**

IV.2 In vitro Photoprotective assay

The sun protection factor (SPF) assessment is a widely adopted method to evaluate the photoprotective potential of various substances, including plant extracts. The methodology for determining the in vitro SPF values involves calculating the UV absorption characteristics of the samples across the critical UV wavelength range, typically from 290 nm to 320 nm **(Mansur et al., 1986).**

The study conducted on *Salvia balansae* crude extracts (SBCE) employed this standardised approach to investigate their photoprotective capabilities. The results presented in **Table 10** revealed remarkable SPF values ranging from 26.64 to 46.34 at a concentration of 1 mg/mL, indicating a high level of photoprotection according to the European Commission's criteria **(Commission of the European Communities, 2006).** Notably, the flower extracts exhibited the highest photoprotective potential among the different plant organs, with no significant difference observed between the SPF values of leaves and flowers, except for the methanolic extracts. Interestingly, the methanolic stem extracts demonstrated superior sun protection capacity compared to leaf extracts.

The photoprotective potential of phenolic compounds and flavonoids present in plant extracts such as *Salvia balansae* can be attributed to their unique structural features and biochemical properties **(Hashemi et al., 2021).** These compounds exhibit strong absorption in the ultraviolet (UV) region due to their conjugated aromatic systems and the presence of hydroxyl groups, allowing them to efficiently absorb and dissipate UV radiation **(Li et al.,**

2023). Additionally, they possess potent antioxidant properties, enabling them to scavenge and neutralise reactive oxygen species (ROS) and free radicals generated by UV exposure, thereby mitigating oxidative stress and preventing cellular damage **(Ebrahimzadeh et al., 2014).** Furthermore, phenolic compounds and flavonoids demonstrate anti-inflammatory and immunomodulatory effects, which can suppress the inflammatory response triggered by UV radiation and minimize its detrimental effects on the skin **(Kostyuk et al., 2018)**.

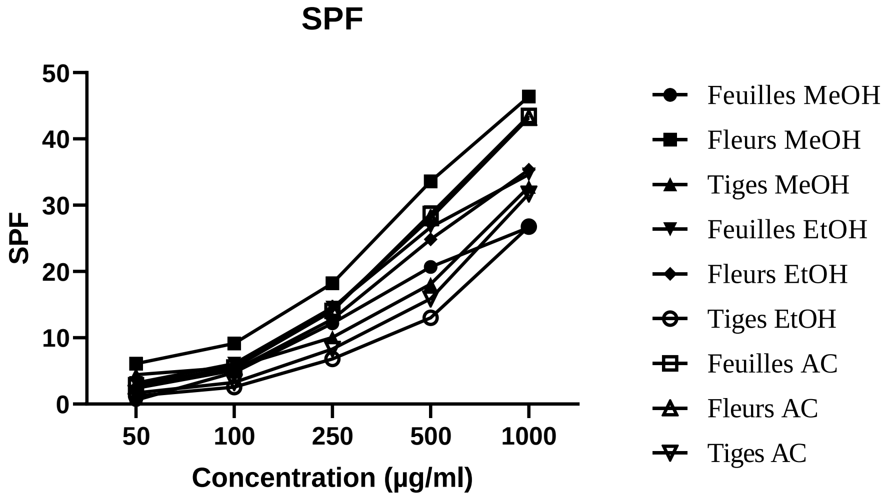


Figure 22. SPF Determination of *Salvia balansae* Extracts

These findings corroborate previous studies that have attributed the photoprotective properties of plant extracts to their rich phytochemical composition, particularly phenolic compounds and flavonoids **(Krgović et al., 2022; Manisha Pralhad & Sanjay Ravindra, 2020)**. These secondary metabolites are known to possess potent antioxidant and UV-absorbing capabilities, acting as natural defences against UV radiation-induced oxidative stress and cellular damage **(Lefahal et al., 2018; Saewan & Jimtaisong, 2015).**

Table 10. SPF (Sun protection factor) values of *Salvia balansae* different crude extracts.

	MeOH			**EtOH**			**AC**		
C (µg/ml)	***Leaves***	***Flowers***	***Stems***	***Leaves***	***Flowers***	***Stems***	***Leaves***	***Flowers***	***Stems***
50	0.62 ± 0.05	6.10 ± 0.39	32.76 ± 0.07	4.44 ± 0.38	3.20 ± 0.19	2.40 ± 0.09	1.22 ± 0.09	2.86 ± 0.31	2.64 ± 0.09
100	4,78 ± 0.03	9.14 ± 0.03	5.55 ± 0.04	6.11 ± 0,20	5.10 ± 0.11	2.56 ± 0.18	5.50 ± 0.23	5.65 ± 0.26	3.25 ± 0.10
250	12.20 ± 0.90	18.25 ± 0.12	10.06 ± 0.14	14.56 ± 0.29	12.82 ± 0.49	6.80 ± 0.12	14.08 ± 0.40	14.40 ± 0.45	8.32 ± 0.23
500	20.69 ± 0.18	33.62 ± 0.19	18.11 ± 0.15	26.70 ± 0.19	24.87 ± 0.52	13.04 ± 0.25	28.70 ± 1.02	28.07 ± 0.34	15.91 ± 0.34
1000	26.66 ± 0.04	46.38 ± 0.03	32.76 ± 0.07	34.63 ± 0.43	35.35 ± 0.57	26.76 ± 0.23	43.50 ± 0.05	43.19 ± 0.32	31.72 ± 0.34

Furthermore, the SBCE exhibited higher SPF values at 1 mg/mL concentration compared to other plant species, such as *Salvia officinalis* (SPF = 39 at 2 mg/mL) and *Mentha pulegium* (SPF = 36.31), as reported in the literature **(El Aanachi et al., 2021; Yakoubi et al., 2021)**.

It is important to note that the observed photoprotective effects of SBCE are also likely due to the synergistic interactions among the various phytochemicals present in the extracts, rather than the action of a single compound. The complex mixture of phenolic compounds, flavonoids, and other secondary metabolites may exhibit complementary or additive effects, enhancing the overall photoprotective capacity **(Ayad et al., 2023; Son et al., 2023).**

IV.2.1 Correlation of phenolic Compounds in SBCE with sun protection capacity

In the present study, Pearson's correlations were employed to investigate the relationship between phenolic compounds present in different extracts of *S. balansae* and their antioxidant and photoprotective capacities. The findings revealed a significant positive correlation between the Sun Protection Factor (SPF) and Apigenin-7-O-glucoside ($r = 0.74$, $P = 0.014$), as well as Ortho-diphenols ($r = 0.78$, $P = 0.013$). Conversely, SPF exhibited significant negative correlations with the antioxidant assays CUPRAC ($r = -0.82$, $P = 0.07$) and ABTS ($r = -0.78$, $P = 0.013$).

Flavonoids such as apigenin-7-O-glucoside are well-documented for their photoprotective properties, as indicated in numerous studies **(Ebrahimzadeh et al., 2014; Lahmadi et al., 2022; Poudel et al., 2022).** This effectiveness is primarily due to their capability to absorb UV radiation and their inherent antioxidant properties, Additionally, its potent antioxidant properties enable it to neutralize free radicals generated by UV exposure, thereby mitigating oxidative stress and preventing skin damage **(Saewan & Jimtaisong, 2013).** The significant positive correlation between SPF and ortho-diphenols in *Salvia balansae* extracts indicates that these compounds enhance photoprotective efficacy through potent antioxidant activity. Ortho-diphenols effectively neutralise free radicals and chelate metal ions, reducing oxidative stress caused by UV radiation **(Kostyuk et al., 2018).** Their molecular structure, featuring adjacent hydroxyl groups, is key to this radical-scavenging ability. Consequently, ortho-diphenols strengthen sun protection formulations by mitigating UV-induced damage and maintaining skin barrier integrity **(Hashemi et al., 2021; Saewan & Jimtaisong, 2015).**

The correlation between antioxidant activity and SPF in *Salvia balansae* extracts reveals that higher antioxidant activity, measured by assays like CUPRAC and ABTS, is associated with increased photoprotective capacity. Antioxidants such as polyphenols and flavonoids neutralize UV-induced free radicals, reducing oxidative stress and preventing cellular damage in the skin, thereby enhancing SPF **(Li et al., 2023; Son et al., 2023)**. This synergistic effect highlights the critical role of antioxidants in supporting effective sun protection by not only blocking UV radiation but also mitigating its harmful effects **(Ayad et al., 2023; Hashemi et al., 2021; Lahmadi et al., 2022).**

The significant correlations between antioxidant activities and SPF in *Salvia balansae* extracts emphasize the importance of incorporating antioxidants into photoprotective formulations. These compounds not only enhance the efficacy of sunscreens by providing additional protection against oxidative stress but also contribute to overall skin health.

IV.3 Anti-inflammatory activity

The anti-inflammatory activity of *Salvia balansae* crude extracts was evaluated using an in vitro protein denaturation assay, which serves as a valuable screening method for identifying potential anti-inflammatory agents. Protein denaturation, characterised by the disruption of native protein structure and conformation, is a critical process implicated in the pathogenesis of various inflammatory and autoimmune disorders **(Matsarskaia et al., 2020; Silvestrini et al., 2022)**. Notably, certain non-steroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to mitigate protein denaturation, in addition to their well-established inhibition of pro-inflammatory prostaglandin synthesis **(Maturana et al., 2019).**

According to the results displayed in **Table 11**, the methanol extract exhibited the highest anti-inflammatory activity, inhibiting protein denaturation by 78.48% at the maximum tested concentration of 2500 µg/mL. This potent activity can be attributed to the efficient extraction of polar bioactive compounds, such as polyphenols and flavonoids, which are known to possess anti-inflammatory properties through various molecular mechanisms.

The anti-inflammatory potency followed the order: methanol leaf extract > ethanol leaf extract > acetone leaf extract, suggesting that the leaf extracts were more effective than those obtained from flowers and stems, regardless of the solvent used. This observation aligns with previous findings that have reported higher concentrations of bioactive compounds, such as polyphenols and flavonoids, in the leaves of *Salvia* species **(Fotovvat et al., 2018; Francik et al., 2020)**.

Within each solvent group, the leaf extracts consistently exhibited higher anti-inflammatory activity compared to the corresponding flower and stem extracts. For instance, at 500 µg/mL, the methanol leaf extract inhibited protein denaturation by 27.54%, while the methanol flower and stem extracts showed inhibition of 17.87% and 17.20%, respectively.

The variations in anti-inflammatory activity among the methanol, ethanol, and acetone extracts can be attributed to the differences in solvent polarity and the solubility properties of the bioactive compounds present in *S. balansae* **(Mohammedi & Atik, 2011)**. Methanol, being a polar protic solvent, was able to efficiently extract the polar anti-inflammatory compounds, which may have contributed to the higher activity observed in the methanol leaf extract compared to the ethanol and acetone leaf extracts.

Table 11. In-vitro anti-inflammatory activity of *salvia balansae* by BSA denaturation assay

C (µg/ml)	**MeOH**			**EtOH**			**AC**			**Sodium Diclofénac**
	L	***F***	***S***	***L***	***F***	***S***	***L***	***F***	***S***	
62,5	3.38 ± 2.13	6.05 ± 0.73	0.72 ± 0.42	7.88 ± 0.34	2.04 ± 0.33	3.36 ± 1.41	7.71 ± 0.33	8.7 ± 0.03	9.44 ± 2.93	56.64 ± 2.17
125	8.62 ± 0,77	9.43 ± 1.13	5.40 ± 0.62	9.34 ± 0.6	4.5 ± 0.23	6.49 ± 0.36	14.57 ± 0.73	11.01 ± 0.34	13.25 ± 2.13	76.69 ± 1.23
250	17.27 ± 1.45	12.31 ± 1.18	13.57 ± 0.79	13.97 ± 2.31	11.06 ± 1.61	8.53 ± 1.49	16.56 ± 0.87	12.92 ± 0.49	15.47 ± 0.6	99.29 ± 0.19
375	23.98 ± 0.67	14.61 ± 0.29	15.98 ± 0.74	18.92 ± 1.73	15.46 ± 1.86	11.75 ± 1.05	19.89 ± 0.33	14.60 ± 0.65	19.66 ± 0.78	99.68 ± 0.28
500	27.54 ± 0.89	17.87 ± 1.31	17.20 ± 0.44	27.51 ± 0.89	20.94 ± 1.33	13.49 ± 2.19	22.15 ± 0.62	18.49 ± 1.35	23.86 ± 0.93	99.98 ± 0.04
1250	71.55 ± 0.61	27.19 ± 0.27	36.78 ± 1.67	56.90 ± 0.30	34.12 ± 0.91	24.80 ± 0.81	60.42 ± 1.9	40.91 ± 0.65	47.78 ± 0.66	/
2500	78.48 ± 0.71	44.75 ± 0.57	50.70 ± 1.01	65.31 ± 0.3	58.47 ± 0.44	52.32 ± 0.40	77.22 ± 1.67	54.69 ± 1.42	62.97 ± 0.55	/

MeOH, Methanol; **EtOH**, Ethanol; **Ac**, Acetone; **L**, Leaves; **F**, Flowers; **S**, Stems.

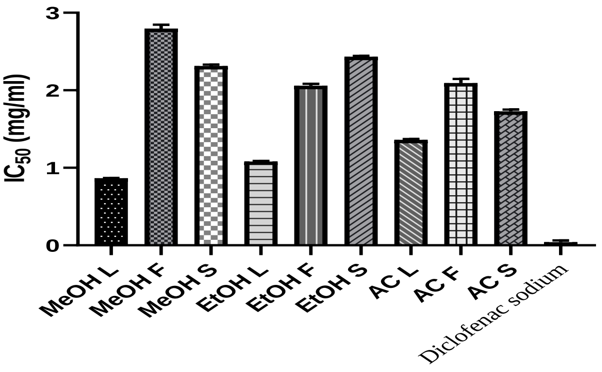


Figure 23. IC_{50} Values for the anti-inflammatory activity of *Salvia balansae* extracts

One potential mechanism involves the antioxidant activity of these compounds, which can scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS), preventing oxidative stress-induced protein denaturation and subsequent inflammatory responses **(Marino et al., 2022; Richards & Chaurasia, 2022).**

Moreover, these bioactive compounds may modulate key inflammatory signaling pathways by inhibiting the activity of pro-inflammatory enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing the production of inflammatory mediators such as prostaglandins and leukotrienes **(Bonesi et al., 2017; Tundis et al., 2017)**. Additionally, they may suppress the activation and nuclear translocation of transcription factors like nuclear factor-kappa B (NF-κB), which regulates the expression of various pro-inflammatory genes encoding cytokines, chemokines, and adhesion molecules **(Azab et al., 2016; Pan et al., 2010).**

Furthermore, The present study has confirmed the presence of the flavonoids luteolin and apigenin in *Salvia balansae* extracts. These compounds are known for their potent anti-inflammatory properties, which could contribute significantly to the observed inhibition of protein denaturation and the overall anti-inflammatory activity exhibited by the *S. balansae* extracts. Luteolin and apigenin have been reported to modulate multiple molecular targets and pathways involved in the inflammatory response, including the inhibition of pro-inflammatory mediators such as prostaglandin E2, nitric oxide, and cytokines like tumor necrosis factor-alpha and interleukins **(Bonesi et al., 2017; Kamatou et al., 2010)**. Their presence in *S. balansae*, along with potential synergistic interactions with other bioactive phytochemicals, could explain the promising anti-inflammatory effects observed in the extracts.

IV.3.1 Correlation of phenolic compounds in SBCE with anti-inflammatory capacity

Our findings indicated significant negative correlations between anti-inflammatory activity and the concentrations of protocatechuic acid (r = -0.69, P= 0.036) and cirsilineol (r = -0.93, P= 0.0007). This suggests that higher levels of these compounds are linked to reduced anti-inflammatory effects in the BSA denaturation assay.

Protocatechuic acid, a phenolic compound, is known for its antioxidant properties **(Li et al., 2011)**. However, its role in inflammation is complex. Several studies proved that higher concentrations of protocatechuic acid interfere with specific inflammatory pathways **(Albarakati, 2022; Kakkar & Bais, 2014; Wang et al., 2015)**. Whereas it might inhibit key signalling molecules or enzymes involved in the anti-inflammatory response, such as cyclooxygenase (COX) enzymes, thereby reducing the anti-inflammatory efficacy observed in the crude extract. This inhibition could decrease the synthesis of anti-inflammatory mediators, resulting in a lower overall anti-inflammatory effect **(Farombi et al., 2016).**

Cirsilineol, a flavonoid found in various medicinal plants, also exhibits complex bioactivity **(Panche et al., 2016).** Its significant negative correlation with anti-inflammatory activity suggests that at higher concentrations, cirsilineol may exert pro-inflammatory effects or inhibit mechanisms that typically mitigate inflammation.

Studies have proved that cirsilineol might downregulate anti-inflammatory cytokines or inhibit the activity of transcription factors such as NF-κB, which are essential for the expression of anti-inflammatory genes **(Kumar & Pandey, 2013; Pan et al., 2010; Puangpraphant et al., 2022).** Alternatively, it may competitively inhibit other bioactive compounds within the crude extract with more potent anti-inflammatory properties **(Lala et al., 2020)**.

These findings align with previous studies on the bioactivity of phenolic compounds and flavonoids **(Bonesi et al., 2017; D'Amelia et al., 2017; Georgiev & Pavlov, 2017)**. While many compounds in these categories have demonstrated potent antioxidant and anti-inflammatory effects, their efficacy can depend highly on concentration and specific molecular interactions within complex biological systems. For example, studies have shown that certain concentrations of flavonoids can shift from being anti-inflammatory to pro-inflammatory due to changes in cellular uptake, bioavailability, and interaction with cellular targets **(Al-Khayri et al., 2022)**.

IV.4 α-Amylase enzyme inhibition assay

The genus *Salvia*, belonging to the Lamiaceae family, has been extensively investigated for its potential anti-diabetic properties. Several studies have reported the inhibitory effects of crude extracts and isolated compounds from various *Salvia* species against key enzymes involved in carbohydrate metabolism, particularly α-amylase and α-glucosidase **(Abd Rashed & Rathi, 2021; Brindisi et al., 2021; Mamache et al., 2020; Shojaeifard et al., 2023).**

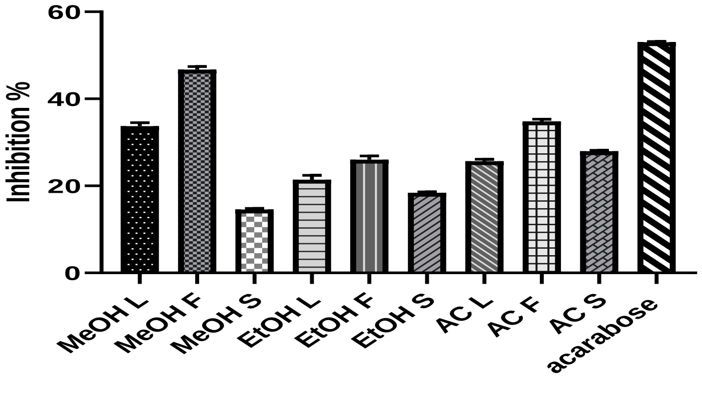


Figure 24. Comparative α-amylase inhibitory activity of *S. balansae* extracts at 400 µg/mL

The present study demonstrates the promising antidiabetic activity of *Salvia balansae* crude extracts, with a particular emphasis on the flower extracts exhibiting superior α-amylase inhibitory potential compared to leaf and stem extracts across different solvent systems. Notably, the methanolic flower extract displayed the highest inhibition rate (46.74 ± 0.70%) at 400 µg/mL, suggesting a selective accumulation or biosynthesis of antidiabetic phytochemicals in the floral organs **(Brindisi et al., 2021; Lu & Yeap Foo, 2002)**. This finding aligns with previous reports highlighting the efficacy of flower extracts from other plant species, such as Calotropis procera, Phaulopsis falcisepala, and Bombax ceiba, in inhibiting carbohydrate-digesting enzymes **(Abiodun et al., 2018; Familoni et al., 2019; Iftikhar et al., 2022).**

The potent α-amylase inhibitory activity observed in the *S. balansae* flower extracts can be attributed to the presence of bioactive compounds like rosmarinic acid and luteolin glycosides, which are known to accumulate preferentially in *Salvia* flowers **(D'Amelia et al., 2017; Jassbi et al., 2016)**. These polyphenolic compounds have been widely reported to exhibit antidiabetic effects through their ability to inhibit carbohydrate-hydrolyzing enzymes by forming stable complexes with the enzymes through non-covalent interactions, such as hydrogen bonding, hydrophobic interactions, and van der Waals forces **(Proença et al., 2022; Yang et al., 2020).**

Furthermore, the choice of extraction solvent played a crucial role in recovering the α-amylase inhibitors, with methanol being the most effective due to its moderate polarity. This observation is consistent with previous studies, where methanol facilitated efficient extraction of phenolic compounds and glycosidic derivatives possessing antidiabetic properties **(Ahmadi et al., 2021; Ogundajo et al., 2016; Prakash, 2022).** The moderate polarity of methanol allows for the solubilization of a wide range of polar and semi-polar compounds, including flavonoids, phenolic acids, and glycosides, which are known to exhibit α-amylase inhibitory activity **(Ahmadi et al., 2021; Proença et al., 2022).**

However, it is important to note that the optimal solvent may vary depending on the plant species, targeted phytochemicals, and the nature of the plant material **(Familoni et al., 2019; Nouri et al., 2014)**. For instance, **Familoni et al. (2019)** reported that acetone exhibited higher antidiabetic activity compared to methanol when extracting from Acalypha godseffiana leaves, while **(Nouri et al., 2014)** found ethanol to be more potent than methanol for extracting α-amylase inhibitors from betel leaves. These variations highlight the need for solvent optimization based on the specific plant source and the targeted bioactive compounds.

The findings of this study contribute to the growing body of evidence supporting the antidiabetic potential of *Salvia* species, particularly through the inhibition of α-amylase, a key enzyme responsible for regulating postprandial glucose levels. The preferential accumulation of antidiabetic compounds in the flowers and the efficient extraction by methanol collectively contribute to the potent α-amylase inhibitory activity exhibited by the *S. balansae* flower extracts.

IV.4.1 Correlation of phenolic compounds in SBCE with α-amylase inhibition capacity

The investigation into the antidiabetic activity of *Salvia balansae* using the alpha-amylase inhibition assay provides initial insights into the plant's potential to manage diabetes. Although the extracts did not exhibit strong alpha-amylase inhibitory activity across all tested concentrations, significant positive correlations with certain bioactive compounds were observed, particularly at the highest concentration tested (400 µg/ml).

The significant positive correlations with polyphenols (r=0.705, P= 0,033), ortho-diphenols (r=0.682, P= 0,042), and flavonoids such as luteolin-7-O-glucoside (r=0.721, P=0,028) and apigenin (r=0.767, P=0,016) suggest that these compounds contribute to the observed inhibitory effects. Polyphenols and ortho-diphenols are well-known for their antioxidant properties, which play a crucial role in mitigating oxidative stress, a key factor in the pathogenesis of diabetes **(Abbas et al., 2017; Marino et al., 2022)**. Additionally, flavonoids like luteolin-7-O-glucoside and apigenin have been documented for their enzyme-inhibitory activities, including alpha-amylase inhibition, which is directly relevant to antidiabetic action **(Bahadori et al., 2017; Proença et al., 2022).**

At the molecular level, these compounds can scavenge free radicals, chelate metal ions, and modulate the activities of enzymes involved in carbohydrate metabolism. By reducing oxidative stress and inhibiting alpha-amylase, they can lower the rate of carbohydrate digestion and glucose absorption, thereby contributing to better glycemic control **(de Paulo Farias et al., 2021; Nie & Cooper, 2021)**.

While the data indicate that *Salvia balansae* has bioactive compounds with potential antidiabetic effects, the overall alpha-amylase inhibitory activity of the crude extracts was not robust. Therefore, while the plant shows promise, further detailed studies are required.

IV.4.2 Chemometric analysis

The comprehensive analysis of Salvia balansae offers significant insights into its phytochemical profile and biological activities, contributing to the growing body of knowledge on medicinal plants in the Lamiaceae family. This study employs multivariate statistical techniques, including Principal Component Analysis (PCA) and Unweighted Pair Group Method with Arithmetic Mean (UPGMA), to elucidate the complex relationships among various phytochemical constituents and their associated bioactivities.

The PCA analysis, conducted on the correlation matrix of the 33 variables, generated eight components. The first two factors explained 53.17% of the variance seen among the nine SBCEs. This substantial percentage indicates that these two factors are crucial in differentiating among the extracts **(Figure 25).**

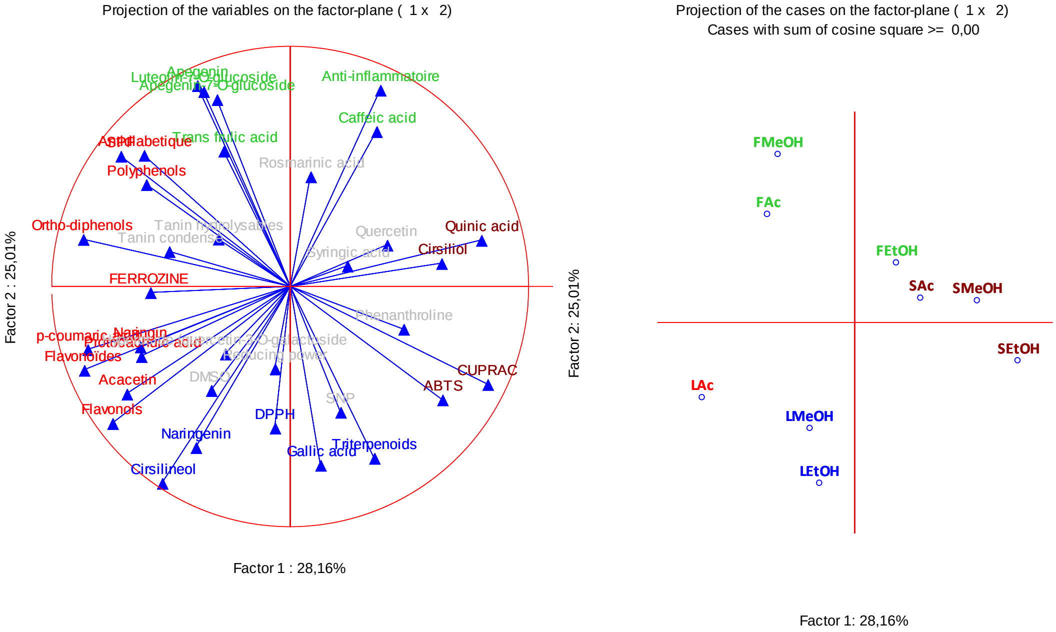


Figure 25. Principal Component Analysis (Factor 1/2) of the Chemical Composition and Biological Activities of (SBCEs).

SBCEs were divided into four distinct groups. The first group, represented by the stem extracts, is located on the positive part of axis one and characterised by high contents of quinic acid and cirsiliol, with low antioxidant activity assessed by CUPRAC and ABTS. The second group, opposed to this, is formed by the leaves acetonic extract, characterised by high concentrations of protocatechuic acid, p-coumaric acid, naringin, acacetin, polyphenols, flavonoids, flavonols, and o-diphenols, and high SPF and antidiabetic activities.

S. balansae flower extracts were placed in the third group (positive part of axis two) due to phytochemicals such as caffeic acid, trans-ferulic acid, apigenin-7-O-glucoside, luteolin-7-O-glucoside, apigenin, and low anti-inflammatory activity.

The methanol and ethanol extracts of *S. balansae* leaves constitute the fourth group located in the negative part of Axis Two, characterized by high concentrations of DPPH, TT, cirsilineol, naringenin, and gallic acid.

The third factor **(Figure 26)**, accounting for 17.72% of the variance among the nine SBCEs, separated them into two distinct groups. The flower and stem acetonic extracts are characterised by high concentrations of syringic acid, quercetin, condensed and hydrolysable tannins, DMSO, phenanthroline, and SNP, while the methanolic extracts are characterised by a high content of rosmarinic acid.

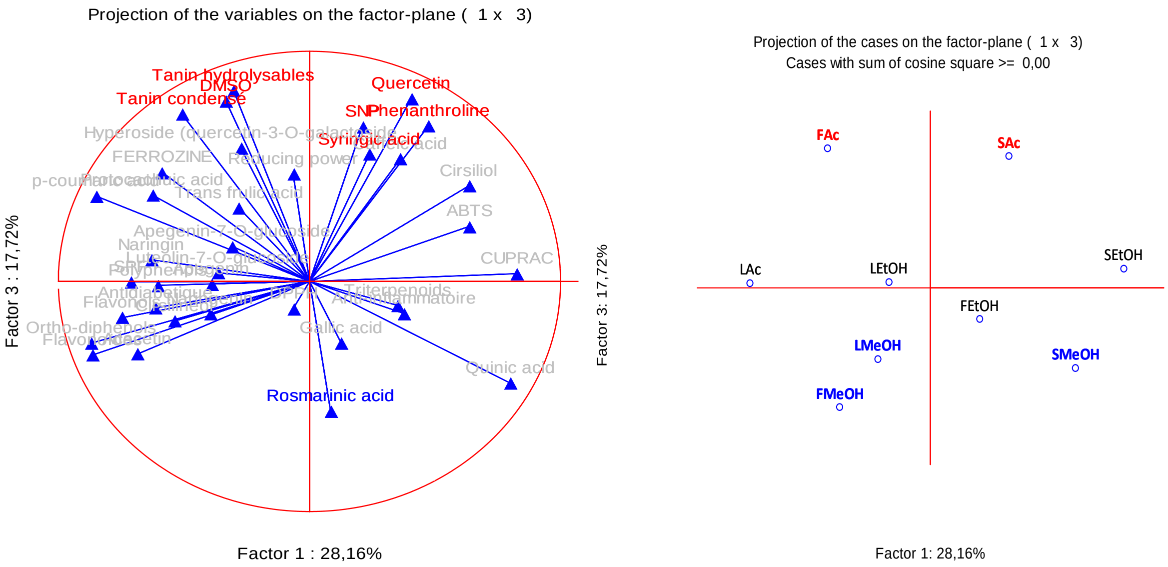


Figure 26. Principal Component Analysis (Factor 1/3) of the Chemical Composition and Biological Activities of (SBCEs).

UPGMA analysis results **(Figure 27)** showed that two main clusters were obtained, which were divided into a few sub-clusters at the linkage distance between 800 and 1000. The acetonic and leaves ethanolic extracts are placed in the first cluster, while the methanolic and the rest of the ethanolic extracts are in the second cluster.

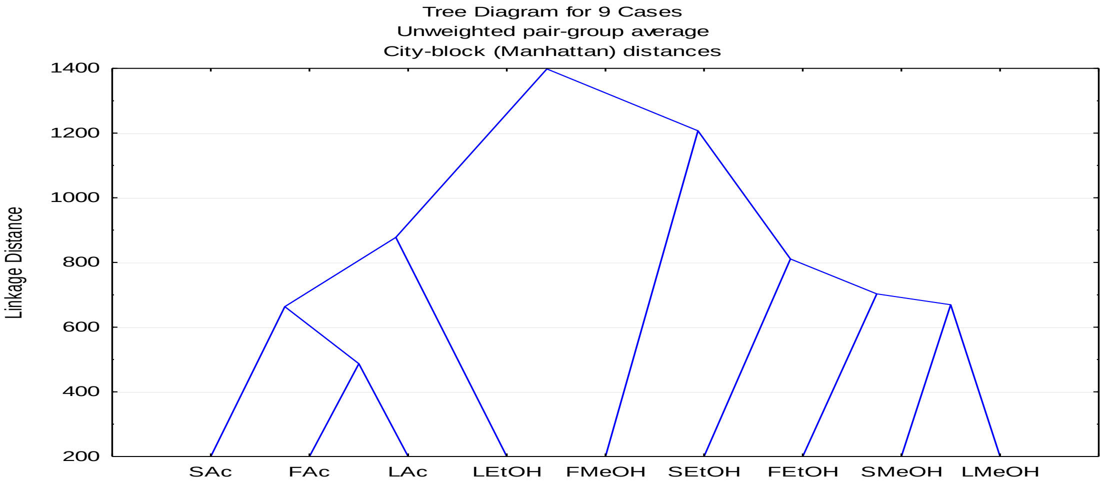


Figure 27. Dendrogram of SBCEs, based on Manhattan Similarity distance.

It can be concluded from all these that in the distribution of examined extracts, the most dominant influence is biological activities and phytochemical contents, which both have a very similar influence regarding the positioning of these extracts on the score plot.

General Conclusion

This comprehensive investigation into *Salvia balansae* represents a significant advancement in our understanding of this endemic Algerian species and its potential therapeutic applications. Through a multifaceted approach including phytochemical profiling and biological activity assessments, this study has unveiled the remarkable potential of *S. balansae* as a source of bioactive compounds with diverse medicinal properties.

The phytochemical screening revealed the presence of a wide array of secondary metabolites, including flavonoids, tannins, saponins, terpenoids, quinones, cardiac glycosides, sterols, phytosteroids, coumarins, betacyanins, diterpenes, carbohydrates, and reducing sugars. These compounds are well-documented for their health-promoting properties, underscoring the potential of *S. balansae* as a source of natural therapeutic agents.

The quantitative analysis, using various solvents (methanol, ethanol, and acetone), showed that S. balansae extracts have high contents of phenolics, flavonoids, flavonols, tannins, triterpenoids, and ortho-diphenols. These compounds are well-known for their diverse biological activities, which were confirmed through multiple assays. The extraction efficiency varied depending on the compound and plant part, with methanol and acetone extracts often showing higher extraction efficiency for different compounds.

The LC-MS analysis identified 18 phenolic compounds, including eight phenolic acids and ten flavonoids, with quinic acid and rosmarinic acid emerging as predominant constituents. This phytochemical diversity underpins the plant's remarkable biological activities, including potent antioxidant, photoprotective, anti-inflammatory, and antidiabetic properties.

The strong antioxidant effects shown by *S. balansae* extracts, especially from the flowers, suggest this plant could be a valuable source of natural antioxidants. We found clear links between antioxidant activity and certain types of compounds, particularly ortho-diphenols. This not only confirms these compounds' role in creating antioxidant effects but also gives us useful information for targeted extraction and product development.

The impressive sun protection potential of *S. balansae* extracts, with SPF values similar to or better than some commercial sunscreens, opens up new possibilities for developing natural sun protection products. Surprisingly, stem extracts performed particularly well in this area, reminding us of the importance of studying all parts of a plant in this kind of research.

Moreover, the significant anti-inflammatory and antidiabetic effects we observed suggest that *S. balansae* could be useful in developing new treatments. The differences we saw between plant parts and extraction solvents provide crucial insights for optimising the extraction and formulation of active compounds for specific medical uses.

This research not only adds greatly to our scientific understanding of *S. balansae* but also lays the groundwork for its sustainable use in medicine, cosmetics, and nutrition. The plant's multiple benefits, including antioxidant, sun protection, anti-inflammatory, and antidiabetic effects, show its potential as a versatile natural product with many possible applications.

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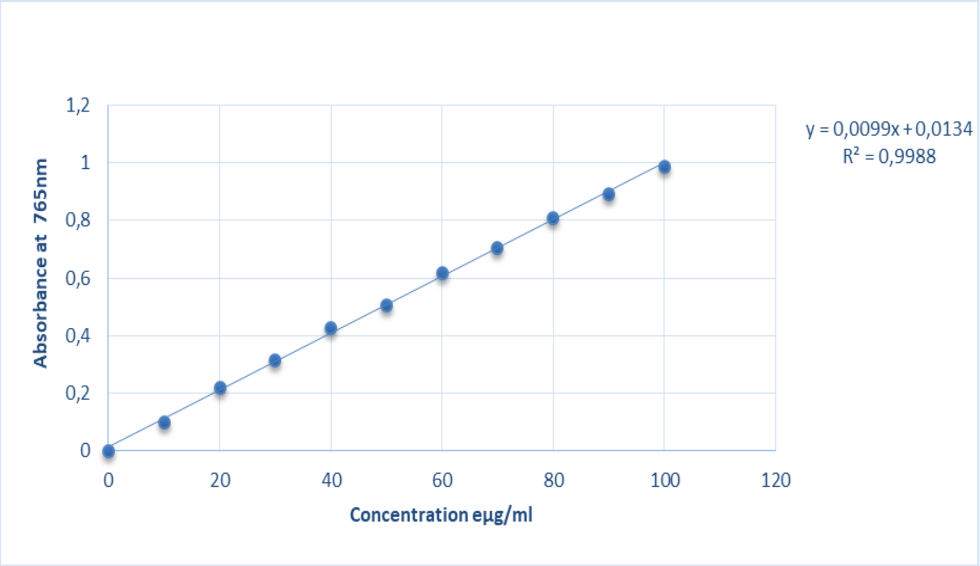
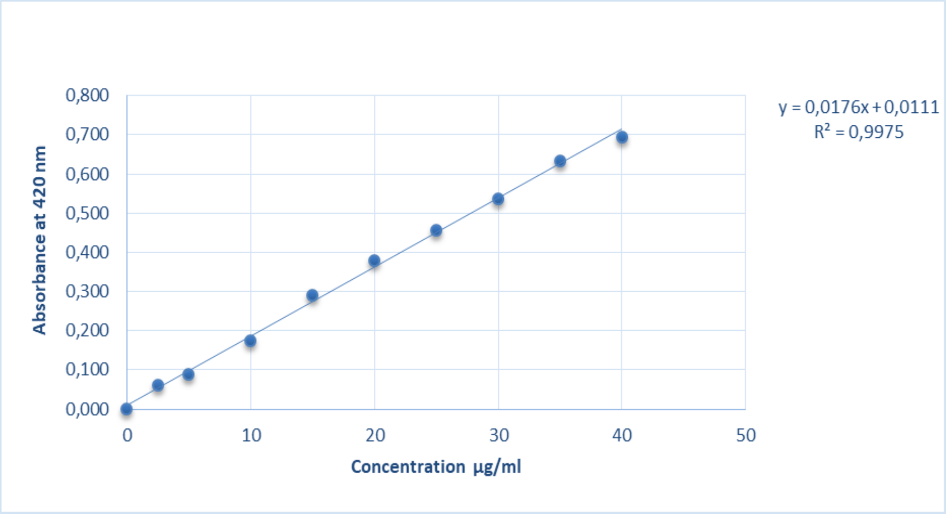
Annexes

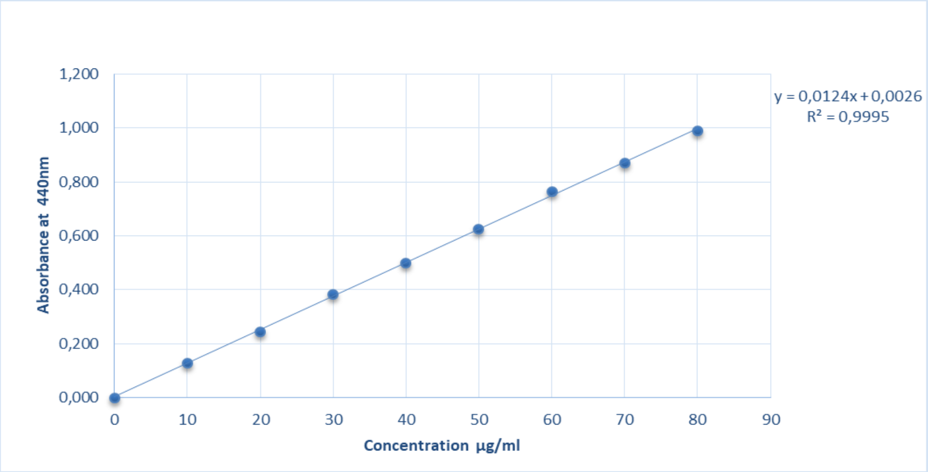
Annexes



Annexe 1. Gallic Acid Calibration Curve of polyphenols

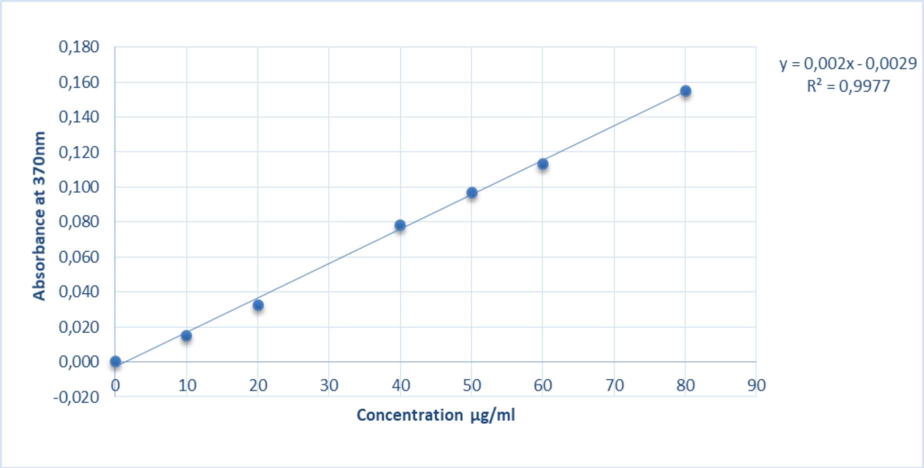


Annexe 2. Quercetin Calibration Curve for Flavonoids



Annexe 3. Quercetin Calibration Curve for Flavonols

Annexes



Annexe 3. Gallic Acid Calibration Curve of ortho-diphenol

Annexes

	Quinic acid	Gallic acid	Protocachuic acid	Caffeic acid	Syringic acid	p-coumaric acid	Trans frulic acid	Rosmarinic acid	Naringenin	Naringin	Apegenin-7-O-glucoside	Hyperoside (quercetin-3-O-galactoside	Quercetin	Luteolin-7-O-glucoside	Apegenin	Cirsiliol	Cirsilineol	Acacetin	Polyphenols	Flavonoïdes	Flavonols	Tanin condensé	Tanin hydrolysables	Triterpenoids	Ortho-diphenols	FERROZINE	ABTS	DPPH	CUPRAC	DMSO	Reducing power	Phenanthroline	SNP	SPF	Anti-inflammatoire	Antidiabetique
Quinic acid	1,000000	0,168490	-0,683998	0,222631	-0,232128	-0,899500	-0,151348	0,337190	-0,279172	-0,499685	-0,077625	-0,472570	0,032054	-0,083651	-0,087652	0,230075	-0,513166	-0,526779	-0,525543	-0,607716	-0,581841	-0,651436	-0,469755	0,322186	-0,576415	-0,591101	0,416915	-0,216531	0,609699	-0,758056	-0,565675	0,133027	-0,266340	-0,532443	0,546565	-0,284585
Gallic acid	0,168490	1,000000	0,257865	-0,448005	-0,407300	-0,053982	-0,393369	-0,067529	0,334997	0,188762	-0,501580	0,025198	-0,344294	-0,458706	-0,553979	-0,328778	0,606515	0,100343	-0,506902	0,209080	0,508551	-0,304327	-0,279539	0,755654	-0,204169	-0,203850	0,685801	0,567399	0,371225	0,068424	0,006277	0,054465	0,211144	-0,571207	-0,560444	-0,403660
Protocachuic acid	-0,683998	0,257865	1,000000	0,012967	-0,016280	0,605822	0,414127	-0,430754	0,165138	0,823431	0,268994	0,674201	-0,096950	0,242359	0,110527	-0,538607	0,543712	0,366359	0,123748	0,527892	0,600442	0,599212	0,462183	0,247518	0,233529	0,285266	0,004521	0,403564	-0,305748	0,529055	0,116112	0,149145	0,047960	0,131326	-0,699158	0,312999
Caffeic acid	0,222631	-0,448005	0,012967	1,000000	0,318387	-0,368037	0,687583	-0,073474	-0,747136	-0,197984	0,656168	0,071101	0,572811	0,556054	0,442988	0,297757	-0,803038	-0,697933	-0,090383	-0,714955	-0,706728	0,372645	0,529216	-0,189417	-0,460395	-0,083671	0,185833	-0,353904	0,089904	-0,059104	-0,175440	0,481891	-0,023654	0,008015	0,485460	0,073454
Syringic acid	-0,232128	-0,407300	-0,016280	0,318387	1,000000	0,012075	-0,215216	0,061185	-0,267774	-0,014125	-0,194524	0,454686	0,701811	-0,188748	-0,194409	0,782512	-0,249772	-0,346689	0,357170	-0,428732	-0,498728	0,279745	0,091918	-0,213201	-0,238622	-0,230173	-0,015765	-0,225486	0,107140	0,373761	0,434247	0,303419	0,282931	-0,204292	-0,075050	0,010917
p-coumaric acid	-0,899500	-0,053982	0,605822	-0,368037	0,012075	1,000000	0,066439	-0,316538	0,560774	0,521776	-0,001762	0,448461	-0,039674	0,016945	0,054160	-0,284519	0,603710	0,570511	0,487384	0,693080	0,724553	0,680067	0,514732	-0,272750	0,668152	0,779646	-0,355792	0,020256	-0,647870	0,738051	0,375166	-0,194128	0,300147	0,495875	-0,533027	0,305389
Trans frulic acid	-0,151348	-0,393369	0,414127	0,687583	-0,215216	0,066439	1,000000	-0,300790	-0,418446	0,188840	0,925443	0,069513	0,020995	0,810071	0,706543	-0,416745	-0,379810	-0,074341	0,008566	-0,039152	-0,104864	0,513351	0,644019	-0,214919	0,034605	0,300995	-0,195496	-0,117033	-0,330462	-0,038404	-0,307610	0,169193	-0,267900	0,468410	0,254201	0,352447
Rosmarinic acid	0,337190	-0,067529	-0,430754	-0,073474	0,061185	-0,316538	-0,300790	1,000000	-0,296166	-0,201400	0,019502	-0,399509	-0,185246	0,232585	0,264399	0,131159	-0,277805	-0,305600	0,529366	-0,106678	-0,243807	-0,327007	-0,522022	-0,406854	0,343696	-0,474978	-0,231886	-0,374426	-0,301796	-0,551381	-0,272445	-0,626107	-0,559615	0,106384	0,411294	0,403928
Naringenin	-0,279172	0,334997	0,165138	-0,747136	-0,267774	0,560774	-0,418446	-0,296166	1,000000	0,353110	-0,548858	0,209392	-0,262995	-0,564569	-0,503277	-0,220655	0,776977	0,720704	0,007687	0,613815	0,658467	0,108328	-0,074463	0,310611	0,286679	0,385607	-0,046361	-0,002070	-0,094768	0,276308	-0,054923	-0,227026	0,216960	-0,132107	-0,612829	-0,106483
Naringin	-0,499685	0,188762	0,823431	-0,197984	-0,014125	0,521776	0,188840	-0,201400	0,353110	1,000000	0,168208	0,785674	-0,119748	0,200441	0,151501	-0,505236	0,579434	0,452001	0,252441	0,650313	0,579150	0,372892	0,134687	0,292855	0,358283	0,107298	-0,217710	0,214165	-0,255128	0,236838	-0,187519	0,039276	-0,267718	0,046221	-0,625454	0,593924
Apegenin-7-O-glucoside	-0,077625	-0,501580	0,268994	0,656168	-0,194524	-0,001762	0,925443	0,019502	-0,548858	0,168208	1,000000	-0,000804	0,000531	0,966845	0,914296	-0,387969	-0,502873	-0,182002	0,215759	-0,025603	-0,167976	0,380267	0,489424	-0,419590	0,223173	0,205209	-0,381795	-0,223747	-0,446841	-0,214984	-0,365936	0,009926	-0,485008	0,604664	0,466885	0,596180
Hyperoside (quercetin-3-O-g	-0,472570	0,025198	0,674201	0,071101	0,454686	0,448461	0,069513	-0,399509	0,209392	0,785674	-0,000804	1,000000	0,479428	-0,021453	-0,047773	0,058835	0,324759	0,076285	0,116498	0,207705	0,226040	0,485949	0,351691	0,283221	-0,018507	0,147346	0,030895	0,098310	0,063385	0,546653	0,131043	0,517590	0,188118	-0,189265	-0,540242	0,331501
Quercetin	0,032054	-0,344294	-0,096950	0,572811	0,701811	-0,039674	0,020995	-0,185246	-0,262995	-0,119748	0,000531	0,479428	1,000000	-0,054340	-0,037594	0,778893	-0,480802	-0,660249	-0,031719	-0,647869	-0,545911	0,377984	0,484823	-0,104828	-0,441772	0,119689	0,290062	-0,408631	0,299752	0,418395	0,241718	0,706035	0,503052	-0,262824	0,203432	-0,076344
Luteolin-7-O-glucoside	-0,083651	-0,458706	0,242359	0,556054	-0,188748	0,016945	0,810071	0,232585	-0,564569	0,200441	0,966845	-0,021453	-0,054340	1,000000	0,965894	-0,399293	-0,468480	-0,208038	0,360064	0,042975	-0,113259	0,314389	0,376549	-0,500093	0,371987	0,147106	-0,444412	-0,236557	-0,540648	-0,262518	-0,357558	-0,129982	-0,576825	0,651809	0,487846	0,721934
Apegenin	-0,087652	-0,553979	0,110527	0,442988	-0,194409	0,054160	0,706543	0,264399	-0,503277	0,151501	0,914296	-0,047773	-0,037594	0,965894	1,000000	-0,347344	-0,477314	-0,171159	0,409401	0,095622	-0,099071	0,225454	0,316679	-0,603358	0,470666	0,220444	-0,577340	-0,275952	-0,552631	-0,277506	-0,308071	-0,160681	-0,574127	0,740424	0,584324	0,767043
Cirsiliol	0,230075	-0,328778	-0,538607	0,297757	0,782512	-0,284519	-0,416745	0,131159	-0,220655	-0,505236	-0,387969	0,058835	0,778893	-0,399293	-0,347344	1,000000	-0,480163	-0,588463	0,037933	-0,738739	-0,705991	-0,008226	-0,006041	-0,177463	-0,469218	-0,205082	0,241228	-0,427248	0,377814	0,172457	0,324054	0,353818	0,450234	-0,383291	0,269608	-0,335523
Cirsilineol	-0,513166	0,606515	0,543712	-0,803038	-0,249772	0,603710	-0,379810	-0,277805	0,776977	0,579434	-0,502873	0,324759	-0,480802	-0,468480	-0,477314	-0,480163	1,000000	0,769494	0,017852	0,801473	0,888089	0,046655	-0,159999	0,432462	0,353355	0,203100	0,014019	0,521263	-0,124983	0,392596	0,208903	-0,233768	0,167476	-0,098249	-0,881174	-0,056940
Acacetin	-0,526779	0,100343	0,366359	-0,697933	-0,346689	0,570511	-0,074341	-0,305600	0,720704	0,452001	-0,182002	0,076285	-0,660249	-0,208038	-0,171159	-0,588463	0,769494	1,000000	0,185611	0,863046	0,721626	0,065009	-0,155507	0,105525	0,513703	0,290816	-0,473886	0,302259	-0,359163	0,122182	0,005664	-0,462542	-0,144930	0,285651	-0,586544	0,110332
Polyphenols	-0,525543	-0,506902	0,123748	-0,090383	0,357170	0,487384	0,008566	0,529366	0,007687	0,252441	0,215759	0,116498	-0,031719	0,360064	0,409401	0,037933	0,017852	0,185611	1,000000	0,332440	0,092640	0,416059	0,054858	-0,742535	0,763932	0,151799	-0,717844	-0,444307	-0,829635	0,100657	0,064715	-0,620453	-0,342582	0,597851	0,024266	0,705407
Flavonoïdes	-0,607716	0,209080	0,527892	-0,714955	-0,428732	0,693080	-0,039152	-0,106678	0,613815	0,650313	-0,025603	0,207705	-0,647869	0,042975	0,095622	-0,738739	0,801473	0,863046	0,332440	1,000000	0,902287	0,102070	-0,088010	0,008876	0,760855	0,369002	-0,505367	0,351777	-0,525470	0,167360	0,020127	-0,487513	-0,241205	0,438255	-0,539139	0,416715
Flavonols	-0,581841	0,508551	0,600442	-0,706728	-0,498728	0,724553	-0,104864	-0,243807	0,658467	0,579150	-0,167976	0,226040	-0,545911	-0,113259	-0,099071	-0,705991	0,888089	0,721626	0,092640	0,902287	1,000000	0,154754	0,065505	0,194618	0,593355	0,476937	-0,127775	0,472962	-0,376012	0,383595	0,163566	-0,300920	0,080846	0,253203	-0,659909	0,154082
Tanin condensé	-0,651436	-0,304327	0,599212	0,372645	0,279745	0,680067	0,513351	-0,327007	0,108328	0,372892	0,380267	0,485949	0,377984	0,314389	0,225454	-0,008226	0,046655	0,065009	0,416059	0,102070	0,154754	1,000000	0,859427	-0,305771	0,236540	0,617989	-0,104094	-0,358954	-0,552800	0,650601	0,115208	0,102846	0,276203	0,328681	-0,272048	0,282625
Tanin hydrolysables	-0,469755	-0,279539	0,462183	0,529216	0,091918	0,514732	0,644019	-0,522022	-0,074463	0,134687	0,489424	0,351691	0,484823	0,376549	0,316679	-0,006041	-0,159999	-0,155507	0,054858	-0,088010	0,065505	0,859427	1,000000	-0,261181	0,031986	0,749013	0,077340	-0,228278	-0,318006	0,645859	0,195841	0,398702	0,452768	0,342464	-0,013863	0,082395
Triterpenoids	0,322186	0,755654	0,247518	-0,189417	-0,213201	-0,272750	-0,214919	-0,406854	0,310611	0,292855	-0,419590	0,283221	-0,104828	-0,500093	-0,603358	-0,177463	0,432462	0,105525	-0,742535	0,008876	0,194618	-0,305771	-0,261181	1,000000	-0,592861	-0,365904	0,672688	0,500092	0,719540	-0,046956	-0,207097	0,443056	0,145938	-0,809653	-0,541890	-0,447500
Ortho-diphenols	-0,576415	-0,204169	0,233529	-0,460395	-0,238622	0,668152	0,034605	0,343696	0,286679	0,358283	0,223173	-0,018507	-0,441772	0,371987	0,470666	-0,469218	0,353355	0,513703	0,763932	0,760855	0,593355	0,236540	0,031986	-0,592861	1,000000	0,445332	-0,748084	-0,113953	-0,876286	0,082611	0,035588	-0,717906	-0,353805	0,781452	-0,059508	0,682774
FERROZINE	-0,591101	-0,203850	0,285266	-0,083671	-0,230173	0,779646	0,300995	-0,474978	0,385607	0,107298	0,205209	0,147346	0,119689	0,147106	0,220444	-0,205082	0,203100	0,290816	0,151799	0,369002	0,476937	0,617989	0,749013	-0,365904	0,445332	1,000000	-0,216037	-0,142977	-0,485204	0,626434	0,285599	0,034016	0,445704	0,571881	-0,073636	0,090967
ABTS	0,416915	0,685801	0,004521	0,185833	-0,015765	-0,355792	-0,195496	-0,231886	-0,046361	-0,217710	-0,381795	0,030895	0,290062	-0,444412	-0,577340	0,241228	0,014019	-0,473886	-0,717844	-0,505367	-0,127775	-0,104094	0,077340	0,672688	-0,748084	-0,216037	1,000000	0,227175	0,671593	0,171660	0,068761	0,544338	0,542844	-0,783347	-0,215184	-0,692953
DPPH	-0,216531	0,567399	0,403564	-0,353904	-0,225486	0,020256	-0,117033	-0,374426	-0,002070	0,214165	-0,223747	0,098310	-0,408631	-0,236557	-0,275952	-0,427248	0,521263	0,302259	-0,444307	0,351777	0,472962	-0,358954	-0,228278	0,500092	-0,113953	-0,142977	0,227175	1,000000	0,323166	0,189551	0,441388	0,196145	0,168220	-0,134293	-0,481407	-0,312253
CUPRAC	0,609699	0,371225	-0,305748	0,089904	0,107140	-0,647870	-0,330462	-0,301796	-0,094768	-0,255128	-0,446841	0,063385	0,299752	-0,540648	-0,552631	0,377814	-0,124983	-0,359163	-0,829635	-0,525470	-0,376012	-0,552800	-0,318006	0,719540	-0,876286	-0,485204	0,671593	0,323166	1,000000	-0,149573	0,013435	0,687710	0,306042	-0,821775	-0,002552	-0,641603
DMSO	-0,758056	0,068424	0,529055	-0,059104	0,373761	0,738051	-0,038404	-0,551381	0,276308	0,236838	-0,214984	0,546653	0,418395	-0,262518	-0,277506	0,172457	0,392596	0,122182	0,100657	0,167360	0,383595	0,650601	0,645859	-0,046956	0,082611	0,626434	0,171660	0,189551	-0,149573	1,000000	0,736086	0,347953	0,797175	0,080737	-0,543689	-0,185409
Reducing power	-0,565675	0,006277	0,116112	-0,175440	0,434247	0,375166	-0,307610	-0,272445	-0,054923	-0,187519	-0,365936	0,131043	0,241718	-0,357558	-0,308071	0,324054	0,208903	0,005664	0,064715	0,020127	0,163566	0,115208	0,195841	-0,207097	0,035588	0,285599	0,068761	0,441388	0,013435	0,736086	1,000000	0,200436	0,710425	0,135132	-0,257977	-0,364292
Phenanthroline	0,133027	0,054465	0,149145	0,481891	0,303419	-0,194128	0,169193	-0,626107	-0,227026	0,039276	0,009926	0,517590	0,706035	-0,129982	-0,160681	0,353818	-0,233768	-0,462542	-0,620453	-0,487513	-0,300920	0,102846	0,398702	0,443056	-0,717906	0,034016	0,544338	0,196145	0,687710	0,347953	0,200436	1,000000	0,515442	-0,461601	-0,019827	-0,332373
SNP	-0,266340	0,211144	0,047960	-0,023654	0,282931	0,300147	-0,267900	-0,559615	0,216960	-0,267718	-0,485008	0,188118	0,503052	-0,576825	-0,574127	0,450234	0,167476	-0,144930	-0,342582	-0,241205	0,080846	0,276203	0,452768	0,145938	-0,353805	0,445704	0,542844	0,168220	0,306042	0,797175	0,710425	0,515442	1,000000	-0,266143	-0,299842	-0,679740
SPF	-0,532443	-0,571207	0,131326	0,008015	-0,204292	0,495875	0,468410	0,106384	-0,132107	0,046221	0,604664	-0,189265	-0,262824	0,651809	0,740424	-0,383291	-0,098249	0,285651	0,597851	0,438255	0,253203	0,328681	0,342464	-0,809653	0,781452	0,571881	-0,783347	-0,134293	-0,821775	0,080737	0,135132	-0,461601	-0,266143	1,000000	0,311224	0,559715
Anti-inflammatoire	0,546565	-0,560444	-0,699158	0,485460	-0,075050	-0,533027	0,254201	0,411294	-0,612829	-0,625454	0,466885	-0,540242	0,203432	0,487846	0,584324	0,269608	-0,881174	-0,586544	0,024266	-0,539139	-0,659909	-0,272048	-0,013863	-0,541890	-0,059508	-0,073636	-0,215184	-0,481407	-0,002552	-0,543689	-0,257977	-0,019827	-0,299842	0,311224	1,000000	0,154687
Antidiabetique	-0,284585	-0,403660	0,312999	0,073454	0,010917	0,305389	0,352447	0,403928	-0,106483	0,593924	0,596180	0,331501	-0,076344	0,721934	0,767043	-0,335523	-0,056940	0,110332	0,705407	0,416715	0,154082	0,282625	0,082395	-0,447500	0,682774	0,090967	-0,692953	-0,312253	-0,641603	-0,185409	-0,364292	-0,332373	-0,679740	0,559715	0,154687	1,000000

Phytochemical Study and Biological Activities of the Species *Salvia balansae* Noë ex Coss

Abstract

Salvia balansae, an endemic perennial plant native to Algeria, particularly in the Mostaganem and Aures regions, exhibits significant medicinal potential. This study aims to explore the chemical composition and biological activities of *Salvia balansae* extracts obtained from different plant organs (leaves, flowers, and stems) collected from the Aures Mountains using various solvents (ethanol, methanol, and acetone). The maceration technique was employed to extract the chemical constituents, and the extracts were analyzed for their total phenolic compounds, flavonoids, flavonols, condensed and hydrolysable tannin, triterpenoid, and ortho-diphenols content using using microplate reader technique. Advanced analytical techniques, such as liquid chromatography coupled with mass spectrometry (LC-MS), were used to identify the specific phenolic compounds.

The antioxidant activity of the extracts was assessed through multiple in vitro assays, including DPPH, ABTS, FIC, FRAP, Phenanthroline, CUPRAC, SNPAC, and Superoxide radical scavenging activity by alkaline DMSO assay. Additionally, the photoprotective properties were evaluated, given the increasing interest in natural sunscreen formulations. Principal Component Analysis (PCA) and Unweighted Pair-Group Method with Arithmetic Mean (UPGMA) were applied to discern the similarities and differences among the extracts concerning their chemical composition, secondary metabolite content, and biological activities.

Furthermore, the anti-inflammatory activity of the extracts was evaluated using the Bovine Serum Albumin (BSA) method, and the antidiabetic potential was assessed through the alpha-amylase inhibition assay. Results revealed that S. balansae extracts exhibit significant antioxidant, photoprotective, anti-inflammatory, and antidiabetic activities. This is attributed to their rich phenolic content. Moreover, the study identified several key phenolic compounds and demonstrated the impact of solvent type and plant organ on the efficacy of the extracts.

This research represents the first comprehensive investigation into the phytochemical and biological properties of *Salvia balansae* from the Aures Mountains, highlighting its potential as a source of natural antioxidants, photoprotective, anti-inflammatory, and antidiabetic agents.

Keywords: *Salvia balansae*, Endemic plant, LC-MS, phenolic compounds, biological activities, Triterpenoids.

ملخص

يعتبر *Salvia balansae* نبات معمر مستوطن في الجزائر، خصوصًا في مناطق مستغانم والأوراس، و يتمتع بخصائص طبية كثيرة. تهدف هذه الدراسة إلى استكشاف التركيب الكيميائي والأنشطة البيولوجية لمستخلصات *Salvia balansae* المستخرجة من أجزاء مختلفة من النبات (الأوراق، الأزهار، والسيقان) المتحصل عليها من جبال الأوراس باستخدام مذيبات مختلفة (الإيثانول، الميثانول، والأسيتون). تم استخدام تقنية النقع لاستخراج المركبات الكيميائية، وتم تحليل المستخلصات لتحديد محتواها من المركبات الفينولية الكلية، الفلافونويدات، الفلافونولات، التانينات المكثفة والقابلة للتحلل، التريتربينويدات، والأرثو-دي فينولات باستخدام تقنية قارئ الألواح الدقيقة. تم استخدام تقنيات التحليل الكروماتوغرافي السائل المتصل بمطياف الكتلة (LC-MS) لتحديد المركبات الفينولية الخاصة بها.

تم تقييم النشاط المضاد للأكسدة للمستخلصات من خلال العديد من الاختبارات المخبرية، بما في ذلك DPPH ، ABTS، FIC، FRAP، Phenanthroline، CUPRAC، SNPAC، ونشاط إزالة الجذور المؤكسدة الفائقة باستخدام اختبارDMSO القلوي. بالإضافة إلى ذلك، تم تقييم الخصائص الواقية من الضوء نظرًا للاهتمام المتزايد بالتركيبات الطبيعية للمراهم الواقية للشمس. تم تطبيق تحليل المكونات الرئيسية (PCA) وطريقة UPGMA (طريقة التجميع غير الموزونة بمتوسط الحساب) لاكتشاف التشابهات والاختلافات بين المستخلصات فيما يتعلق بالتركيب الكيميائي، محتوى المستقلبات الثانوية، والأنشطة البيولوجية.

علاوة على ذلك، تم تقييم النشاط المضاد للالتهابات للمستخلصات باستخدام طريقة ألبومين مصل البقري (BSA) ، وتم تقييم الإمكانية المضادة للسكري من خلال اختبار تثبيط إنزيم ألفا-أميلاز. كشفت النتائج أن مستخلصات *S. balansae* ، خصوصًا تلك المستخرجة من جبال الأوراس، تظهر أنشطة مضادة للأكسدة، واقية من الضوء، مضادة للالتهابات، ومضادة للسكري بشكل كبير. يُعزى ذلك إلى غناها بالمركبات الفينولية والفلافونويدات. علاوة على ذلك، حددت الدراسة العديد من المركبات الفينولية الرئيسية وأظهرت تأثير نوع المذيب وجزء النبات على فعالية المستخلصات.

تمثل هذه الدراسة التحقيق الأول الشامل في الخصائص الكيميائية والبيولوجية *Salvia balansae* من جبال الأوراس، مما يبرز إمكاناتها كمصدر لمضادات الأكسدة الطبيعية، العوامل الواقية من الضوء، المضادة للالتهابات، والمضادة للسكري.

الكلمات المفتاحية: *Salvia balansae* ، نبات مستوطن ، LC-MS، مركبات فينولية، الأنشطة البيولوجية، التريتربينويدات.