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Defended publicly on :
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Spécialité : **Biologie moléculaire et cellulaire**

par

Melle. Asma DJAHAFI

Intitulée

Etude de l'effet cytotoxique et génotoxique de quelques plantes médicinales en Algérie

Soutenu publiquement le :
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الملخص

يعتبر الطب التقليدي اضافة مهمة لعلاج الكثير من الأمراض رغم وجود نقص ملحوظ حول المعلومات الضرورية الخاصة بالممارسات التقليدية للنباتات الطبية والعطرية وثأثيراتها الجانبية في الجزائر و لهذا تهدف هذه الدراسة الى جرد أهم النباتات العطرية والطبية المستخدمة في الطب الجزائري التقليدي على مستوى منطقة تيارت (شمال غرب الجزائر) و ذلك من أجل انشاء فهرس للنباتات الطبية واستخداماتها العلاجية من طرف السكان المحليين للمنطقة و في نفس الوقت الى تقييم مكوناتها الكيميائية النباتية و امكانية سلامتها الحيوية عن طريق اجراء اختبارات السمية الخلوية و الجينية.

أولا تم اجراء دراسة عرقية دوائية في منطقة تيارت في البدء للتعرف على جميع النباتات الطبية المستعملة من قبل السكان المحليين لهذه المنطقة حيث أظهرت هذه الدراسة استخدام 107 نوعًا نباتيًا ينتمي إلى 45 عائلة نباتية و 97 جنسًا لمعالجة مختلف الأمراض. اكثر العائلات النباتية تمثيلا كانت الشفويات، الخيميات و النجميات و أكثر الأنواع ذكرًا كانت السناء المكي (FC=27)، االقطف و التالغودة (FC=23)، البسباس (FC=22) و البابونج (FC=21). بالنسبة للأنواع النباتية المتمثلة في كل من التالغودة، التسكرة، اليقطين، التفاح و البشنة فقد تم ذكرها لأول مرة كنباتات طبية في الجزائر.

فيما بعد، تم اختيار كل من القطف (*Atriplex halimus* L.) ، التالغودة (*Bunium incrassatum* Amo) و التسكرة (*Echinops spinosus* L.) من أجل تقييم النشاط المضاد للأكسدة و دراسة السمية الخلوية والجينية حيث كشفت النتائج المتحصل عليها أن جميع المستخلصات النباتية تمتاز بنشاط مضاد للأكسدة وخاصة مستخلصات التالغودة و التسكرة التي سجلت قيم أعلى من مستخلص القطف. بالاضافة الى ذلك ، أثبتت التحاليل ان جميع المستخلصات المختبرة غنية بالمركبات البوليفينولية ولديها القدرة على تدمير كريات الدم الحمراء بنسبة ضئيلة.من جهة أخرى، بينت نتائج اختبار مؤشر الانقسام الميتوزي أن جميع المستخلصات النباتية ليس لديها تأثيرات مميتة أو شبه مميتة باستثناء مستخلص القطف عند التركيز 1 مغ/مل .في نفس الوقت تم تحديد العديد من التشوهات الصبغية ، بما في ذلك اللزوجة الكروموسومية ، كروموسومات الطور الاستوائي الكولشسيني ، طور نهائي نجمي ،الكسور و الجسور الصبغية ، الكروموسومات المتأخرة، عديدية الصيغة الصبغية ، الخلايا ثنائية النواة والنويات. من المثير للاهتمام و بالرغم من ان جميع المستخلصات النباتية التي تم اختبارها تسببت في خفض معدل النمو و تثبيط مؤشر الانقسام الميتوزي الا أن عدد التشوهات الكروموسومية الملحوظة لم يتجاوز عتبة الخطر عند الجرعة التقليدية الموصى بها.

تؤكد النتائج المتحصل عليها أن المعرفة الثقليدية الجزائرية ذات قيمة و أهمية كبيرة من حيث التنوع النباتي والممارسات التقليدية المحلية. ومع ذلك، ينبغي توخي الحذر أثناء استخدام النباتات الطبية في الطب التقليدي لتجنب أي نوع من التسمم.

الكلمات الدالة

دراسة عرقية دوائية، الطب التقليدي، العلاج بالنباتات ، المركبات الكيميائية النباتبة، نشاط مضاد الأكسدة ، السمية الخلوية ، السمية الجينية، تيارت، الجزائر.

Abstract

Herbal medicine is gaining increasing interest in the management of various diseases, but little is known about traditional practices and herbal toxicity in Algeria. The present study aims first to identify the used aromatic and medicinal plants in Algerian traditional medicine, in the region of Tiaret, in order to safeguard the local cultural heritage and national pharmacopoeia, then to assess the phytochemical profile and safety of use of the main cited plants throughout cyto-genotoxicity analyses.

The ethnopharmacological study revealed the use of 107 plant species belonging to 45 families and 97 genera for the management of diverse ailments. The most represented plant families are the Lamiaceae, Apiaceae, and Asteraceae. However, the most cited plant species are *Senna alexandrina* Mill. (FC=27), *Atriplex halimus* L., *Bunium incrassatum* Amo (FC=23 each), *Foeniculum vulgare* Mill. (FC=22), and *Matricaria chamomilla* L. (FC=21). Interestingly, *B. incrassatum* Amo, *Echinops spinosu* L., *Cucurbita moschata* Duchesne, *Malus domestica* Borkh, and *Pennisetum glaucum* (L.) R.Br. are reported for the first time as medicinal plants in Algeria.

Subsequently, *A. halimus*, *B. incrassatum*, and *E. spinosus* were selected for the antioxidant activity and cyto-genotoxicity studies. The antioxidant activity was high in *B. incrassatum* and *E. spinosus* extracts than *A. halimus* extract. Nevertheless, the three tested plants constitute a rich source of secondary metabolites. Moreover, the tested plants extracts exhibited a low *in vitro* hemolytic activity. Analysis of the mitotic index demonstrated that the tested plants extracts do not exhibit lethal or sublethal effects at the studied concentrations, except for the aqueous extract of *A. halimus* at concentrations above 1 mg/ml. Besides, various chromosomal aberrations have been identified, including stickiness, C-metaphase, disturbances, chromosomal bridges, vagrant chromosomes, polyploidy, binucleate and micronuclei. However, although the tested plants extracts presented a mito-depressive effect, the number of the observed aberrations remained remains below the danger threshold at the recommended traditional dosage.

Based on the obtained results, Algerian traditional knowledge is very rich in terms of plant diversity and traditional medicinal practices for the management of various health problems. However, the use of aromatic and medicinal plants in traditional medicine should be directed very carefully to avoid any kind of toxicity.

Keywords

Ethnopharmacology; Traditional medicine; Herbal medicine; Phytochemical compounds; Antioxidant activity; Cytotoxicity; Genotoxicity; Tiaret; Algeria.

Résumé

La phytothérapie a suscité un grand intérêt pour le traitement de diverses maladies. Cependant, un manque flagrant d'informations est constaté concernant les pratiques traditionnelles et la toxicité des plantes médicinales en Algérie. La présente étude vise à documenter les plantes médicinales utilisées dans les pratiques traditionnelles locales de la région de Tiaret (Algérie) afin de sauvegarder la pharmacopée locale et d'évaluer le profil phyto-chimique et la biosécurité des principales plantes citées à travers des tests de cyto-génotoxicité.

L'étude ethnopharmacologique a permis de documenter l'utilisation de 107 plantes médicinales appartenant à 45 familles et 97 genres. Les familles végétales les plus représentées sont les Lamiacées, les Apiacées et les Astéracées. Cependant, les espèces végétales les plus citées sont *Senna alexandrina* Mill. (FC=27), *Atriplex halimus* L. et *Bunium incrassatum* Amo (FC=23, chacun), *Foeniculum vulgare* Mill. (FC=22) et *Matricaria chamomilla* L. (FC=21). Il est à noter que *Bunium incrassatum* Amo, *Echinops spinosus* L., *Cucurbita moschata* Duchesne, *Malus domestica* Borkh et *Pennisetum glaucum* (L.) R.Br. sont citées pour la première fois comme des plantes médicinales en Algérie.

Par ailleurs, *A. halimus*, *B. incrassatum* et *E. spinosus* ont été sélectionées pour l'évaluation de l'activité antioxydante et l'effect cyto-genotoxique. L'activité antioxydante la plus élevée a été observée chez les extraits de *B. incrassatum* et *E. spinosus*. Toutefois, tous les extraits de plantes testés représentent une riche source de molécules bioactives possédant une faible activité hémolytique. De plus, l'évaluation de l'indice mitotique a révélé que les extraits de plantes testées ne présentent pas des effets létaux ou sublétaux à l'exception de l'extrait d'*A. halimus* à la concentration 1 mg/ml. De même, plusieurs aberrations chromosomiques ont été identifiées, notamment, l'aspect collant des chromosomes, la métaphase-C, les perturbations chromosomiques, les ponts chromosomiques, les chromosomes vagabonds, la polyploïdie, les cellules binucléés et les micronoyaux. Cependant, le nombre d'aberrations chromosomiques détectées conformément au dosage traditionnel recommandé demeure inférieur au seuil du danger même si les extraits étudiés possèdent un effet mito-dépressif.

Dans l'ensemble, le savoir faire local Algérien est précieux en terme de diversité végétale et de pratiques traditionnelles. Cependant, l'utilisation des plantes médicinales doit être conduite avec prudence afin d'éviter tout type de toxicité.

Mots clés

Ethnopharmacologie; La médecine traditionnelle; Phytothérapie; Composés phytochimiques; Activité antioxydante; Cytotoxicité; Génotoxicité; Tiaret; Algérie.

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Dedications

I dedicate this work to

To my dear parents;

Mom for her support and encouragement during all my years of study, without whom I would never have succeeded, and Dad (May Allah be Most Merciful to him and welcome him to his vast Paradise).

To all my dear family;

My sisters and brothers, who have always supported and encouraging me in my hardest moments with their best wishes.

To my dear friends and loved ones with whom I spent my most beautiful moments.

Asma

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List of abbreviations

AAE/g:	Equivalent ascorbic acid per gram.
ANOVA:	Analysis of variance.
CAs:	Chromosomal aberrations.
df:	Degree of freedom.
DPPH:	2,2-diphenyl-1-picrylhydrazyl.
EC_{50}:	Effective concentration 50%.
EY:	Extraction yield.
F:	*F*-statistic.
FC:	Frequency of citation.
F_{IC}:	Informant consensus factor.
FRAP:	Ferric Reducing Antioxidant Potency.
IC_{50}:	Inhibitory concentration 50%.
GAE/g:	Gallic acid equivalent per gram.
QE/g:	Quercetin equivalent per gram.
TAE/g:	Tannic acid equivalent per gram.
MI:	Mitotic index.
MS:	Mean sum *of* squares.
P:	*P*-value.
PBS:	Phosphate buffer saline.
PI:	Phase index.
r:	Correlation coefficient.
ROS:	Reactive oxygen species.
RSA:	Radical scavenging activity percentage.
SS:	Sum *of* squares.
UR:	Use report.
UV:	Use value.
WHO:	World Health Organization.

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General introduction

General introduction

Medicinal plants have been used since ancient times as healing agents in traditional medicines; they constitute the most economical and easily accessible source to meet primary health needs especially in poor regions (Ait Abderrahim et al., 2019). Many patients worldwide use herbal remedies to meet their basic healthcare needs (Aydın et al., 2016) and more than 80% of the world's population relies heavily on medicinal plants (Ihegboro et al., 2020). Although, the insufficiency and the high cost of conventional treatments, besides the failure of modern medicine to develop effective therapies for various diseases, have all contributed to the use of medicinal plants (Taïbi et al., 2020).

In fact, medicinal plants constitute a rich source of active compounds with a wide range of biological activities that are widely used for the treatment and management of a variety of diseases (Benarba, 2016). Due to their minor side effects, various therapeutic properties, and synergistic effects, medicinal plants are considered among the best available sources in the modern pharmaceutical industry for the synthesis of new drugs (Dar et al., 2017). They are rich in several substances such as phenolic compounds, terpenoids, and vitamins which are used in both traditional medicine and human food (Jamshidi-Kia et al., 2020).

Unfortunately, despite of the wide beneficial effects of medicinal plants and their high potential for drugs discovery, only a limited number plant species has been scientifically studied for their biological activities (Yuan et al., 2016).

The Mediterranean Basin is the third richest hotspot in the world and it comprises many interesting plant species with numerous ecological, nutritional, and therapeutic properties that could be investigated for bioprospecting and value-addition for the development and synthesis of multiple functional foods and novel therapeutic remedies (Berrabah et al., 2019). As a part of the Mediterranean region, Algeria is characterized by an extremely diverse flora, with 3183 plant species encompassing many endemic and vulnerable species, because of the diversity of its geographic location, climate, and topographic conditions. In addition, various traditional medicinal practices have been developed due to the country's diversity in terms of ethnic groups, cultures, languages, and beliefs (Taïbi et al., 2020). Although numerous ethnobotanical and ethnomedicinal studies have been conducted in various regions of Algeria, further studies are required to document the immense variety of taxa and protect the valuable ancestral knowledge (Benarba et al., 2015; Taïbi et al., 2021).

In general, the use of medicinal plants is considered much safer and more secure with less side effects on human health than modern synthetic drugs (Anywar et al., 2021), which are not only more expensive and ineffective for treating various diseases but also can induce many side effects (Jain et al., 2019). Numerous investigations on the biological properties of aromatic and medicinal plants used in traditional medicines have demonstrated their efficacy and safety, particularly on animals (Mensah et al., 2019). Furthermore, several studies dealing with medicinal plants toxicity are usually misinterpreted because they use organic solvents such as methanol and dichloromethane rather than aqueous extract which are commonly used in traditional practices (Mensah et al., 2019).

Otherwise, the use of medicinal plants meets many challenges such as the of lack of sufficient knowledge about their dosage, adverse effects and toxicity (Subramanian et al., 2018). Although, it has been reported that the difference between a poison and a remedy is the dosage of that substance (Aftab and Hakeem, 2021; Mensah et al., 2019). Several investigations have reported the harmful effects of some medicinal plants, which resulted in acute or chronic intoxications including allergic, hematologic, neurological, gastrointestinal, hepatotoxic, cardiovascular and carcinogenic effects (Aydın et al., 2016). Unfortunately, until present, there are not enough clear scientific evidences on the virtues, efficacy, and safety of African medicinal plants, including Algerian plant species, employed in traditional practices (Anywar et al., 2021).

The aim of the present study is (i) to document and safeguard the traditional local knowledge of the region of Tiaret (North West of Algeria) in terms of traditional medicines for the treatment of various diseases then, (ii) to evaluate, on a scientific basis, the safety of use of some commonly employed aromatic and medicinal plants for therapeutic purposes, namely *Atriplex halimus* L., *Bunium incrassatum* (Boiss) Batt. and Trab., and *Echinops spinosus* L., via the analyses of the phytochemical composition, antioxidant, cytotoxic and genotoxic activities.

Literature review

Literature review

1. Traditional medicine

Traditional medicine is the oldest form of therapeutic system that has been used in health care as well as in the prevention and treatment of various physical and mental illnesses in the world. It refers to all forms of indigenous medicines such as traditional Chinese medicine, Ayurveda, and Unani Arabic medicine (Yuan et al., 2016).

According to the World Health Organization (2018), a large number of people worldwide depend heavily on traditional herbal medicine to improve their primary health care. Around 40% of total drug consumption comes from traditional medicine in China. Nevertheless, it has been reported that the use of traditional herbal medicine is more than synthesized pharmaceutical products in Japan. However, more than 80% of the population in Africa depends on traditional medicine and herbal remedies to answer their primary health needs (Dar et al., 2017; Mahomoodally, 2013; Zougagh et al., 2019).

In Arab countries, people have also returned to traditional healers, particularly in rural areas, to employ home cures and respond to personal care. More than 450 medicinal plants have been used in traditional Arab-Islamic medicine to cure a variety of human disorders in most Arab and Islamic nations as well as in the Mediterranean region. Due to the popularity of herbal remedies, which are thought to be perennial, less expensive, and safe compared to synthetic treatments that have negative side effects, this medicine, which is founded on cultural beliefs and religion, is still practiced today and considered to be one of the greatest traditional medical systems in the world (Saad and Said, 2011; Taïbi et al., 2020).

The ethnomedicinal and ethnopharmacological investigations refer to all interdisciplinary research fields which study the traditional cultural knowledge of peoples concerning the diversity and uses of medicinal plants, their therapeutic effects, their potential health benefits, as well as their toxicity and health risks which constitute the basis of complementary medicine systems (Gurib-Fakim, 2006). Their studies are essential to identify significant medicinal plant species in the area and to record prevailing knowledge about those that are in danger of disappearing (Benarba et al., 2015).

This deep and valuable ethnomedical knowledge about the diversity and use of medicinal plants for the treatment of different ailments in traditional cultures is probably developed by trials and errors over many centuries, where the most important recipes that are due to vast experience accumulated have been carefully passed down from generation to generation (Mahomoodally, 2013).

The successful use of traditional medicine can contribute to the discovery of lead compounds and the development of new drug candidates as it provides the opportunity to examine drug activity and explore different physicochemical, biochemical, pharmacokinetic, and toxicological characteristics (Jamshidi-Kia et al., 2018).

This is why this form of medicine is considered too valuable to be ignored in modern drug research and development. Interestingly, a single medicinal herb or plant can contain a wide range of phytochemical compounds such as polyphenols, alkaloids, terpenoids, and flavonoids, where their use alone or in combination can produce the desired pharmacological effect. Additionally, it should be noted that many valuable herbal medicines have been discovered through their use in traditional medicine and are used today in modern medicine (Gurib-Fakim, 2006).

However, from the point of view of many practitioners of Western medical science, who clime that the systems of traditional medicine adopted by most people worldwide are unreliable, it is necessary to create remarkable synergy in order to develop reformed drugs and synthesize new drugs for the management of various ailments using both ethnopharmacological and ethnomedical experiments with powerful modern scientific techniques and methods (Yuan et al., 2016).

Thus, ethnopharmacological and ethnomedicinal studies have become more than useful to provide valuable sources of knowledge and to discover the most important local natural products in order to safeguard traditional medicinal culture (Taïbi et al., 2020).

1.1. Aromatic and medicinal plants

The term "medicinal plant" encompasses all species of the plant kingdom that have therapeutic purposes. These medicinal herbs are considered as a rich source of secondary metabolites, which are widely used in the development and synthesis of various pharmaceutical drugs such as laxatives, antibiotics, and anticoagulants (Jamshidi-Kia et al., 2018; Rasool Hassan, 2012).

Throughout the world, herbal medicine has been used in the treatment of health problems, mainly in developing countries where more than 3.3 billion people in these countries depend on natural products and herbal remedies to answer their primary health needs (Ganaie, 2021; Singh, 2015). Despite the presence of modern medicine that offers several chemical and synthetic drugs for several diseases, medicinal plants have often maintained popularity for various reasons such as their effectiveness, accessibility, cheaper costs, and that patients tolerate them well (Sohani, 2019).

In recent years, the use of traditional medicine has become very important on a global scale, where more than 50.000 species of the plant kingdom are used in the synthesis of pharmaceuticals and cosmetics products and as herbal remedies (Jamshidi-Kia et al., 2018). Today, the world is gradually turning to herbal medicine, which is known to be effective against various diseases (Jain et al., 2019). It has been reported that around 25% of all synthetic drugs are prepared from plants, directly or indirectly (Hamburger and Hostettmann, 1991).

1.2. Medicinal plants use in traditional medicine

At the time, there was not enough information about the causes of diseases, useful plants for treating them, and the ways to use them, it was all empirical. Over time, the reasons for using medicinal plants and their therapeutic purposes have been discovered. Today, about 80% of the people in the world, especially in poor regions, depend on traditional herbal remedies which can better protect against many diseases such as diarrhea, fever, colds, and dental problems (Berrabah et al., 2019; Jamshidi-Kia et al., 2018).

This traditional herbal medicine refers to all uses of medicinal plants in the treatment of diseases on a local or regional scale. It has been widely used in developing and developed countries for thousands of years because they are natural and cause relatively fewer complications (Hoareau and DaSilva, 1999).

Various types of herbal remedies are used to address primary health needs and are mainly prepared from several parts of plants, including leaves, stems, roots, seeds, fruits, barks, or even the whole plant, and their active compounds have direct or indirect therapeutic effects (Gurib-Fakim, 2006; Singh, 2015).

1.3. Medicinal plants of therapeutic interests

Herbal medicine, which constitutes the use of plants or plant extracts for medicinal purposes, is still the mainstay of health care, mainly in developing countries (Saad and Said, 2011). They play a major role in the fight against numerous diseases including cancer, hepatitis, and AIDS. Several pharmacologic studies on plant extracts have led to the detection of many drugs with pharmaceutical value (Dar et al., 2017). Over the past 20–30 years, the analysis of herbal products has greatly progressed (Kabera et al., 2014).

In 1928, Merck produced morphine on an industrial scale. From the 1950s until the end of the 1970s, approximately 100 new pharmaceutical products of plant origin were presented, including vincristine, reserpine, and deserpidine. However, from 1971 up to 1990, other medicines were also synthesized among them E-guggulsterone, artmisinin, lectinam, teniposide, plaunotol, and nabilone. In contrast, in 1991 and 1995, the appearance of drugs including irinotecan, toptecan, paclitaxel and gomishin, in addition to the isolation of serpentine and their uses in the treatment of hypo and hypertension (Dar et al., 2017; Ren-Ren et al., 2015).

1.4. Economic importance of plants used in phytotherapy

Herbal medicine has increased across the world. According to the statistical estimates of the Exim Bank, the annual world trade in botanicals-related products is over US$ 60 billion, with an annual growth rate of 7%. Furthermore, it has been reported that the whole global demand for different herbal products is approximately US$ 14 billion per year and will reach more than US$ 5 trillion in 2050, which means the global demand for plant products is increasing at the rate of 15% to 25% per year (Ganaie, 2021).

2. Secondary metabolites of aromatic and medicinal plants

Plants produce an impressive range of organic compounds. These compounds are divided into two categories: the first represents the primary metabolites, which are phytochemical substances that exist in all cells and play a vital role in the metabolism and reproduction of cells including lipids, steroids, proteins, nucleic acids, fatty acids, and carbohydrates (Russell and Duthie, 2011).

The second category includes secondary metabolites resulting from subsequent chemical reactions that are not necessary to the development of the cells but play an important role in the survival of species (Pagare et al., 2015; Singh, 2015).

These secondary metabolites are generally responsible for the biological characteristics of plant species used worldwide and their chemical structures are diverse when compared to primary metabolites (Sohani, 2019; Vuolo et al., 2019). They can be classified into three different categories including terpenoids, phenolic compounds, and alkaloids (Kabera et al., 2014).

2.1. Phenolic compounds

Phenolic compounds regroup a vast range of organic molecules. They are secondary metabolites characterized by the presence of phenol groups with an aromatic ring that lead to very complex polymeric substances. To date, more than 8000 molecules have been identified and biosynthesized from products of the shikimic acid pathway (Vuolo et al., 2019).

These molecules possess a wide range of therapeutic properties among them antimutagenic, antioxidant, anticancer, and anti-inflammatory activities as they prevent various diseases and protect from oxidative stress (Ganaie, 2021; Jamwal et al., 2018). Based on their chemical structure, they can be divided into several sub-classes (Hussein and El-Anssary, 2019). The most important of them are phenolic acids, flavonoids, and tannins (Vuolo et al., 2019).

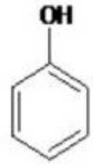


Figure 1. Basic structure of phenol (Kabera et al., 2014).

2.1.1. Phenolic acids

The term phenolic acid can be applied to all organic compounds possessing a single phenyl group substituted by a carboxylic group with one or more OH groups (Laura et al., 2019). These compounds are produced through the phenylpropanoid pathway and possess several biological properties including antidiabetic, antioxidant, anticancer, antimicrobial, and neuroprotective (Kumar and Goel, 2019). They can be divided into two groups: hydroxybenzoic acids and hydroxycinnamic acids.

- Hydroxybenzoic acids: show the same common structure (C6-C1) with some variations in their basic structure. They include gallic, vanillic, gentisic and syringic acids (Giada, 2013).
- Hydroxycinnamic acids: possess the basic structure (C6-C3) that is generally found in ferulic, sinapic and caffeic acids (Vuolo et al., 2019).

2.1.2. Flavonoids

Flavonoids designate a very wide range of phenols where more than 10.000 compounds have been identified (Teoh, 2016). These flavonoids are hydroxylated phenolic substances (Ganaie, 2021) whose basic structure is 2-phenyl chromane or a C6-C3-C6 skeleton (Gajbhiye et al., 2019). It includes an aromatic ring worn on a chroman ring in position 2, 3 or 4 (Hussein and El-Anssary, 2019).

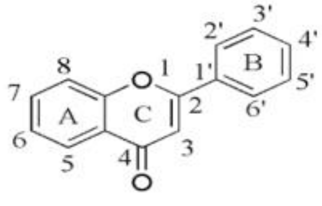


Figure 2. Basic structure of flavonoids (Wang et al., 2018).

In plants, flavonoids can be either presented as aglycones or as O- or C-glycosides (Gurib-Fakim, 2006). They are fluently found in fruits, vegetables, nuts, and other parts of plants (Jain et al., 2019), as they are partly responsible for the coloring of flowers, fruits, and sometimes leaves (Ahmed et al., 2017). On the basis of the oxidation level, they can be divided into different classes, the most common of which are anthocyanins, flavones, and flavonols (Vuolo et al., 2019).

This group is very popular. It offers a wide range of therapeutic properties among them antimalarial, vaso-relaxants, anti-allergic, immunomodulators, anti-inflammatory, antiviral, antimicrobial, antitumor, antidiabetic, whose best described activity is their antioxidant activity (Ballout et al., 2019; Wang et al., 2018).

Consequently, it has played a major role in the treatment of various ailments since ancient times, such as blood circulation problems, hormonal imbalances, and cancers (Ahmed et al., 2017; Gajbhiye et al., 2019; Kabera et al., 2014). Their daily intake does not exceed 500 mg (Wang et al., 2018).

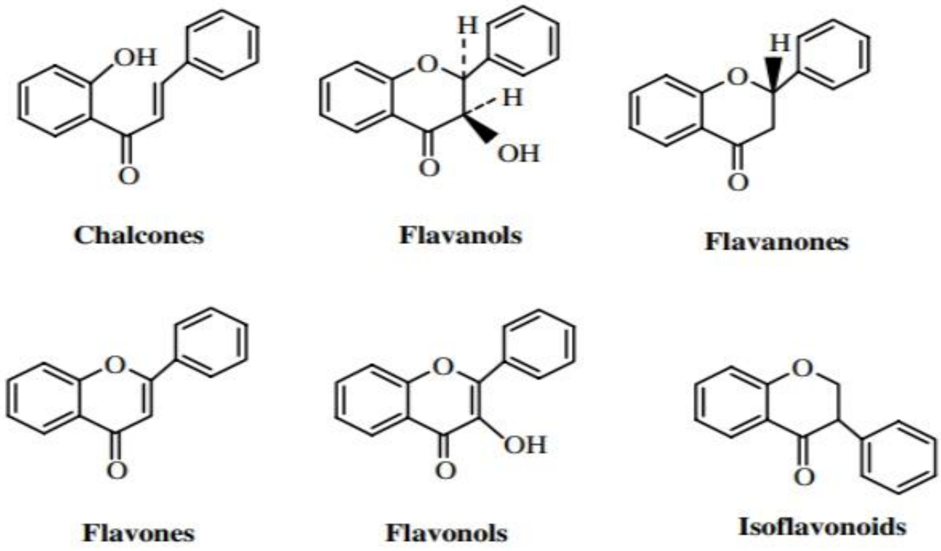


Figure 3. Chemical structure of certain flavonoids (Gurib-Fakim, 2006).

2.1.3. Tannins

Tannins are one kind of phenolic compound that has a molecular weight range from 500 Da to 3000 Da (Vuolo et al., 2019). They are found in different parts of plants. Principally, they are located in the vacuoles, synthesized via the shikimic acid pathway, and have the ability to precipitate proteins (Hassanpour et al., 2011).

These molecules are composed of a very diverse group of oligomers and polymers with a wide range of pharmacological properties such as anticancer, anti-HIV, and antidiarrheal activities whose antioxidant activity is involved in the protection of cells from oxidative damage and their stringent properties expedite the healing of wounds (Ganaie, 2021; Gurib-Fakim, 2006). Based on their chemical structure, they are subdivided into two groups:

 Hydrolyzable tannins: are compounds that have the characteristic of being hydrolyzed by acids or enzymes. They are generally formed from several molecules of phenolic acids united to a central molecule of glucose by ester linkages. They include gallotannins and ellagitannins, which are respectively composed of gallic acid and ellagic acid units (Ahmed et al., 2017; Hussein and El-Anssary, 2019).

 Condensed tannins: are molecules commonly called proanthocyanidins that are fluently found in food plants. Structurally, they are polymers or oligomers of 3-flavanols and 3,4-flavandiols and they are more complex than hydrolyzable tannins (Vuolo et al., 2019).

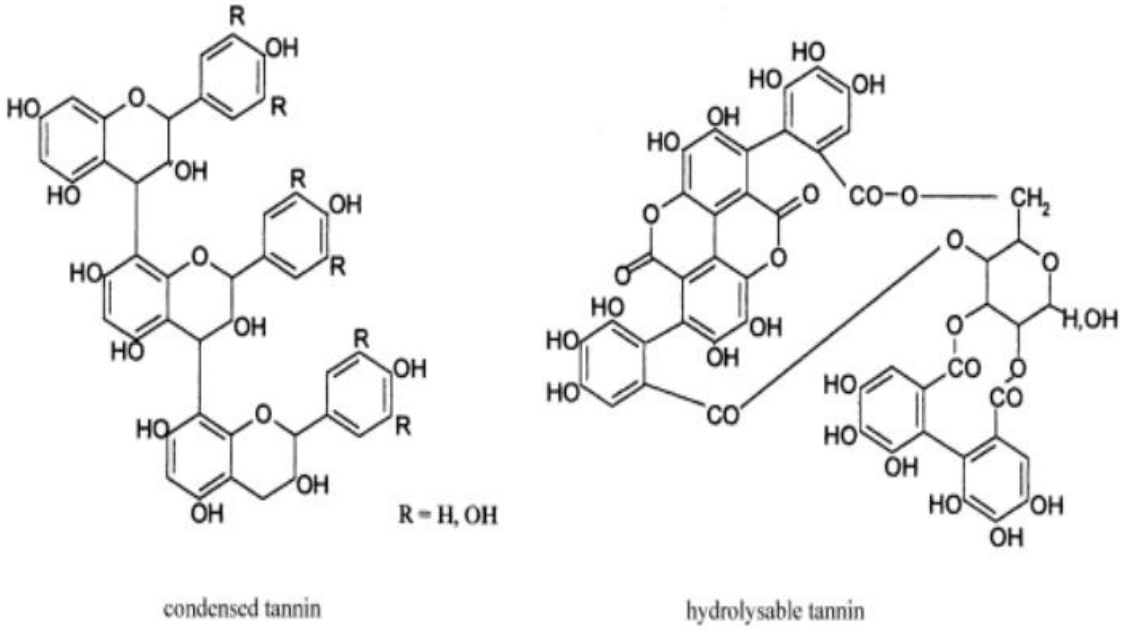


Figure 4. Chemical structure of tannins types (Hassanpour et al., 2011).

2.2. Alkaloids

Alkaloids represent a very diverse family of low molecular weight nitrogenous organic compounds, with more than 20.000 different molecules identified (Yang and Stöckigt, 2010). These molecules have nitrogen molecules in a heterocycle. Other than carbon, hydrogen, and nitrogen, they can also contain oxygen, sulfur, and rarely other constituents such as chlorine and phosphorus (Kabera et al., 2014).

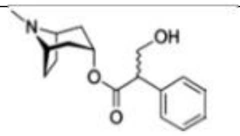
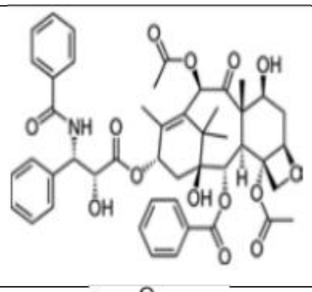
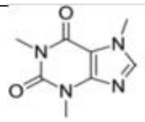
This family is produced by a large variety of organisms including bacteria, fungi, animals, and plants, of which approximately 20% are vascular plant species. It is biosynthesized principally from amino acids such as tyrosine, lysine, tryptophan, and aspartic acid as it plays a defensive role against herbivores and pathogen attacks (Ballout et al., 2019; Pagare et al., 2015).

Traditionally, it is used in the treatment of various ailments and its remedies have several effects, including cough suppressants, sedatives, and purgatives (Yang and Stöckigt, 2010). Several research studies have demonstrated that alkaloids have been used for 3000 years as medicines, teas, and potions and their pharmacological activities have been discovered over time, such as hypertensive, allelopathic, antibacterial, mutagenic, antifungal, and antiviral activities (Hussein and El-Anssary, 2019).

These alkaloids play a major role in the treatment of various health problems such as jaunadice, cough, cardiovascular problem and gout (Gurib-Fakim, 2006). Due to their importance and powerful effects, about 12.000 alkaloids have been exploited as medicines and pharmaceutical products among them colchicine as an antigout, vincristine as an anticancer agent, and codeine as an analgesic (Ahmed et al., 2017). They are divided into three groups:

- **True alkaloids :** refer to molecules that are biosynthetically derived from an amino acid and a heterocyclic ring with nitrogen such as atropine and nicotine (Roy, 2017).
- **Proto-alkaloids:** refer to all compounds that contain a nitrogen atom derived from an amino acid that is not part of the heterocyclic ring such as taxol and ephedrine (Ballout et al., 2019).
- **Pseudo-alkaloids:** are compounds that do not derive from amino acids such as caffeine and theobromine (Roy, 2017).

Table 1. principals class of alkaloids based on their biogenesis (Ballout et al., 2019).

Classes	**Examples**	**Biological structure**	**Pharmacological properties**
True alkaloid	Atropine		Anticholinergic
Proto-alkaloid	Taxol		Used for treating ovarian, breast, and lung cancer
Pseudo-alkaloid	Cafeine		Antioxidant and anti-inflammatory agents

2.3. Terpenoids

Terpenoids represent a collection of organic molecules produced by the plant kingdom. They constitute over one third of all known secondary metabolites. So far, over 40.000 compounds have been discovered (Ahmed et al., 2017; Pagare et al., 2015). These molecules are derived from isoprene polymers. Principally, they are formed by the union of five-carbon isopentenoid pyrophosphate units and they have a wide range of medicinal properties, including antihypertensive, antimicrobial, and insecticidal (Kabera et al., 2014).

Thus, it is very important in the human diet and it is used as drugs or as dietary supplements to protect or prevent various diseases such as cancer (Jamwal et al., 2018). On the basis of the number of isoprene units and their degree of incorporation, several subgroups are distinguished including hemiterpenes, monoterpenes, sesquiterpenes, diterpenes up to poly-terpenes (Russell and Duthie, 2011).

3. Therapeutic properties of aromatic and medicinal plants

Therapeutic properties come mainly from the characteristics of their bioactive substances. Several studies have reported various pharmacological activities including antioxidant, antimicrobial, anti-ulcer, anticholinesterase, anticancer, antihypertensive, as well as analgesic, stimulant, capillary-enforcing, adaptive, sedative, analeptic spasmolytic, and cholagogue agents (Lovkova et al., 2001).

Antioxidant activity is one of the most appreciated properties of medicinal plants that has a beneficial effect on human and animal health since it prevents oxidative damage caused mainly by reactive oxygen species (ROS) (Adegbola et al., 2017). The ROS, produced *in vivo*., are either free radicals characterized by unpaired electron(s) (superoxide anion O2•- and hydroxyl radical OH•) or non-radical molecules having all their peripheral electrons paired (hydrogen peroxide H_2O_2) (Aftab and Hakeem, 2021; Jamshidi-Kia et al., 2020). When the natural antioxidant defense system cannot neutralize the excessive production of these ROS, oxidative stress is generated, causing damage to macromolecules such as DNA, proteins, and lipids, leading to the triggering of numerous chronic diseases (Jain et al., 2019).

Anti-inflammatory and antimicrobial activities of medicinal plants have created the basis of many applications in alternative medicines and natural therapy. Anti-inflammatory activity can prevent inflammation, which is a complex biological reaction, either acute or chronic, of our body to dangerous stimuli (Alonso et al., 2018). It can be treated with two types of anti-inflammatory drugs, namely steroidal and nonsteroidal anti-inflammatory drugs, both of which have substantial side effects (Villagómez-Rodríguez et al., 2019). However, antimicrobial activity aims to treat microbial infections because the excessive use of drugs and conventional antibiotics generates several pathologies multidrug-resistant (Aït Abderrahim et al., 2019). This microbial resistance and its progression have conducted to substantial concern in the treatment of several infectious diseases which threaten human health (Khameneh et al., 2019).

In recent years, several studies have shown the effectiveness of certain natural substances containing bioactive molecules such as vitamins, terpenoids, and phenolic compounds in inhibiting ROS and reducing degenerative diseases. Thus, their great importance for the human body (Aftab and Hakeem, 2021; Jamshidi-Kia et al., 2020).

4. Side effects and toxicity of aromatic and medicinal plants

Despite all the beneficial therapeutic properties possessed by medicinal plants, several of their components have been shown to be potentially toxic, mutagenic, and carcinogenic, threatening health and leading to acute toxicity and patient death. Therefore, some of these medicinal plants are considered toxic because they affect the survival and normal functioning of the individual due to their side effects on the health and biological functions of the body (Mensah et al., 2019; Oyedare et al., 2009).

Adverse effects are harmful and unexpected changes such as nausea, diarrhea, insomnia, headaches, vomiting, hair loss, dizziness, and weakness that result from exposure to poisonous substances (Subramanian et al., 2018). However, toxicity is the ability of any agent to cause harmful effects on the whole organism and its substructure. It can result in allergic reactions, the abnormal weight of organs, and enzyme dysfunction. Depending on the amount and duration of exposure, it can lead to acute and chronic effects (Mensah et al., 2019). Acute toxicity is the harmful effect caused by a single exposure to a poisonous substance over a short duration. However, chronic toxicity is an adverse effect that affects a living organism following exposure to a harmful agent over a long period, which can lead to irreversible toxicity (Aftab and Hakeem, 2021).

Toxicity of medicinal plants and their extracts varies according to the chemical compounds that are contained in them. Anywar et al. (2021) state in their study that the preparation and use of herbal medicines can be harmful to human health, causing dysfunction in a number of organ systems, including the kidneys and liver. Similarly, the WHO reports nearly 5000 adverse effects from plants while the US Food and Drug Administration demonstrates 2621 side effects, including 101 fatalities associated with dietary supplements (Subramanian et al., 2018).

In Africa, studies report that many African medicinal plants used in traditional medicine or as food are potentially cytotoxic, mutagenic, and carcinogenic. It has been reported that 400 African plants had cytotoxic effects, of which 56% of them are listed as having significant cytotoxic activities against some normal cells, including the MRC-5 human fibroblastic pulmonary epithelium, human renal epithelium, and human monocytes. Thus, they may be harmful to humans (Mensah et al., 2019). Hence, most medicinal herbs used in traditional medicine, in addition to modern pharmaceutical chemicals, must undergo extensive toxicity testing to assess their quality, efficacy, and safety of their preparations, which most herbal medicines do not (Oyeyemi et al., 2015).

5. Cytotoxic and genotoxic effects of aromatic and medicinal plants

5.1. Cell cycle

The cell cycle is a complex and highly ordered process by which a single diploid cell divides, giving rise to two diploid daughter cells. It requires a series of events that result in the reproduction of DNA and the segregation of identical chromosomal copies into two daughter cells, leading to the transmission of genetic information from one generation to another (Schafer, 1998).

Cell cycle has two main phases, namely interphase and M phase. Interphase is the period during which a cell stores nutrients and energy essential for division and initiation of the cell cycle (Istifli et al., 2019). It includes three phases: G1, S, and G2. The G1 phase, the first gap, is an interval during which the cell prepares for DNA synthesis. It is considered as a critical period during which cells are stimulated by extracellular signals that can cause them to enter the S phase or exit the cycle. The S phase corresponds to DNA synthesis. The G2 phase, the second gap, designates the interval during which the cell prepares for the M-phase. Cells in the G0 phase refer to quiescent cells which are at rest but capable of reentering a cell cycle (Schafer, 1998).

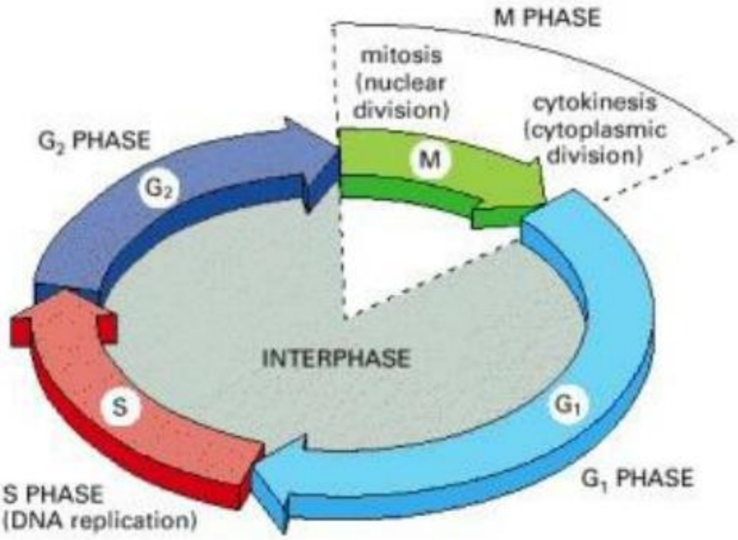


Figure 5. Cell cycle phases (Alberts et al., 2002).

The M phase mainly includes two major events: mitosis (nuclear division) and cytokinesis (cell division). Mitosis encompasses five phases. Prophase, which is characterized by the condensation of chromosomes and the assembly of the mitotic spindle, Prometaphase, which is marked by the disappearance of the nuclear envelope and the attachment of sister chromatids to the microtubules of the mitotic spindle at the level of the kinetochore, Metaphase represents the stage during which the sister chromatids are aligned in equatorial plates waiting for the chromosome segregation signal (Zhang and Dawe, 2011).

Additionally, anaphase, which leads to the separation of sister chromatids which are moved to opposite ends of the spindle, and finally, telophase, which is marked by the disappearance of the microtubules of the mitotic spindle, the reconstitution of the nuclear envelope, and the recondensation of the chromosomes into individual daughter nuclei, Moreover, cytokinesis that takes place during telophase through the contractile ring in animals or through the transverse cell plate in plants, leads eventually to the separation of the cytoplasm and the formation of a new cell wall between the membranes of the daughter cells (Alberts et al., 2002; Takahashi and Umeda, 2013).

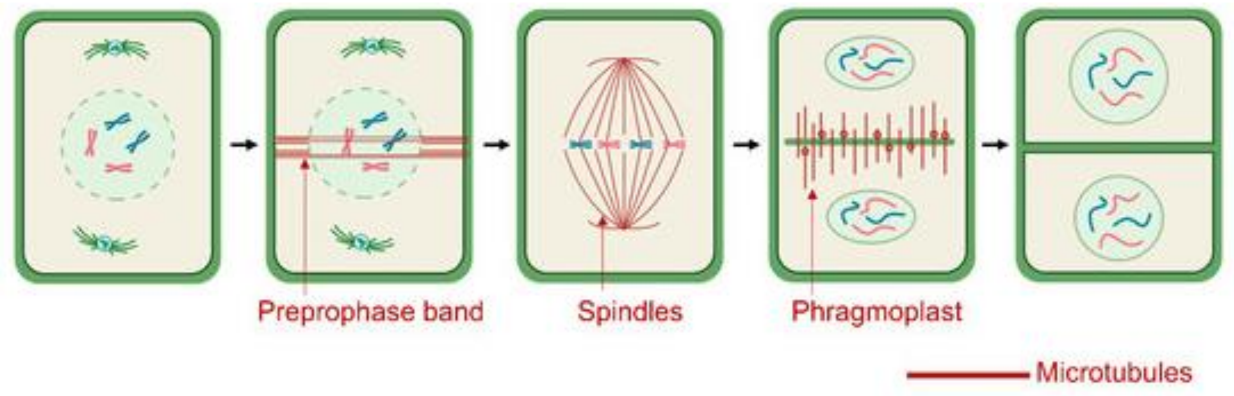


Figure 6. The different events of eukaryotic cell cycle (Hsiao & Hung, 2023).

5.2. Chromosomal aberrations

Chromosomal aberrations refer to all changes that affect the integrity of the chromosome, either spontaneously or after exposure to harmful agents. They can occur during the different stages of cell division, and they are of two types; structural or numerical chromosomal aberrations (Nagarathna et al., 2013). Structural chromosomal aberrations (clastogen) are changes in the structure of chromosomes, such as chromosomal breaks, loss of acentric chromosomal fragments, and joints. However, numerical chromosomal aberrations (eugenic) are changes related to the loss or gain of chromosomes causing genetic diseases or leading to death, such as aneuploidies and polyploidies (Radhika and Jyothi, 2019). Thus, chromosomal aberrations are considered good genotoxicity indicators of harmful substances, particularly their clastogenic and aneugenic actions (Leme and Marin-Morales, 2009).

5.3. Cytotoxic agents and cytotoxicity

Cytotoxicity is cell response to the harmful effect of a substance either through triggering programmed cell death (apoptosis) or initiating the process of necrosis (accidental cell death) (Istifli et al., 2019).

A cytotoxic agent is any harmful agent that can induce toxicity within a cell; it can inhibit its growth, alter its proliferation, and occasionally lead to its death. These cytotoxic agents are of different chemical, biological, and physical natures. Chemical compounds correspond to cytostatic agents. However, physical agents include environmental conditions like heat, ultrasonic vibrations, and radiation (Tülay Aşkin, 2018). Furthermore, biological components represent the poisonous of bacteria, viruses, animals, and plants origins, the most recognized of which are antibiotics and endo/exotoxins produced by bacteria (Herdiana et al., 2021). The cytotoxic agents affect the cell by modulating mitochondrial permeability or inhibiting the biosynthesis of several molecules, such as DNA, RNA, and microtubules (Oh et al., 2017).

5.4. Cytotoxicity testing

Cytotoxicity tests are bioassays intended to assess the harmful potency of a substance on the living cells (Istifli et al., 2019). They can be performed *in vitro* and/or *in vivo* using different cell types with various techniques. Several parameters can be assessed, including cell morphology, growth, and replication (Liu et al., 2018).

The most frequently used test is the MTT/XTT assay, based on the assessment of cell viability by measuring cellular metabolic activity (Istifli et al., 2019). The Neutral red cell cytotoxicity (NR) assay is a technique that aims to assess cellular function by relying on the integrity of the cell's lysosome membrane (Liu et al., 2018). The Brine shrimp lethality assay is a test that uses small aquatic animals, such as brine shrimp, as models (Gurib-Fakim, 2006). The *Allium cepa* test aims to assess disturbances of the mitotic cycle and root growth inhibition (Fiskesjö, 1985).

5.5. Hemolytic activity as an initial screening of cytotoxicity

The hemolysis process is a phenomenon that refers to the destruction of red blood cells due to cell membrane disruption (Noudeh et al., 2010). It includes two types; (i) intravascular hemolysis which is the destruction of the red blood cells in the blood vessels, and (ii) extravascular hemolysis which is the phagocytosis of erythrocytes by the monocyte-macrophage system of organs, including the liver and spleen (Rapido et al., 2017). This process affecting the erythrocyte cell membrane may be due to the consumption of medicinal plants that can induce cytotoxic effects on these cells (Mohammedi and Atik, 2014; Tabassum et al., 2022).

In vitro hemolytic activity is one of the cytotoxicity tests that can assess the toxicity in normal healthy cells due to the information that provides on the interaction between components and biological entities at the cellular scale (Ghosh et al., 2018; Ghramh et al., 2019). Their usefulness comes from their multiple advantages, such as their speed, reproducibility, and availability, as they reduce the use of laboratory animals. Moreover, it uses erythrocytes, the simplest available type of human cells, and the highly specialized tissue primarily responsible for delivering oxygen to tissues and exercising carbon dioxide (Pagano and Faggio, 2015). Thus, any alteration of this type of cell by deforming its membrane could be fatal. Therefore, red blood cells act as a good model for evaluating the cytotoxic effects, and *in vitro* hemolytic assay represents a crucial starting point in this regard (Ghosh et al., 2018).

5.6. Genotoxicity and genotoxic agents

Genotoxicity corresponds to the ability of a substance to damage genetic material within a cell (Ren et al., 2017). Genotoxic agents are substances able to induce genetic damage within cells. They are of chemical, physical, and biological nature (López-Romero et al., 2018). Chemical agents are exogenous molecules, including alkylating agents, base analogs, and intercalating agents (Słoczyńska et al., 2014). Physical agents correspond to the various types of radiation, like ionizing and ultraviolet (Chatterjee and Walker, 2017). Biological agents refer to living organisms such as viruses, bacteria, plants, parasites, and fungi, especially those which produce secondary metabolites (López-Romero et al., 2018). The different agents can act directly by interacting with the DNA in chromatin or chromosomes or indirectly through various types of proteins involved in the replication or in maintaining chromosomal stability (Magdolenova et al., 2014; Radhika and Jyothi, 2019).

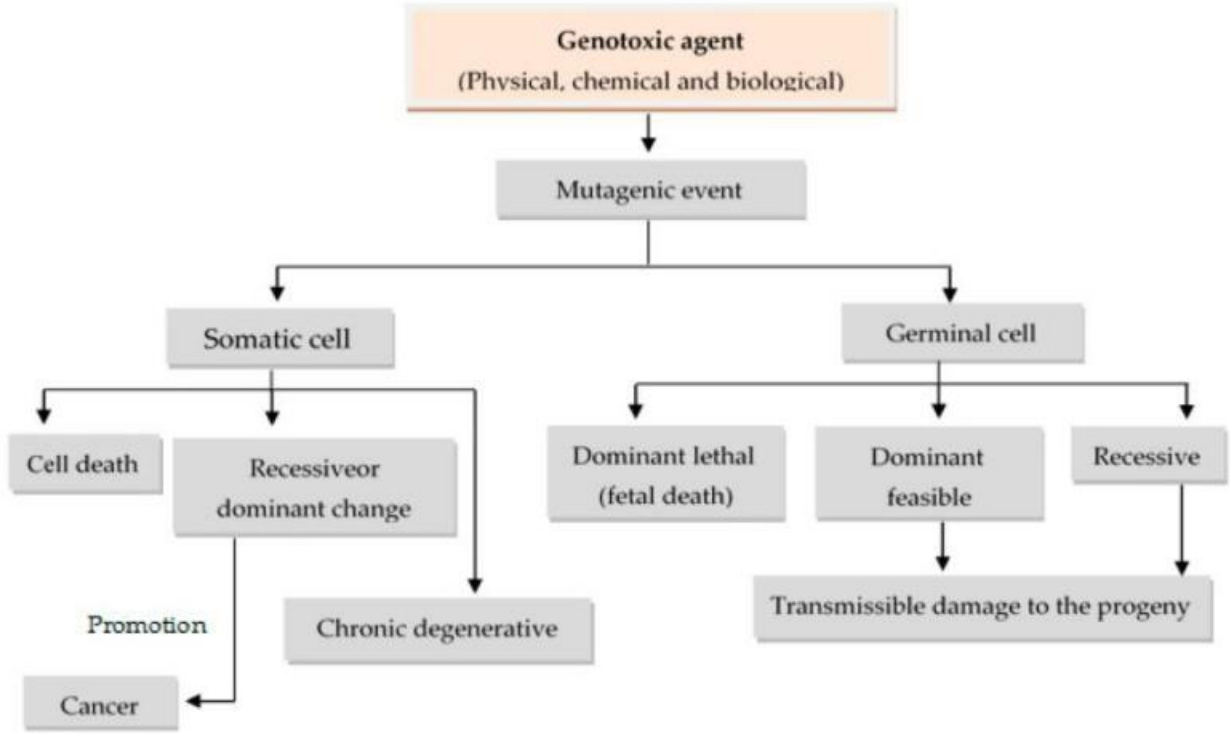


Figure 7. Different effects produced by genotoxic agents (López-Romero et al., 2018).

5.7. Genotoxicity testing

Genotoxicity testing is an essential toxicological endpoint used *in vivo* or *in vitro* to assess the biosafety of harmful substances at the genetic level (Nagarathna et al., 2013). They can perform on prokaryotic cells, such as bacteria, by detecting gene mutations or on eukaryotic cells, such as mammals and plants, which in addition to gene mutations, identify chromosomal damage and aneuploidies (Leme and Marin-Morales, 2009).

The most frequently used test is the Ames assay based on *Salmonella typhimurium*, histidine-auxotrophic mutants, as a model. Likewise, the Comet assay is a microelectrophoresis technique that aims to detect single and double-strand breaks in the DNA of lysed cells suspended in an agarose gel (Radhika and Jyothi, 2019). The chromosomal aberration and micronucleus are assays to detect chromosomal damage and disruption in the mitotic apparatus induced during cell division stages (Aydın et al., 2016).

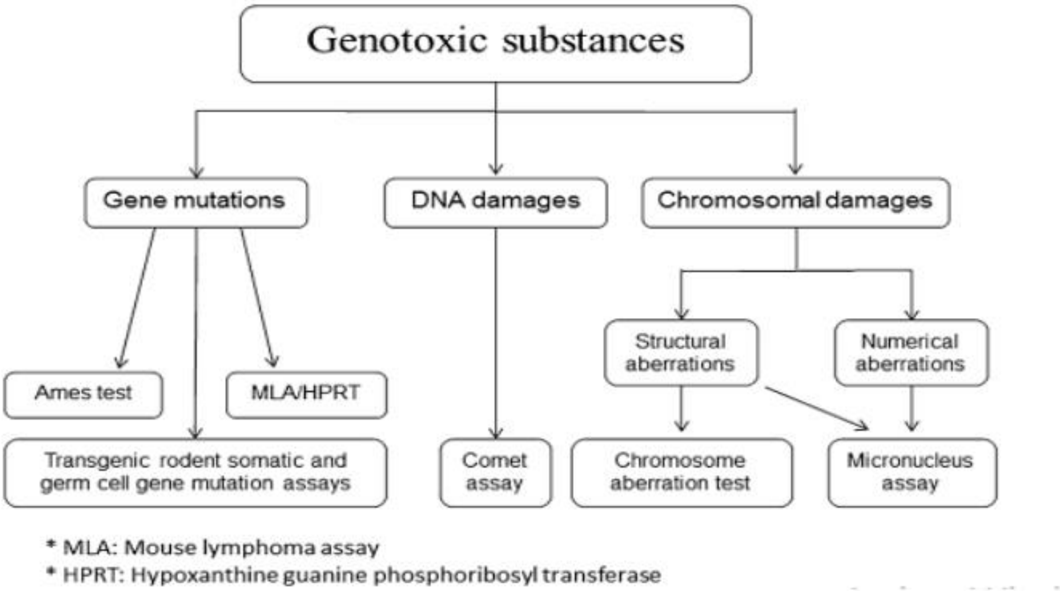


Figure 8. Most genotoxicity testing used for the assessment of genotoxic substances (Ren et al., 2017).

5.8. *Allium cepa* test as cyto-genotoxicity assay

Higher plants are considered excellent genetic models used to detect the cytotoxic and genotoxic effects of different genotoxic agents. They are widely used in studies monitoring the genotoxic effects of chemicals and environmental pollutants (Feretti et al., 2007). Interestingly, *Allium cepa* is the most favorable model due to its multiple advantages, such as low cost, speed in growth, simplicity of manipulation, and sensitivity of the onion roots to toxic materials, besides its large chromosomes, which are visible and easily observable under an optical microscope, and its reduced number (2n=16) (Leme and Marin-Morales, 2009; Rosculete et al., 2019).

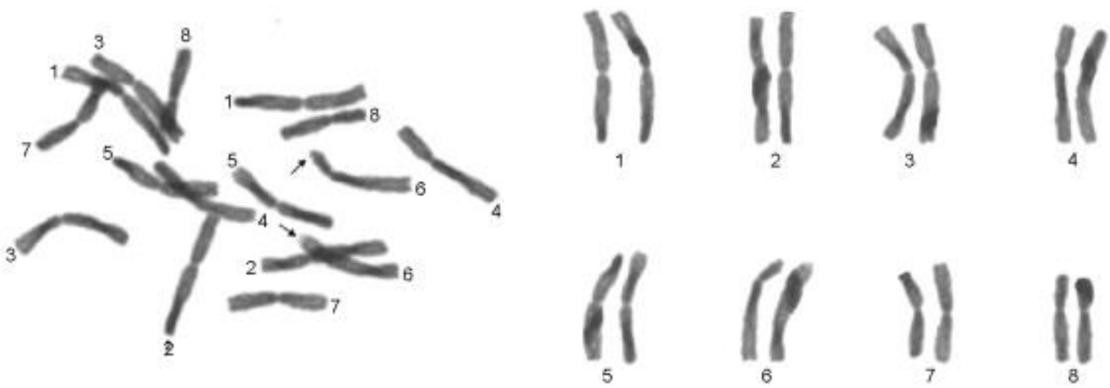


Figure 9. *Allium cepa* karyotype, 2n=16 (Leme and Marin-Morales, 2009).

In reality, the importance of the *Allium cepa* test comes from the possibility of measuring macroscopic and microscopic parameters for evaluating DNA damages, such as chromosomal aberrations, which prove the presence of genotoxicity, as well as for disturbances of the mitotic cycle and root growth inhibition, which are general parameters of cytotoxicity (Fiskesjö, 1985; Mota et al., 2022). Results of *Allium cepa* test are similar and comparable to those obtained by tests carried out on animal cell lines (Bonciu et al., 2018; Cabuga, 2017; Herrero et al., 2012).

Chapter I

Chapter 1: Herbal remedies of the region of Tiaret, North-West of Algeria

1. Introduction

The use of aromatic and medicinal plants and their derivatives for food and therapeutic purposes is very common worldwide since ancient times. Currently, almost 80 % of the world's population, mainly in developing countries, depend on herbal medicines to answer their basic primary health needs for the management of numerous diseases (WHO, 2004, 2018). The difficulties to obtain essential health services along with the failure of modern medicine in finding effective treatments for several diseases have promoted remarkably the resurgence of traditional medicine (Taïbi et al., 2020). In addition, the indiscriminate use of chemicals and synthetic drugs led to the emergence of pathogenic multidrug resistant microbes responsible of severe health issues (Ait Abderrahim et al., 2019).

In Algeria, phytotherapy constitutes an integral part of the local culture of population which holds an important knowledge acquired empirically from a generation to another. Indeed, Algeria is characterized by a very rich and highly diversified flora due to its geographical location and the significant diversity of its climatic and topographic conditions (Azzi et al., 2012; Berrabah et al., 2019; Boussaid et al., 2018). The diversity of plant taxa is represented by 3,183 plant species which constitutes an important opportunity for focused screening of biological compounds based on traditional usages (CBD, 2020; Taïbi et al., 2020).

Indeed, the ethnomedicinal approach resulted in the search of aromatic and medicinal plants as a promising source of various bioactive compounds which constitutes the basis of new drug discovery with less or no side effects. Therefore, ethnomedicinal and ethnopharmacological studies are very required to disclose local medicinal plant species, and to document and save local popular knowledge (Orhan, 2014). Although numerous ethnobotanical and ethnopharmacological studies have been undertaken in various region in Algeria (Azzi et al., 2012; Benarba, 2016; Benarba et al., 2015; Benderradji et al., 2014; Boudjelal et al., 2013; Ouelbani et al., 2016; Sarri et al., 2015; Sarri et al., 2014), this field of study remains insufficiently covered to document the huge diversity of taxa and ancestral knowledge. Also, there is an urgent need to develop a national pharmacopoeia besides national standards and guidelines of collect and uses. Moreover, the collected data are being used as basis in research that needs to be tested in clinical and lab trials.

In this context, the current study is an ethnopharmacological investigation aiming to document the use of traditional medicines based on aromatic and medicinal plants used by traditional healers for the management of various ailments in the region of Tiaret (North-West of

Algeria). To our knowledge, this is the first ethnopharmacological investigation carried out in the region on high number of herbalists and traditional healers. The obtained data are believed to enrich national and world's databases of traditional knowledge and safeguard the cultural heritage as recognized by the UNESCO in 2003.

2. Methodology

2.1. Study area

The present study is achieved in the region of Tiaret, north west of Algeria. Interrogated residing population is distributed mainly in nine principal towns i.e. Ain Deheb, Frenda, Ksar Chellala, Medroussa, Mehdia, Rahouia, Sougueur, Thekhmaret and Tiaret besides numerous villages nearby (Fig. 1).

Figure 1. Geographical location of the region of Tiaret, North Western Algeria (with red color border filled white) (Google Maps 2020).

The study area includes a part of the Tell Atlas chain located at 1,150 m above mean sea level (a.m.s.l) on Mount of Guezoul and the Massif of Saida and Frenda at 1,200 m a.m.s.l. The study area covers also the mounts of Nadhor on the edge of the steppe plains of Ain Deheb and the Eastern zone of Chott Ech Chergui to the south. In general, the relief is very heterogeneous including a mountainous area to the north, high plains in the center and semi-arid areas and steppe to the south. This significant natural potential includes more than 1,600,000 ha of agricultural lands dominated by the culture of cereal and fruit trees, 142,422 ha of forest area characterized by a rugged and wooded relief covered mainly by holm oaks and Aleppo pines, and 143,000 ha of steppes dominated by the typical formation of *Stipa tenacissima* L., *Artemisia herba-alba* Asso, *Atriplex halimus* L. and the associated vegetation. The variety of relief implies as well a very heterogeneous soil types which are characterized in general by the presence of lime accumulation, low content of organic matter and high sensitivity to erosion and degradation (Achir, 2016).

The climate is semiarid typically Mediterranean characterized by a harsh cold winter and hot and dry summer. Climatic data recorded from 1986 to 2018 indicated that annual rainfall ranges from 200 to 400 mm per year with a seasonal fluctuation ranging from 157 mm in winter to 31 mm in summer with an average temperature of 37.2 °C. The warmest months are from Jun to September, while the coldest months are from November to March (Taïbi, 2009).

The health sector of the region is composed of five public hospital establishments, three specialized hospital establishments along with many proximity public health establishments for an estimated population of 1,007,635 inhabitants. According to the epidemiological assessment launched in 2017, this region had a high rate (21.1 %) of deaths caused by different diseases (mainly cardiovascular diseases, cancer, chronic respiratory diseases, chronic kidney diseases and diabetes among others). This may be due to several factors such as the significant deficit in specialist doctors, the lack of equipment, the poverty of the populations, the difficulty of access to medications among others which have led unfortunately to a remarkable deterioration of people’s health in the region. Historically, the region of Tiaret was an important political and economic center in the north west of Algeria and constitutes a crossroads of several civilizations namely Ziride, Hammadite, Abdelwadid, Rostemide, Ottoman Empire and French colonization (Kouzmine et al., 2009). In addition to its location as a connection city between east and west regions of the country, Tiaret region is also considered as the Saharan gate which ensures the connection and the passage of travelers from the north to the south regions of Algeria. The historical view and geographical location make the region of Tiaret a place of diffusion and center of transfer of a great traditional knowledge. Local population works mainly in agriculture (animal farming, pastoralism and plant farming), commercial sector and service industries. Socio-demographic characteristics of the informants are exposed in Table 1.

Table 1. Socio-demographic features of the informants.

Socio-demographic features		Number	Percentage (%)
Age	<30	10	15.63
	30-45	29	45.31
	45-60	18	28.13
	>60	7	10.94
Gender	Male	60	93.75
	Female	4	6.25
Habitat	Urban	28	43.75
	Rural	36	56.25
Education	Illiterate	6	9.38
	Primary	5	7.81
	Middle	21	32.81
	Secondary	28	43.75
	University	4	6.25

2.2. Data collection

- **Participants**

The present ethnopharmacological study was conducted through field studies achieved from December 2018 to May 2020 to list the most medicinal plants used for the treatment of various diseases in the region of Tiaret, North-West of Algeria.

In total, sixty-four herbalists and traditional practitioners were interviewed throughout this study (n=64). The study directed in agreement with the requirements of the declarations of Helsinki was approved by the scientific committee (PVCSF/FSNV/27 Nov 2018) for ethical criterion in the faculty of Natural and Life Sciences, Ibn Khaldoun University of Tiaret (Algeria). Hence, semi-structured interviews based on note-taking while interviewing were conducted with the local dialect and generally took place in public spaces to collect the ethnomedicinal data as described by Martin (1995).

Informant consent was obtained through oral agreement prior to the interviews to authorize the collection, use and publication of data, then informants were asked to list aromatic and medicinal plants used for the treatment of various ailments and were requested to provide detailed information about their uses (Albuquerque et al., 2014).

Interviews covered popular and vernacular names of the used species, parts used, mode of preparation and administration, dosage, period of treatment and toxicity or side effects among other information. Local names were provided mostly in Arabic language and informants were asked whether they would be willing to deliver a sample or to recognize it in photos if the material was not available.

- **Identification of medicinal plant species**

The collected specimens were pressed and dried on site then the voucher specimens were identified by specialists and conserved in the laboratory at the Faculty of Natural and Life Sciences, University of Tiaret (Algeria). The identity of plant species was verified according to the available bibliographical resources and scientific names were confirmed in accordance with the International Index of Plant Name (http://www.ipni.org) and the Plant List database (http://www.theplantlist.org).

2.3. Data analysis

The obtained ethnopharmacological data were assigned into various ailments categories which have been reported by informants. The use report (UR) was assessed by calculating the total uses for the plant species by all informants within each use-category for that plant (Prance et al., 1987).

$$UR = \sum_{u=u1}^{uNC} \sum_{i=i1}^{iN} UR_{ui}$$

Frequency of Citation (FC) is calculated as the sum of informants that cite a use for the plant species (Prance et al., 1987).

$$FC = \sum_{i=i1}^{iN} UR_i$$

The use value (UV) is a quantitative method that can be used in order to prove the relative importance of the plant species known locally. It was calculated following the adaptation of da Silva *et al*. (2014) using the following formula:

$$UV = \frac{\sum UR_{ip}}{n_{ip}}$$

where UV is the use value of the plant species p mentioned by the informant i; ΣUR_{ip} is the number of uses reports of the plant species s mentioned in each event by the informant i; n_{ip} is the number of events in which the informant i cited the plant species p.

The homogeneity on the informants' knowledge was evaluated by calculating the Informants' Consensus Factor (F_{IC}) (Andrade-Cetto & Heinrich, 2011) using the formula:

$$F_{IC} = \frac{(N_{ur} - N_t)}{(N_{ur} - 1)}$$

Where N_{ur} is the number of use reports for a particular ailment category and N_t is the number of species cited for the same ailment by all informants. The values of the index range between 0 and 1, where values close to '1' indicate the highest level of consensus.

All the statistical analyses were performed using the computing environment R (R Development Core Team, 2013). Continuous data were represented as mean ± standard deviation while frequencies and percentages were calculated for categorical variables.

3. Results

3.1. Sociodemographic features

In the present study, the number of men herbalists was higher than that of women (60 men versus 4 women). Overall, most of the herbalists involved in this study were aged between 30 and 45 years-old (45 %). However, those aged over 60 years-old are less represented (about 11 %). Besides, most of the herbalists have secondary (42 %) or middle (33 %) institutional level while around 9 % were illiterate. Nevertheless, only 4 herbalists (6 %) are undergraduate or graduate from the university.

3.2. Botanical diversity of ethnomedicinal plants

Overall, herbalists have reported the use of 107 medicinal plant species belonging to 45 families and 97 genera for the treatment of various ailments (Table 2). Lamiaceae was the most represented botanical family with 15 plant species (33 %), followed by Apiaceae with 11 species (24 %), Asteraceae with 10 species (22 %), Fabaceae and Rosaceae with 6 species each (13 %). However, the remaining botanical families were represented by equal or less than three species each (Figure 2).

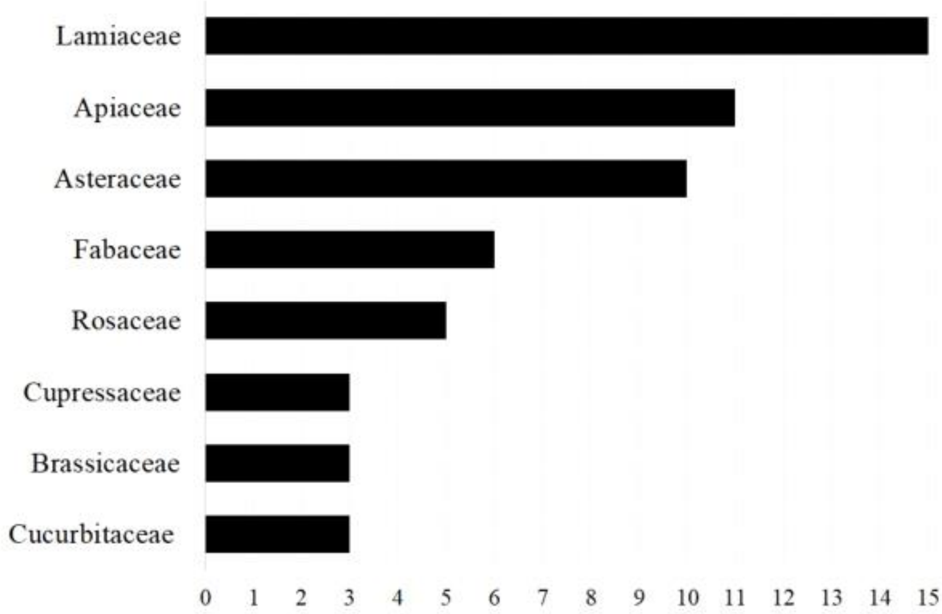


Figure 2. Number of species per botanical family.

The reported plant species include both monocotyledonous (9 species, 8.41 %) and dicotyledonous (94 species, 87.85 %) classes most of them are herbs (60 species, 56.07 %) while shrubs represent 27.1 % (29 species) and trees 16.82 % (18 species). In addition, 4 species of Gymnospermae (3.74 %) have been reported. In fact, 57 % of the species used by the local population are spontaneous, while 43 % are cultivated and used either for direct consumption or vended commercially such as *Allium* spp., *Daucus carota* L., *Vicia faba* L. among others.

Remarkably, several species belong to the Algerian steppe region and Sahara namely *Artemisia* spp., *Atriplex halimus* L., *Haloxylon scoparium* Pomel, *Origanum majorana* L., *Peganum harmala* L. and *Pistacia* spp. among others. Besides, 8 % of the used plants by respondents are introduced species such as *Curcuma longa* L., *Boswellia sacra* Flueck. and *Saussurea costus* (Falc.) Lipsch.

3.3. Plant parts used

Leaves are the most frequent used plant part (27%), followed by aerial parts (23%), seeds (15%), roots (9%), flowers (7%), fruits (6%). However, the use of stems, barks, tubers, rhizomes and bulbs is less frequent and was cited less than 5% each (Figure 3).

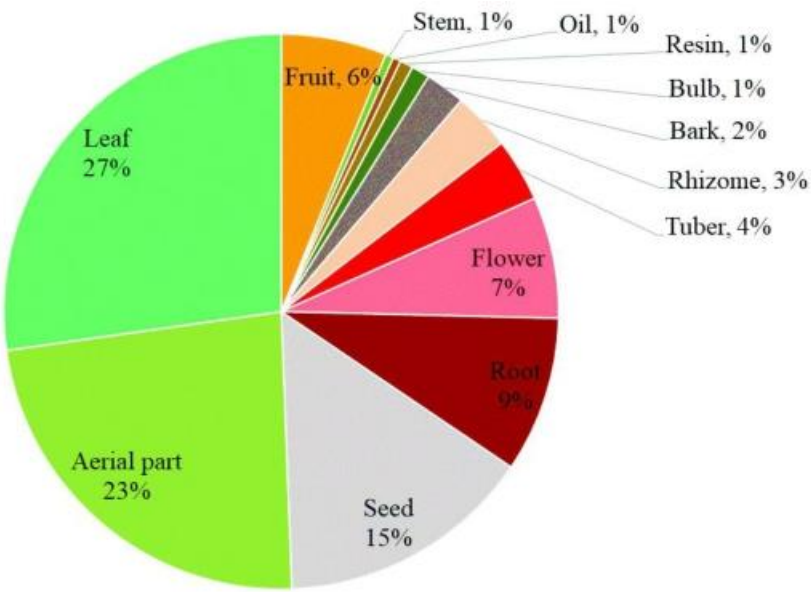


Figure 3. Plant parts used and their frequency.

3.4. Modes of preparation and administration

Most of plants are used as infusion (47 %), decoction (28 %) or even powdered (10 %) to be ingested or used in other mixtures and preparations. However, some plant parts are eaten raw (6 %) or used for inhalation (2 %) and maceration (1 %) (Figure 4). Moreover, herbalists prescribe most of their preparations through oral administration (91 %) followed by topical application (7 %) and nasal and gargling (1 % each) as they advise the use of mixtures based on several plant species with other ingredients such as honey, olive oil, goat milk and butter, water, yogurt, couscous, eggs, etc.

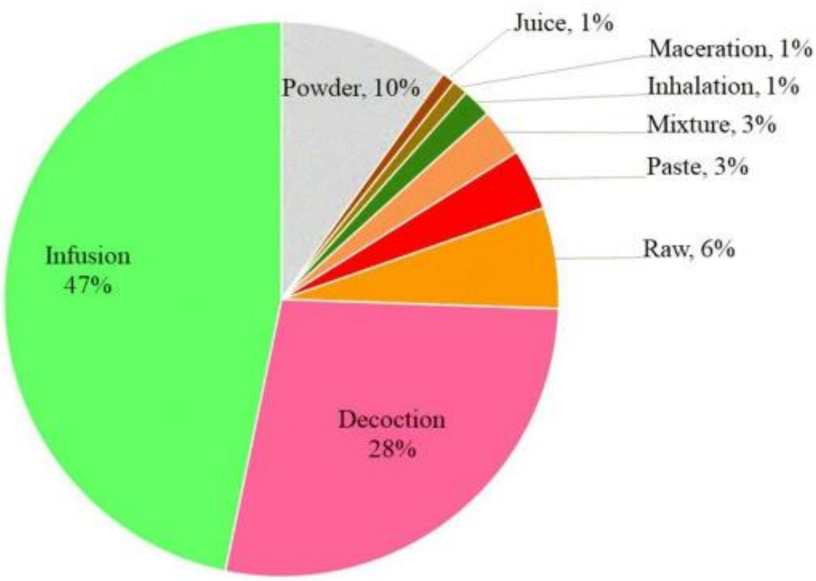


Figure 4. Modes of preparation of the reported ethnomedicinal plant species.

Table 2. Medicinal and aromatic plant species used in the region of Tiaret (north-west of Algeria).

Plant family: ***Species*(voucher)**	**Vernacular name**	**FC**	**UR**	**UV**	**Used parts**	**Mode of preparation**	**Mode of administration**	**Therapeutic uses**
Amaranthaceae								
Atriplex halimus L. (TDF023)	القطف El-gettaf	23	32	0.50	Leaves	Decoction, infusion, powder	Oral, topical	Cancer, cysts, high blood pressure, thyroid disorders, ulcer, uterine fibroids.
Haloxylon scoparium Pomel (TDF032)	الرمث El-remth	11	12	0.19	Aerial parts	Decoction, infusion, powder	Oral, topical	Allergy, cancer, cholesterol, colon, cysts, intoxications, skin, snake bites.
Amaryllidaceae								
Allium cepa L. (TDF107)	البصل El-bessal	1	1	0.02	Bulbs	Raw	Oral/Topical	Hepatitis
Allium sativum L. (TDF047)	الثوم El-thoum	4	7	0.11	Bulbs	Inhalation, raw	Nasal, oral, topical	Alopecia areata, antimicrobial, cancer, depurative, high blood pressure, influenza.
Anacardiaceae								
Pistacia atlantica Desf. (TDK053)	البطمة El-botma	1	1	0.02	Barks	Powder	Oral	Thyroid disorders
Pistacia lentiscus L. (TDF025)	الضرو El-dharw	8	11	0.17	Fruit oils, leaves	Decoction, infusion, paste,	Oral, topical	Allergy, burns, colon, depurative, stomach.

						raw		
Apiaceae								
Ammi visnaga (L.) Lam. (TDF009)	النوخة El-noukha	11	15	0.23	Aerial parts	Decoction, infusion	Oral	Analgesic, calming, high blood pressure, influenza, thyroid disorders, vomiting
Apium graveolens L. (TDF029)	الكرافس El-krafes	2	5	0.08	Aerial parts	Infusion	Oral	Anguish, colon, dysuria, renal lithiasis, strengthening.
Bunium incrassatum Amo (TDF013)	تالغودة Talghouda	23	29	0.45	Tubers	Infusion, powder	Oral	Allergy, asthma, cough, cysts, tonsillitis, thyroid disorders.
Carum carvi L. (TDT086)	الكروية El-karwiya	2	3	0.05	Seeds	Infusion	Oral	Calming, colon, bloating.
Coriandrum sativum L. (TDT049)	الكسبر El-kosbor	2	2	0.03	Seeds	Decoction, infusion	Oral	Diabetes.
Cuminum cyminum L. (TDT063)	الكمون El-kemoun	5	12	0.19	Seeds	Infusion, powder	Oral	Analgesic, bloating, calming, cholesterol, colon, cough, fever inflammation, influenza, rheumatism.
Daucus carota L. (TDC094)	الجزر El-jazar	2	4	0.06	Seeds	Infusion, juice	Oral	Colon, depurative, prostate, ulcer.
Foeniculum vulgare Mill. (TDF001)	البسباس El-besbas	22	29	0.45	Seeds	Decoction, infusion,	Oral, topical	Anemia, anxiety, bloating, colon, constipation, hair

								loss, obesity, tonsillitis, wrinkles.
Petroselinum crispum (Mill.) Fuss (TDF084)	المعدنوس El-maadnous	1	1	0.02	Aerial parts	Infusion	Oral	Cancer.
Pimpinella anisum L. (TDF027)	اليانسون El-yanssoun	6	6	0.09	Seeds	Infusion	Oral	Calming, colon, influenza.
Thapsia garganica L. (TDF085)	الدرياس El-dereyas	1	2	0.03	Roots	Powder	Oral, topical	Anorexia, wounds.
Aristolochiaceae								
Aristolochia Longa L. (TDF040)	برستم Berestom	7	8	0.12	Roots	Mixture, powder	Oral	Cancer, diabetes.
Asparagaceae								
Asparagus officinalis L. (TDF105)	السكوم El-sekoum	1	1	0.02	Aerial parts	Decoction	Oral	Rheumatism.
Asteraceae								
Anacyclus pyrethrum (L.) Lag. (TDT067)	تقنطس Tegontos	3	3	0.05	Roots	Decoction, infusion, powder	Oral	Cough, thrombosis.
Artemisia absinthium L. (TDT073)	الشهيبة Chehaiba	4	8	0.12	Aerial parts, roots	Decoction, infusion	Oral	Colon, diarrhea, dysuria, heart, intestinal parasitosis, liver, osteoarthritis, uterine fibroids.
Artemisia campestris	التقفت	5	6	0.09	Aerial parts	Decoction,	Oral	Allergy, analgesic,

L. (TDT060)	Tegoufet					infusion		cholesterol, colon, intoxications, stomach.
Artemisia herba-alba Asso (TDF003)	الشيح El-chih	17	24	0.37	Aerial parts	Decoction, infusion, inhalation, Paste	Nasal, oral, topical	Calming, colon, diabetes, diarrhea, hair loss, heart, high blood pressure, influenza, intestinal parasitosis, low blood pressure.
Cynara scolymus L. (TDT081)	القرناع El-gorenaa	1	1	0.02	Leaves	Infusion	Oral	Cholesterol.
Dittrichia viscosa (L.) Greuter (TDF104)	أمقرمان Amaquramane	1	1	0.02	Leaves	Paste	Oral	Rheumatism.
Echinops spinosus L. (TDF106)	تسكرة Tessekra	1	3	0.05	Roots	Decoction	Oral	Cough, influenza, pregnancy.
Matricaria chamomilla L. (TDF019)	البابونج El-babounej	21	31	0.48	Flowers	Decoction, infusion, Paste	Oral, topical	Analgesic, anguish, calming, cephalalgia, colon, cough, depurative, diarrhea, hair loss, inflammation, influenza, insomnia, migraine.
Saussurea costus	القسط الهندي	1	1	0.02	Roots	Powder	Oral	Tonsillitis.

(Falc.) Lipsch. (TDF083)	Elkast l'hindi							
Silybum marianum (L.) Gaertn. (TDR097)	شوك الجمل Choukl'djemel	1	1	0.02	Leaves	Infusion	Oral	Constipation.
Berberidaceae								
Berberis vulgaris L. (TDF020)	غريس Griss	15	16	0.25	Aerial parts, roots	Decoction, infusion, maceration, mixture, powder	Oral	Cancer, diabetes, intestinal parasitosis.
Brassicaceae								
Eruca vesicaria (L.) Cav. (TDT050)	الجرجير El-djarjir	1	1	0.02	Leaves	Infusion	Oral	Rheumatism.
Lepidium sativum L. (TDF002)	الحرف El-horef	11	20	0.31	Seeds	Infusion, Raw	Oral, topical	Allergy, asthma, cholesterol, cough, depurative, osteoarthritis, influenza, rheumatism, vitiligo.
Oudneya africana R. Br. (TDF022)	حنة الابل Henet elibil	2	3	0.05	Leaves	Decoction	Oral	Cholesterol, thrombosis.
Burseraceae								
Boswellia sacra Flueck. (TDR100)	اللبان El-louban	3	3	0.05	Resins	Raw	Oral	Asthma, influenza, kidney.

Cactaceae								
Opuntia ficus-indica (L.) Mill. (TDT071)	الهندي El-hindi	4	4	0.06	Fruits, stems	Decoction, paste, Raw	Oral, topical	Diarrhea, hair loss, kidney.
Caryophyllaceae								
Paronychia argentea Lam. (TDK054)	بصاط الملوك Bessat l'mlouk	1	1	0.02	Flowers	Infusion	Oral	Renal lithiasis.
Spergula rubra J. Presl & C. Presl (TDT061)	فتات الحجر Fetat l'hedjar	6	6	0.09	Leaves	Decoction, Infusion	Oral	Kidney, renal lithiasis
Cucurbitaceae								
Citrullus colocynthis (L.) Schrad. (TDF018)	الحنظل El-handhal	3	3	0.05	Fruits	Juice, Raw	Topical	Diabetes, eczema.
Cucurbita moschata Duchesne (TDK057)	اليقطين El- yaqutin	1	1	0.02	Seeds	Decoction	Oral	Renal lithiasis.
Ecballium elaterium (L.) A. Rich. (TDT069)	فقوس الحمير Fegouss el'hmir	2	2	0.03	Fruits	Inhalation, paste	Nasal, topical	Hemorrhoids, hepatitis.
Cupressaceae								
Juniperus phoenicea L. (TDF015)	العرعار Arrar	17	20	0.31	Aerial parts	Decoction, infusion, paste, powder, raw	Oral, topical	Asthma, colon, cough, influenza, rheumatism, ulcer.

Juniperus oxycedrus L. (TDR092)	الطاقة Tagga	1	1	0.02	Aerial parts	Infusion	Oral	Fever.
Tetraclinis articulata (Vahl) Mast. (TDF014)	الدباغ Debagh	2	2	0.03	Fruits	Infusion, powder	Oral	Ulcer.
Cyperaceae								
Cyperus esculentus L. (TDT101)	حب العزيز Hab el-aziz	1	1	0.02	Fruits	Decoction	Oral	Dysuria.
Ephedraceae								
Ephedra alata Decne. (TDF041)	العلندة El-alinda	10	10	0.16	Aerial parts	Decoction, infusion	Oral	Cancer, renal lithiasis.
Ericaceae								
Arbutus unedo L. (TDF044)	اللنج El-lendj	1	1	0.02	Leaves	Infusion	Oral	Renal lithiasis.
Euphorbiaceae								
Euphorbia guyoniana Boiss. & Reut (TDT062)	اللبينة Oum lebina	2	2	0.03	Aerial parts	Decoction, mixture	Oral	Cancer, diabetes.
Ricinus communis L. (TDF098)	الخروع El-kharewaa	1	1	0.02	Seeds	Raw	Oral	Constipation.
Fabaceae								
Ceratonia siliqua L. (TDF010)	الخروب El-kharoub	4	4	0.06	Fruits	Decoction, infusion, powder,	Oral	Anemia, ulcer.

						raw		
Glycyrrhiza glabra L. (TDF017)	عرق سوس Arqsouss	4	5	0.08	Roots	Decoction	Oral	Cough, prostate, rheumatism, stomach, ulcer.
Lupinus albus L. (TDT079)	الترمس المر Termes lmour	2	2	0.03	Fruits	Infusion, raw	Oral, topical	Diabetes.
Senna alexandrina Mill. (TDF005)	السنا المكي Sana el-miki	27	33	0.52	Leaves	Decoction, infusion	Oral	Analgesic, colon, constipation, gout, rheumatism, vomiting.
Trigonella foenum-graecum L. (TDF026)	الحلبة El-helba	14	88	1.37	Seeds	Decoction, infusion, maceration, powder, Raw	Oral	All reported ailments.
Vicia faba L. (TDT072)	الفول El-foul	1	1	0.02	Seeds	Decoction	Oral	Allergy.
Fagaceae								
Quercus rotundifolia Lam. (TDF035)	البلوط El- ballout	2	2	0.03	Fruits	Decoction	Oral	Enuresis.
Gentianaceae								
Centaurium erythraea Rafn (TDT058)	مرارة الحنش meraret el-hneche	4	4	0.06	Flowers, leaves	Infusion	Oral	Colon, diabetes, high blood pressure.
Lamiaceae								

Ajuga iva (L.) Schreb. (TDT068)	شندقورة Chendgoura	2	4	0.06	Aerial parts	Decoction, infusion	Oral	Diabetes, intoxications, snake bites, wounds.
Lavandula stoechas L. (TDF006)	الخزامى El-khezama	10	13	0.20	Flowers, seeds	Decoction, infusion	Gargle, oral	Antimicrobial, colon, dental gingiva, influenza, kidney, mouth infections, uterine fibroids, vomiting.
Marrubium deserti (Noë) Coss. (TDS087)	الجعدة El-jaada	2	2	0.03	Aerial parts	Decoction, paste	Oral, topical	Colon, rheumatism.
Marrubium vulgare L. (TDT070)	تمريوت Timeriouet	3	4	0.06	Aerial parts	Decoction, infusion	Nasal, oral	Asthma, heart, influenza, rheumatism.
Mentha × piperita L. (TDF042)	النعناع El-naa'naa	11	17	0.27	Leaves	Decoction, infusion, Paste	Oral	Calming, diarrhea, high blood pressure, inflammation, influenza, pregnancy, rheumatism, stomach, uterine fibroids.
Mentha pulegium L. (TDT059)	فليو Flio	5	5	0.08	Aerial parts	Decoction, infusion, Paste	Oral, topical	Hair loss, heart, influenza, vomiting.
Mentha suaveolens Ehrh. (TDT075)	تيمرساط Timerssat	1	2	0.03	Leaves	Powder	Oral	Heart, ulcer.
Ocimum basilicum L. (TDR096)	الحبق El-hebaa	1	1	0.02	Leaves	Infusion	Oral	Constipation.

Origanum majorana L. (TDL048)	المردقوش Merdekouch	5	11	0.17	Leaves	Decoction, infusion	Oral	Anxiety, asthma, calming, cough, diabetes, high blood pressure, inflammation, influenza, migraine, rheumatism.
Rosmarinus officinalis L. (TDF039)	اكليل الجبل Iklil eldjabal	13	20	0.31	Leaves	Decoction, infusion, Paste	Oral, topical	Calming, cholesterol, colon, cough, depurative, hair loss, high blood pressure, influenza, obesity, prostate, rheumatism, stomach.
Salvia officinalis L. (TDF004)	الميرامية El-miramiya	13	20	0.31	Leaves	Decoction, infusion	Oral	Analgesic, anorexia, anguish, calming, cholesterol, colon, depurative, hair loss, high blood pressure, inflammation, obesity, pregnancy, renal lithiasis.
Satureja calamintha (L.) Scheele TDS090)	النابطة El-nabta	1	1	0.02	Leaves	Infusion	Oral	Cough.
Teucrium polium L. (TDK051)	الخياطة El-khiyata	7	8	0.12	Aerial parts	Decoction, infusion	Oral	Analgesic, diabetes, heart, ulcer, vomiting, wounds.
Thymus serpyllum L.	الزعتر البري	9	77	1.20	Aerial parts	Decoction,	Oral	All reported ailments.

(TDF033)	Zaater el bari					infusion		
Thymus vulgaris L. (TDF045)	الزعتر Zaater	14	16	0.25	Aerial parts	Decoction, infusion	Oral	Cholesterol, cough, influenza, strengthening.
Lauraceae								
Cinnamomum verum J.Presl (TDF038)	القرفة El-quarfa	11	15	0.23	Barks	Decoction, infusion	Oral	Alopecia areata, asthma, cancer, colon, cough, diabetes, obesity.
Laurus nobilis L. (TDF043)	الرند El-rand	12	18	0.28	Leaves	Decoction, infusion	Oral	Diabetes, high blood pressure, low blood pressure, stomach, strengthening.
Linaceae								
Linum usitatissimum L. (TDF007)	زريعة الكتان Ziriet el kettan	9	14	0.22	Seeds	Infusion, paste, powder	Oral, topical	Allergy, anorexia, cholesterol, diabetes, hair loss, obesity.
Lythraceae								
Lawsonia inermis L. (TDT064)	الحنة El-henna	1	3	0.05	Leaves	Decoction	Oral	Colon, hair loss, ulcer.
Punica granatum L. (TDF030)	الرمان El-roman	10	10	0.16	Barks, flowers, fruits	Decoction, infusion, mixture, powder	Oral	Ulcer.
Malvaceae								

Hibiscus sabdariffa L. (TDF034)	الكركديه El-karkadia	11	14	0.22	Flowers	Decoction, infusion	Oral	Diabetes, high blood pressure, low blood pressure.
Tilia cordata Mill. (TDF082)	الزيزفون Zaizafoun	1	1	0.02	Leaves	Infusion	Oral	Anguish.
Myrtaceae								
Myrtus communis L. (TDF016)	الريحان El-rayehan	11	14	0.22	Leaves	Decoction, infusion, Paste	Oral, topical	Colon, diabetes, dysuria, hair loss, stomach.
Syzygium aromaticum (L.) Merr. & L.M. Perry (TDT078)	القرنفل Krenfol	4	4	0.06	Fruits	Maceration, raw	Oral, topical	Cough, toothache.
Oleaceae								
Olea europaea L. (TDF028)	الزيتون Zitoun	5	6	0.09	Fruit oils, leaves	Infusion, Raw	Oral, topical	Burns, diabetes, high blood pressure.
Papaveraceae								
Papaver rhoeas L. (TDT080)	بن نعمان Ben naa'man	1	1	0.02	Flowers	Infusion	Oral	Asthma.
Pinaceae								
Pinus halepensis Mill. (TD074)	الصنوبر Snawbar	2	3	0.05	Barks, seeds	Paste	Oral, topical	Burns, cough, osteoarthritis.
Plantaginaceae								

Globularia alypum L. (TDT102)	تاسلغة Tasselgha	1	1	0.02	Leaves	Infusion	Oral	Kidney.
Plantago ciliata Desf. (TDS091)	لالمة Lalma	1	1	0.02	Leaves	Inhalation	Nasal	Mouth infections.
Poaceae								
Pennisetum glaucum (L.) R.Br. (TDK055)	البشنة Bechna	2	4	0.06	Seeds	Infusion, powder	Oral	Anorexia, breastfeeding, osteoarthritis.
Zea mays L. (TDF037)	الذرى Dherra	2	2	0.03	Fruits	Infusion	Oral	Dysuria, renal lithiasis.
Ranunculaceae								
Nigella sativa L. (TDF024)	السانوج Sanouj	7	96	1.50	Seeds	Infusion, inhalation, Raw	Nasal, oral	All reported ailments.
Rhamnaceae								
Rhamnus alaternus L. (TDF021)	مليلس Mliless	14	14	0.22	Aerial parts	Decoction, infusion	Oral	Anemia, hepatitis.
Ziziphus lotus (L.) Lam. (TDF008)	السدرة Sedra	6	73	1.14	Fruits, leaves, roots	Decoction, infusion	Oral, topical	All reported ailments.
Rosaceae								
Crataegus monogyna Jacq. (TDA103)	الزعرور Zaarour	1	1	0.02	Fruits	Infusion	Oral	Cephalalgia.
Cydonia oblonga	السفرجل	1	1	0.02	Barks	Decoction	Oral	Ulcer.

Mill. (TDK052)	Sefarjel							
Malus domestica Borkh. (TDK056)	التفاح Tefah	2	2	0.03	Fruits	Maceration	Oral	Cholesterol, high blood pressure.
Prunus dulcis (Mill.) D.A. Webb (TDT077)	اللوز Louz	3	3	0.05	Roots	Decoction	Oral	Anemia.
Prunus persica (L.) Batsch (TDS088)	الخوخ Khoukh	2	2	0.03	Leaves	Infusion	Oral	Cysts.
Rubiaceae								
Rubia tinctorum L. (TDF011)	الفوة El-fowa	18	18	0.28	Roots	Decoction, infusion, powder, raw	Oral	Anemia.
Salicaceae								
Populus nigra L. (TDT065)	الصفصاف Safsaf	1	1	0.02	Leaves	Infusion	Oral	Colon.
Santalaceae								
Viscum album L. (TDR095)	لنجبار Lendjebar	2	2	0.03	Roots	Infusion, powder	Oral	Breastfeeding, obesity.
Thymelaeaceae								
Daphne gnidium L. (TDF031)	لازاز Lazaz	4	4	0.06	Leaves	Infusion, paste	Oral, topical	Hair loss, sinusitis.
Thymelaea hirsuta (L.) Endl. (TDS089)	المثنان Methnan	3	4	0.06	Aerial parts	Inhalation, powder	Oral	Pregnancy, uterine fibroids.

Urticaceae								
Urtica dioica L. (TDF036)	الحريق El-hourig	4	72	1.12	Leaves	Decoction, infusion, Paste	Oral, topical	All reported ailments.
Verbenaceae								
Verbena officinalis L. (TDT066)	اللويزة Lewiza	2	3	0.05	Leaves	Decoction	Oral	Anguish, insomnia stomach.
Xanthorrhoeaceae								
Asphodelus ramosus L. (TDT076)	بلواز Blouaz	2	2	0.03	Roots	Infusion	Nasal	Otitis.
Zingiberaceae								
Curcuma longa L. (TDC093)	الكركم Kerkom	4	4	0.06	Rhizomes	Decoction, infusion, powder	Oral	Antimicrobial, influenza, hepatitis.
Zingiber officinale Roscoe (TDF046)	الزنجبيل Zandjabil	16	27	0.42	Rhizomes	Decoction, infusion, paste, powder	Oral, topical	Antimicrobial, asthma, bloating, calming, cholesterol, colon, cough, influenza, intoxications, obesity, rheumatism, vomiting, weight gain.
Zygophyllaceae								
Peganum harmala L. (TDF099)	الحرمل Harmel	1	1	0.02	Aerial parts	Powder	Oral	Rheumatism.

Zygophyllum album L.F. (TDF012)	العقاية Aggaya	6	7	0.11	Leaves	Decoction, infusion	Oral	Anemia, cancer, diabetes.

3.5. Categories of diseases and therapeutic indications

The ethnomedicinal plants reported throughout this study were used to treat 68 different ailments classified into 13 categories; digestive (52 species), circulatory (39 species), respiratory (37 species), urogenital (33 species), glandular (29 species), neurological and psychological (28 species), dermatological (27 species), osteoarticular (25 species), cancer (15 species), ocular (10 species), oral (8 species), general ailments (21 species) and others (7 species) (Figure 5).

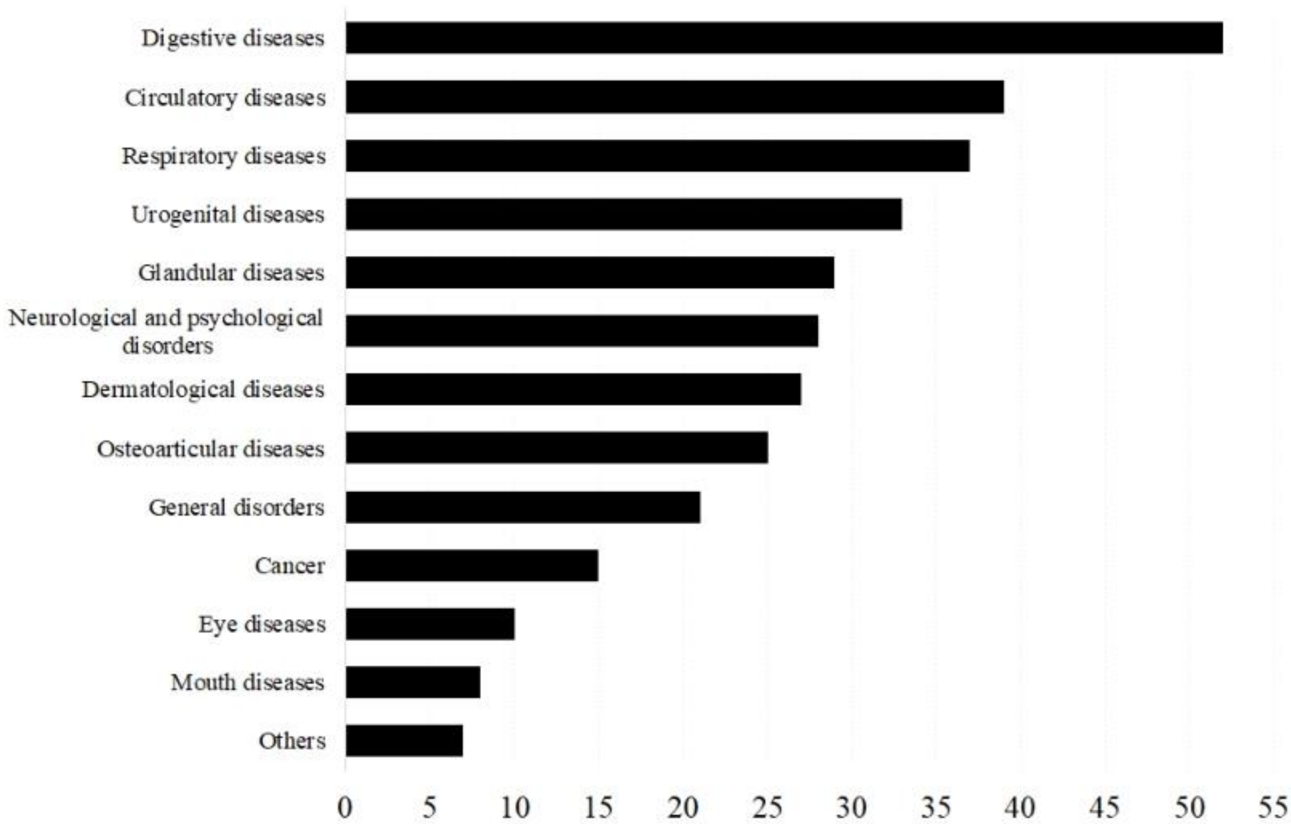


Figure 5. Number of used medicinal plant species in each ailment category.

Furthermore, the obtained results indicated that 31 % of the reported plant species are recommended for the treatment of digestive diseases. However, 16 % of the plant species are used to treat respiratory diseases. Nevertheless, the management of circulatory system, skin alterations and nervous diseases was secured by 10 % of the inventoried plant taxa for each ailment. The remaining 23 % of the cited species are used for the treatment of a wide range of diseases such as urinary ailments and metabolic disorders including diabetes and cancer (Figure 5).

3.6. Most frequently cited taxa

The frequency of citation index (FC) for all the reported species value ranged from 1 to 27 (Table 2). *Senna alexandrina* Mill. was ranked first (FC=27), followed by *Atriplex halimus* L. and *Bunium incrassatum* Amo (FC=23 each), *Foeniculum vulgare* Mill. (FC=22), *Matricaria chamomilla* L. (FC=21), *Rubia tinctorum* L. (FC=18), *Artemisia herba-alba* Asso and *Juniperus phoenicea* L. (FC=17 each).

3.7. New therapeutic uses and new ethnomedicinal plant species

In general, 246 new therapeutic uses of 55 known medicinal plant species belonging to 29 botanical families have been reported for the first time in the north Africa throughout the present study (Table 3). These species are belonging mainly to Apiaceae (8 species), Asteraceae (8 species), Lamiaceae (7 species), Fabaceae (5 species) and Rosaceae (4 species) families. Moreover, five plant species have been reported for the first time as medicinal plants in the north Africa and Algeria throughout the present study namely *Bunium incrassatum* Amo, *Echinops spinosus* L., *Cucurbita moschata* Duchesne, *Pennisetum glaucum* (L.) R.Br and *Malus domestica* Borkh.

Table 3. New medicinal uses the cited plant species compared with previous ethnomedicinal studies carried out in Algeria and Morocco.

Botanical family	Plant species	New therapeutic uses	Other uses in Algeria and Morocco	References
Amaranthaceae	*Atriplex halimus* L.	High blood pressure, ulcer.	Caner, goiter.	(Benarba et al., 2015)
			Eczema.	(Boudjelal et al., 2013)
			Diabetes, uterus cysts.	(Lakhdari et al., 2016)
			Thyroid.	(Ouelbani et al., 2016)
	Haloxylon scoparium Pomel	Allergy, cancer, cholesterol, colon, cysts, intoxications, skin, snake bites	Diabetes.	(Telli et al., 2016)
Anacardiaceae	*Pistacia atlantica* Desf.	Thyroid disorders.	Astringent.	(Benderradji et al., 2014)
			Dental pain, gingivitis, leishmaniasis, thrush.	(Chermat & Gharzouli, 2015)
			Diabetes.	(Telli et al., 2016)
Apiaceae	*Ammi visnaga* (L.) Lam.	High blood pressure, thyroid disorders, vomiting.	Diabetes.	(Azzi et al., 2012)
			Nephritic colic, sedative, urethral lithiasis, vasodilator.	(Bouzabata & Mahomoodally, 2019)
			Kidney, respiratory.	(González-Tejero et al., 2008)
			Asthma, heart attack, joints pains, renal lithiasis, stomachache.	(Bouasla & Bouasla, 2017)
	Apium graveolens L.	Anguish, renal lithiasis, strengthening.	Digestive system.	(Boughrara & Belgacem, 2016)
			Antispasmodic, carminative, diuretic.	(Bouzabata, 2013)

			Hypertension.	(Benarba et al., 2015)
			Diabetes.	(Azzi et al., 2012)
	Bunium incrassatum Amo	Asthma, cysts, thyroid disorders, tonsillitis.	Not reported.	
	Cuminum cyminum L.	Cholesterol, fever, influenza.	Infected wounds, skin infections.	(Volpato et al., 2012)
			Abdominal pains, colon, stomach ulcer.	(Sarri et al., 2015)
			Constipation, gases, kids cough, menstrual pain, stomachache.	(Benarba, 2016)
			Analgesic, antispasmodic, cough, lactation, rheumatism, tranquilizer.	(Ouelbani et al., 2016)
	Daucus carota L.	Colon, depurative, ulcer.	Respiratory, urinary or genital infections	(Bouasla & Bouasla, 2017)
			Cysts, urinary tract.	(Lakhdari et al., 2016)
	Foeniculum vulgare Mill	Anemia, hair loss, tonsillitis, wrinkles.	Antidiarrheal, antispasmodic, carminative.	(Sarri et al., 2015)
			Antiemetic.	(Meddour & Meddour-Sahar, 2016)
			Digestive, mental nervous, nutritional.	(González-Tejero et al., 2008)
			Gastrointestinal system diseases.	(Benarba et al., 2015)
	Petroselinum crispum (Mill) Fuss	Cancer.	Acne, anti-infective, blood circulation, urinary infections.	(Bouasla & Bouasla, 2017)
			Diuretic, hypotensive.	(Bouzabata, 2013)

			Diabetes.	(Azzi et al., 2012)
	Thapsia garganica L.	Anorexia, wounds.	Bronchitis, rheumatic pain.	(Benderradji et al., 2014)
			Anti-inflammatory, eczema.	(Boudjelal et al., 2013)
			Respiratory diseases.	(Boughrara & Belgacem, 2016)
			Antipyretic, weakness, weight loss.	(Meddour & Meddour-Sahar, 2016)
Aristolochiaceae	*Aristolochia longa* L.	Diabetes.	Cancer.	(Benarba et al., 2015)
Asteraceae	*Anacyclus pyrethrum* (L.) Lag.	Thrombosis.	Flatulence, respiratory system diseases, spermatozoids, tonic.	(Ouelbani et al., 2016)
			Female sterility.	(Benarba, 2016)
			Cancer, cough, female sterility.	(Benarba et al., 2015)
			Diabetes.	(Azzi et al., 2012)
	Artemisia absinthium L.	Dysuria, heart, uterine fibroids.	Appetizer, hypertensive, vulnerary.	(Sarri et al., 2014)
			Antiseptic, digestive disorders, wormer.	(Sarri et al., 2015)
			Anti-inflammatory, antiseptic, aperitive, aromatic, bitter tonic, cholagogue, digestive, diuretic, vermifuge.	(Rebbas et al., 2012)
			Antidiabetic, antiseptic injury, diuretic, stomachic.	(Meddour & Meddour-Sahar, 2016)
	Artemisia campestris L.	Allergy, cholesterol.	Analeptic, dandruff, healing, helminthiases, mycosis, spasms	(Hammiche & Maiza, 2006)

			and aid to menstruation, stomach and liver diseases, vulnerary.	
			Intestinal bloating, intestinal parasites.	(Chermat & Gharzouli, 2015)
			After childbirth, hair loss, digestive diseases, fever.	(Ramdane et al., 2015)
	Artemisia herba-alba Asso	Hair loss.	Antigastralgic, antispasmodic, emmenagogue, stomachic, vermifuge.	(Rebbas et al., 2012)
			Antigastralgic, antispasmodic, calming, digestive, emmenagogue, heart, hypertension, memory, sedative, spasms, tics, vermifuge.	(Bouchikh et al., 2016)
			Arterial hypertension.	(Sari et al., 2012)
			Analgesic, blood purification, cancer, respiratory system diseases.	(Ouelbani et al., 2016)
	Cynara scolymus L.	Cholesterol.	Antidiarrheal, appetizer, blood purification, cholagogue, choleretic, diuretic, energy, hypoglycemic, nutritious, stimulating.	(Benderradji et al., 2014)
			Digestive, urogenital diseases.	(Boughrara & Belgacem, 2016)

			Depurative, hypoglycemic.	(Bouzabata, 2013)
	Echinops spinosus L.	Cough, influenza, inflammation, cleaning the female genital apparatus after childbirth	Not reported	
	Matricaria chamomilla L.	Anguish, cephalalgia, colon, cough, hair loss, influenza, insomnia.	Analgesic, anti-inflammatory, antiseptic, antispasmodic, bitter vetch, carminative, emmenagogue, febrifuge, sedative, stomachic, tonic.	(Benderradji et al., 2014)
			Skin diseases.	(Boughrara & Belgacem, 2016)
	Saussurea costus Flueck.	Tonsillitis.	Diabetes.	(Bouzabata & Mahomoodally, 2019)
Berberidaceae	*Berberis vulgaris* L.	Intestinal parasitosis.	Diabetes.	(Bouzabata & Mahomoodally, 2019)
			Cancer.	(Benarba et al., 2015)
Brassicaceae	*Eruca vesicaria* (L.) Cav.	Rheumatism.	Fractures, stomachache, urinary infections.	(Bouasla & Bouasla, 2017)
	Lepidium sativum L.	Cholesterol.	to eliminate dirt from eyes.	(Volpato et al., 2012)
			Anemia, anthelmintic, broken bones, fatigue, hair loss, hypoglycemic for women after childbirth	(Sarri et al., 2014)

			Anemia, antibiotic, anti-hair loss, antioxidant, appetite, dermatological problems, diuretic, goiter, hypoglycemic, immune system, memory, rheumatism and bone problems, tonics, tumors.	(Ouelbani et al., 2016)
			Respiratory tract diseases.	(Benarba et al., 2015)
	Oudneya africana R. Br.	Thrombosis.	Skin diseases and lesions.	(Lakhdari et al., 2016)
			Diabetes.	(Telli et al., 2016)
Burseraceae	*Boswellia sacra* Flueck.	Asthma, influenza, kidney.	Diabetes.	(Bouzabata & Mahomoodally, 2019)
Cactaceae	*Opuntia ficus-indica* (L.) Mill.	Hair loss, kidney.	Antidiabetic, diarrhea.	(Sarri et al., 2015)
			Digestive, muscular, nutritional.	(González-Tejero et al., 2008)
			Diarrhea, hemorrhoids.	(Meddour & Meddour-Sahar, 2016)
			Hemorrhoids, respiratory system diseases.	(Ouelbani et al., 2016)
Cucurbitaceae	*Citrullus colocynthis* L. Schrad.	Eczema.	Antihypertensive, antitumor.	(Boudjelal et al., 2013)
			Headaches, tinea, vitiligo.	(Hammiche & Maiza, 2006)
			Diabetes.	(Azzi et al., 2012)
	Cucurbita moschata Duchesne	Renal lithiasis.	Not reported.	
Cupressaceae	*Tetraclinis articulata* (Vahl) Mast.	Ulcer.	Diabetes	(Azzi et al., 2012)
			Hypoglycemic, hypotensive.	(Bouzabata, 2013)

Cyperaceae	*Cyperus esculentus* L.	Dysuria.	Aphrodisiac, appetite, weight gain.	(Benarba et al., 2015)
			Kids appetite	(Benarba, 2015)
Ephedraceae	*Ephedra alata* Decne.	Cancer, renal lithiasis.	Body weakness, cold, hypertension, influenza, respiratory problems.	(Lakhdari et al., 2016)
Euphorbiaceae	*Euphorbia guyoniana* Boiss. & Reut	Cancer.	Diabetes.	(Telli et al., 2016)
			Diarrhea, scorpion stings, snake bites, skin diseases.	(Lakhdari et al., 2016)
Fabaceae	*Ceratonia siliqua* L.	Anemia, ulcer.	Appetite, antihypertensive, blood purification, cough, rheumatism, salivary secretions.	(Ouelbani et al., 2016)
			Diarrhea.	(Bouasla & Bouasla, 2017)
	Glycyrrhiza glabra L.	Prostate, ulcer.	Anti-virus and fungi, chest diseases, deodorant, eyes treatment, hypertension, rheumatism, spleen and liver pain, stomach pain, teeth cleaner.	(Lakhdari et al., 2016)
			Bronchitis, cough, laryngitis.	(Benarba, 2016)
	Senna alexandrina Mill.	Gout, rheumatism, vomiting.	Articulation pains, constipation, hair falls.	(Bouasla & Bouasla, 2017)
			Constipation, gases, stomachache.	(Benarba, 2016)
	Trigonella foenum-graecum L.	Anorexia, antimicrobial, alopecia areata, burns, cancer, cephalalgia, dental gingiva,	Anxiety, diabetes, purification, stomachache.	(Bouasla & Bouasla, 2017)
			Anemia, anti-inflammatory,	(Ouelbani et al., 2016)

		hair loss, insomnia, measles, migraine, mouth infections, pregnancy, skin, toothache, uterine fibroids, vitiligo, wrinkles.	appetite, digestive disorders, diuretic, immune system diseases, lactation, metabolic system diseases, respiratory system diseases, wounds.	
			Anguish, antidiabetic, eczema.	(Sarri et al., 2015)
			Ear afflictions, eye, snake bites.	(Volpato et al., 2012)
	Vicia faba L.	Allergy.	Eczema, hyperacidity.	(Meddour & Meddour-Sahar, 2016)
			Chronic cough.	(Benarba et al., 2015)
Lamiaceae	*Ajuga iva* (L.) Schreb.	Wounds.	Antidiabetic, antihypertensive, digestive disorders, eczema, leishmanicidal.	(Boudjelal et al., 2013)
			Animal bites, headache, stomach upset.	(Meddour & Meddour-Sahar, 2016)
	Lavandula stoechas L.	Antimicrobial, uterine fibroids.	Asthma, burns, colds, rheumatism.	(Sarri et al., 2015)
			Respiratory and urinary infections, stomachache.	(Bouasla & Bouasla, 2017)
			Digestive problems, diseased hearts and circulatory problems.	(Meddour & Meddour-Sahar, 2016)
	Marrubium deserti (Noë) Coss.	Rheumatism.	Arterial hypertension, fever.	(Ramdane et al., 2015)
			Diabetes, fever, jaundice, respiratory diseases, vascular hypertension.	(Hammiche & Maiza, 2006)

			Eye treatment, hemorrhoids, stomach pain.	(Chermat & Gharzouli, 2015)
	Mentha × piperita L.	Inflammation, influenza, pregnancy, rheumatism, stomach, uterine fibroids.	Anxiety, diarrhea, hypotensive, menstrual pains, skin care, tonic.	(Bouasla & Bouasla, 2017)
			Mental nervous.	(González-Tejero et al., 2008)
			Analgesic, carminative.	(Bouzabata, 2013)
			Articular pain, fever, migraine.	(Ouelbani et al., 2016)
	Mentha suaveolens Ehrh.	Heart.	Antiseptic injury, dizziness, fever, frigidity, headache, stomachic.	(Meddour & Meddour-Sahar, 2016)
	Salvia officinalis L.	Depurative, hair loss, pregnancy, renal lithiasis.	Antidiabetic, antihypertensive, eczema, weight loss.	(Boudjelal et al., 2013)
			Antiperspirant, antispasmodic, carminative, choleretic, hypoglycemic, sedative nervous, stomachic, tonic.	(Benderradji et al., 2014)
			Antispasmodic, digestive, wormer.	(Sarri et al., 2015)
	Thymus serpyllum L.	Allergy, alopecia areata, analgesic, anemia, anguish, anorexia, antimicrobial, anxiety, asthma, burns, breastfeeding, calming, cancer, cephalalgia, cholesterol, cough, cysts, depurative, diabetes, eczema, fever, gout, hair loss,	Digestive system, kidney.	(González-Tejero et al., 2008)

		heart, high blood pressure, inflammation, influenza, insomnia, low blood pressure, measles, migraine, osteoarthritis, otitis, pregnancy, prostate, rheumatism, sinusitis, skin, snake bites, strengthening, thrombosis, thyroid disorders, tonsillitis, uterine fibroids, vitiligo, wounds, wrinkles.		
Lauraceae	*Cinnamomum verum* J. Presl	Alopecia areata, cancer, colon, obesity.	Menstrual pain, respiratory and urinary infections.	(Bouasla & Bouasla, 2017)
			Diabetes.	(Telli et al., 2016)
			Menstruations.	(Ouelbani et al., 2016)
Linaceae	*Linum usitatissimum* L.	Anorexia, hair loss.	Allergy, cough, menstrual pains, respiratory.	(Bouasla & Bouasla, 2017)
			Anti-inflammatory, cancer prevention, headache, hypoglycemic and cholesterol, weight loss.	(Ouelbani et al., 2016)
			Allergy, diabetes, digestive disorders, hypertension.	(Benarba, 2016)
Lythraceae	*Lawsonia inermis* L.	Colon, ulcer.	Diabetes.	(Azzi et al., 2012)

			Kidney diseases.	(Benarba et al., 2015)
Malvaceae	*Hibiscus sabdariffa* L.	Diabetes.	Cholesterol, hypertension.	(Benarba et al., 2015)
Pinaceae	*Pinus halepensis* Mill.	Burns, osteoarthritis.	Disinfectant respiratory tract antifungal.	(Chermat & Gharzouli, 2015)
			Asthma.	(Meddour & Meddour-Sahar, 2016)
			Burns, cough, flu, inflammation of the skin, rheumatism, wounds.	(Rebbas et al., 2012)
Poaceae	*Pennisetum glaucum* (L.) R.Br.	Anorexia, breastfeeding, osteoarthritis.	Not reported.	
Ranunculaceae	*Nigella sativa* L.	Anguish, anorexia, antimicrobial, breastfeeding, cephalalgia, cholesterol, cysts, depurative, fever, gout, heart, inflammation, influenza, insomnia, measles, migraine, osteoarthritis, otitis, pregnancy, prostate, sinusitis, snake bites, strengthening, thrombosis, thyroid disorders, uterine fibroids, wrinkles.	Analgesic, antiseptic, antispasmodic, appetizer, carminative, digestive, diuretic, expectorant.	(Benderradji et al., 2014)
			Allergy, anemia, anxiety, flatulence, respiratory infections, skin care, Allergy.	(Bouasla & Bouasla, 2017)
			Cancer.	(Benarba, 2015)
			Internals hemorrhoids, pharyngitis, tonsillitis.	(Meddour & Meddour-Sahar, 2016)
Rhamnaceae	*Ziziphus lotus* (L.) Lam.	Anguish, alopecia areata, anemia, anorexia, antimicrobial, anxiety,	Anti-inflammatory, eczema, wound healing.	(Boudjelal et al., 2013)
			Hypoglycemic, urinary infections.	(Bouzabata, 2013)

		breastfeeding, cephalalgia, depurative, heart, insomnia, measles, migraine, pregnancy, sinusitis, strengthening, thrombosis, uterine fibroids, vitiligo, wrinkles.	Hypertension, stomach acidity.	(Chermat & Gharzouli, 2015)
			Abdominal pain, boils, burns, constipation, diabetes, diarrhea, fever, lips herpes, sores, tumors.	(Hammiche & Maiza, 2006)
Rosaceae	*Cydonia oblonga* Mill.	Ulcer.	Good breath.	(Bouasla & Bouasla, 2017)
			Cardiovascular, sensory, skin care.	(González-Tejero et al., 2008)
	Malus domestica Borkh.	Cholesterol, high blood pressure.	Not reported.	
	Prunus dulcis (Mill.) D.A. Webb	Anemia.	Disorders, healing, pregnant women, skin allergy, vision.	(Benarba et al., 2015)
			Kidney disease.	(Meddour & Meddour-Sahar, 2016)
	Prunus persica (L.) Batsch	Cysts.	Auditory duct's infections, skin care, cancer.	(Bouasla & Bouasla, 2017)
Thymeleaceae	*Thymelaea hirsuta* (L.) Endl.	Pregnancy.	Sterility, cysts.	(Ouelbani et al., 2016)
			Eczema, leishmanicidal, vermifuge.	(Boudjelal et al., 2013)
Urticaceae	*Urtica dioica* L.	Analgesic, anguish, anorexia, antimicrobial, anxiety, breastfeeding, calming, cancer, cephalalgia, depurative, fever, heart, high blood pressure,	Antidiabetic, anti-inflammatory.	(Boudjelal et al., 2013)
			Anemia, coagulant, thyroid problems, suprarenal gland	(Ouelbani et al., 2016)
			Anemia, Diabetes, weight gain.	(Benarba, 2016)
			Digestive system.	(González-Tejero et al., 2008)

		insomnia, low blood pressure, measles, migraine, pregnancy, sinusitis, snake bites, thrombosis, strengthening, uterine fibroids.		
Zingiberaceae	*Curcuma longa* L.	Antimicrobial, influenza.	Liver diseases.	(Benarba, 2016)
			Aches and pains, anxiety, skin care.	(Bouasla & Bouasla, 2017)
			Colic, body care for the new born, diabetes, dysmenorrhea, eczema, gastric aches, liver attack, myalgia, rheumatism.	(Hammiche & Maiza, 2006)
Zygophyllaceae	*Zygophyllum album* L. F.	Anemia, cancer.	Anti-virus and fungi, diabetes, indigestion, laxative, purgative.	(Lakhdari et al., 2016)

3.8. Endemic, rare and endangered plants species

Among the 107 medicinal plants species reported throughout this study, 6 species are endemic to North Africa-Algeria, Northern and Central Sahara i.e. *Pistacia atlantica* Desf., *Tetraclinus articulata* (Vahl) Mast., *Oudneya africana* R. Br., *Euphorbia guyoniana* Boiss. & Reut, *Teucrium polium* L. and *Marrubium deserti* (Noë) Coss. Six species are considered threatened, rare or endangered i.e. *Artemisia herba-alba* Asso, *Anacyclus pyrethrum* (L.) Lag., *Cuminum cyminum* L., *Saussurea costus* (Falc.) Lipsch., *Boswellia sacra* Flueck. and *Pistacia atlantica* Desf. In addition, 7 species are listed as uncultivated plant species protected by the Algerian law (executive decree corresponding to January 2012) i.e. *Pistacia atlantica* Desf., *Oudneya africana* R.Br., *Teucrium polium* L., *Juniperus oxcyderus* L., *Juniperus phoenicia* L. and *Tetraclinus articulata* (Vahl) Mast. Unfortunately, the intensive use of rare and threatened plant species by the local population might lead to the loss of these genetic resources and consequently to their extinction.

3.9. Use value

The use value index (UV) of the reported medicinal plant species ranged from 1.5 to 0.016 (Table 2). The highest values were reported respectively for *Nigella sativa* L. (UV=1.5), *Trigonella foenum-graecum* L. (UV=1.38), *Thymus serpyllum* L. (UV=1.2), *Ziziphus lotus* (L.) Lam. (UV=1.14), *Urtica dioica* L. (UV=1.13), *Senna alexandrina* Mill. (UV=0.52), *Atriplex halimus* L. (UV=0.5), *Matricaria chamomilla* L. (UV=0.48), *Bunium incrassatum* Amo and *Foeniculum vulgare* Mill. (UV=0.45 each) respectively. However, the lowest use values have been reported for *Saussurea costus* Flueck, *Silybum marianum* (L.) Gaertn, *Tilia cordata* Mill. and *Vicia faba* L. (UV=0.016 each).

3.10. Informant consensus factor

The documented use reports data have been classified into different ailment categories. The informant consensus factor (F_{IC}) was calculated for each ailment category to select the categories of diseases for which the species are traditionally used and the range was from 0.54 to 0.81 (Table 4). The highest F_{IC} value (0.81) was reported for digestive diseases with 52 used plant species and 274 reported uses, followed by cardiovascular and urogenital diseases (0.73 each).

Table 4. Informant consensus factor for commonly used medicinal plants.

Ailment	**Number of taxa**	**Use reports**	**F_{IC}**
Digestive disorders *Bloating, colon, constipation, diarrhea, hemorrhoids, hepatitis, intoxications, liver, intestinal parasitosis, stomach, ulcer, vomiting*	52	274	0.81
Circulatory disorders *Anemia, cholesterol, heart, high blood pressure, low blood pressure, thrombosis*	39	142	0.73
Respiratory disorders *Allergy, asthma, cough, influenza*	37	132	0.72
Urogenital diseases *Cysts, dysuria, enuresis, prostate, kidney, pregnancy, renal lithiasis, strengthening, uterine fibroids*	33	120	0.73
Glandular disorders *Breastfeeding, diabetes, thyroid disorders*	29	86	0.67
Neurological and psychological disorders *Analgesic, anguish, anorexia, anxiety, calming, cephalalgia, insomnia, migraine*	28	94	0.71
Dermatological disorders *Alopecia areata, burns, Eczema, hair loss, skin, vitiligo, wounds, wrinkles*	27	74	0.64
Osteoarticular diseases *Gout, inflammation, osteoarthritis, rheumatism*	25	57	0.57
General disorders *Antimicrobial, depurative, fever, obesity, weight gain*	21	61	0.66
Cancer	15	43	0.66
Eye diseases *Otitis, sinusitis, tonsillitis*	10	24	0.61
Mouth diseases *Dental gingiva, mouth infections, toothache*	8	25	0.71
Others *Measles, snake bites*	7	14	0.54

4. Discussion

Ethnopharmacological studies constitute an economical way to find natural products to be used in the discovery and synthesis of novel drugs to fight several diseases. They play a role in the conservation and enhancement of different natural products, including aromatic and medicinal plants.

4.1. Sociodemographic features

In the present study, the number of men herbalists was higher than that of women (60 men versus 4 women). The observed gender bias might be due to the cultural traditions and structure of the society, where work outside the family, such as this kind of activity, is not allowed for women. Moreover, most herbalists have a secondary or middle institutional level . This could be explained by the fact that the majority of herbalists belongs to rural poor regions where access to school and university is not usually allowed or accessible. Furthermore, almost all the interrogated herbalists acquired their knowledge from other persons and they refer mainly to the experiences of their ascendants or of other traditional healers to use medicinal plants as remedies. It should be noted that older herbalists, mainly illiterates, have shared more knowledge about the diversity and uses of medicinal plants. This is due certainly to the vast experience accumulated along times and transmitted from generation to generation throughout practices especially where no other alternative was available. In fact, the transmission of this valuable ethnomedicinal knowledge is presently in danger of loss especially that modern generations have changed their life style and habitudes and tend to not believe in using plants as remedies (Bouasla & Bouasla, 2017; Sargin et al., 2015).

4.2. Botanical diversity of ethnomedicinal plants

In general, 107 medicinal plant species belonging to 45 families and 97 genera have been reported for the treatment of various ailments. Previous ethnobotanical studies carried out in Algeria have reported 58 plant species (50 genera and 27 families) in the region of M'sila (east Algeria) (Boudjelal et al., 2013), 41 plant species (37 genera and 24 families) in the region of Hodna (east Algeria) (Sarri et al., 2015), 141 plant species (125 genera and 54 families) in the region of Mascara (north west Algeria) (Benarba et al., 2015), 98 species (90 genera and 48 families) in the region of Tizi-ouzou (north center Algeria) (Meddour & Meddour-Sahar, 2016) and 90 species (85 genera and 42 families) in the region of Skikda (north east Algeria) (Bouasla & Bouasla, 2017).

The most represented families were Lamiaceae (15 species), Apiaceae (11 species), Asteraceae (10 species), Fabaceae and Rosaceae (6 species each). The predominance of these plant families in the medicinal flora is well established in Algeria (Benarba et al., 2015; Meddour & Meddour-Sahar, 2016; Sarri et al., 2015; Sarri et al., 2014) and in the whole Mediterranean region (González-Tejero et al., 2008; Slimani et al., 2016). The benefic effects of plant species belonging to these families could be due to the presence of special and effective bioactive compounds holding potential biological activities, e.g. arbutin (Rychlinska & Nowak, 2012), apigenin and naringenin (Stacks, 2015), luteolin (Lopez-Lazaro, 2009), hesperidin (Lee *et al*., 2010) and rutin (Chua, 2013) in the Lamiaceae family. As well, several bioactive compounds such as flavonoids, sesquiterpenes and germacranolide sesquiterpene lactones are found in the Asteraceae family (Babaei et al., 2018; Shoaib et al., 2017), whereas terpenoids, flavonoids, coumarins, polyacetylenes, steroids, sesquiterpenes and flavonols are found in the Apiaceae family (Moazzami Farida et al., 2018).

4.3. Plant parts used

The informants either used the full plant species or only the parts they thought were intriguing. The most common plant parts were leaves (27%). However, the following plant parts were the most likely to be used: aerial parts (23%), seeds (15%), roots (9%), flowers (7%), and fruits (6%). It should be noted that phytochemical compounds differ in quantity and quality according to the plant part in which they are accumulated. The interrogated herbalists throughout the present study are not fully aware of this aspect but they use the different plant parts according to traditional heritage that was developed empirically rather than on scientific basis. Most of ethnobotanical studies have reported the frequent use of leaves in herbal remedies (Adnan et al., 2014; Sher et al., 2015). Leaves are very useful for plants identification, very abundant, easily accessible to local populations and rich with bioactive compounds derived from photosynthesis (Bouasla & Bouasla, 2017; Sargin et al., 2015). Besides, the use of leaves is better for the survival of plants as the use of whole plant or roots can seriously threaten the local flora (Umair et al., 2017).

4.4. Modes of preparation and administration

Most of plants are used as infusion (47%), decoction (28%) or even powdered (10%). The mentioned methods of preparation could be suitable for some plants but not for the others. In fact, the boiling procedure can cause severe degradation of the therapeutic components in some medicinal plants. In addition, the suitable dosage required to reach the expected benefits could not be acknowledged with precision since it was dissimilar among informants interrogated throughout this study. This concern has been raised also by several researchers indicating that the fixed doses to be administered by patients in traditional medicine is still not yet well-defined (Jaradat et al., 2016). Therefore, further studies are needed to determine the concentration of active ingredients with respect to their method of preparation.

For the mode of administration, oral administration is the most prescribed mode (91%), followed by topical application (7%) and nasal and gargling (1% each). These findings are in agreement with those of Ahmad et al. (2014) and Rashid et al. (2015). Oral and topical modes of administration permit rapid physiological action to promote healing power (Rehman et al., 2015).

Furthermore, most herbalists advised the use of mixtures of plant species with other ingredients to improve the taste and enhance the therapeutic effects. Mixtures of various species might have positive synergic effects and attenuate the adverse effects or toxicity of some plants of the mixture (Ait Abderrahim et al., 2019).

4.5. Categories of diseases and therapeutic indications

According to the findings, 31% of the reported plant species are recommended for the treatment of digestive diseases. However, 16% of the plant species are used to treat respiratory diseases. Nevertheless, the management of circulatory system, skin alterations, and nervous diseases was secured by 10% of the inventoried plant taxa for each ailment. The remaining 23% of the cited species are used for the treatment of a wide range of diseases, such as urinary ailments and metabolic disorders, including diabetes and cancer. These findings are in accordance with previous studies carried out in Algeria and in the Mediterranean region. Most of medicinal plants listed by Boudjelal et al. (2013) in the region of M'Sila (north-east of Algeria) were recommended to treat digestive problems, diabetes, blood pressure and cancers. In addition, Ouelbani et al. (2016) have reported the use of medicinal plants mainly for the treatment of gastrointestinal disorders in the region of Constantine and Mila (north-east of Algeria). Similar findings were reported by González-Tejero et al. (2008) and Slimani et al. (2016) in the Mediterranean region.

4.6. Most frequently cited taxa

According to the frequency of citation (FC), the most cited plant species for the treatment of various ailments were, respectively, *Senna alexandrina* Mill. (FC=27), *Atriplex halimus* and *Bunium incrassatum* (FC=23 each), *Foeniculum vulgare* (FC=22), *Matricaria chamomilla* (FC=21), *Rubia tinctorum* (FC=18), *Artemisia herba-alba* and *Juniperus phoenicea* (FC=17 each).

Senna alexandrina Mill. is indicated in this study for the treatment of colon, constipation, gout, rheumatism, vomiting and as an analgesic. By the same, Bouasla & Bouasla (2017) and Elansary et al. (2018) have reported its traditional use for the treatment of constipation, stomach, pain and hair loss. The dried leaves and pods of *S. alexandrina* Mill. contain molecules called sennosides among them sennosides A and B which have carminative, purgative, antidysenteric and expectorant properties (Mishra et al., 2018). Additionally, its leaves are rich in bioactive biomolecules such as tinnevellin glycoside, kaempferol, scutellarein, isorhamnetin-3-O-beta-gentiobioside, apigenin-6,8-di-C-glycoside, D-3-O-methylinositol, Quercimeritrin, emodin-8-O-beta-D-glucopyranoside E and rutin (Wang et al., 2020). This species possesses confirmed antioxidant, anti-inflammatory, antimicrobial, antipyretic, laxative, diuretic, and purgative effects (Elansary et al., 2018; Wang et al., 2020).

Besides, the use of the perennial halophyte shrub *Atriplex halimus* L. is reported for the treatment of cancer, inflammatory diseases and hypertension. Benhammou et al. (2009) have reported its use to treat diabetes and internal parasites while Lakhdari et al. (2016) have noted its use for the management of gastrointestinal, cardiovascular, inflammatory and respiratory diseases besides diabetes and fall of placentae. This species is rich in tannins, flavonoids (flavone, flavanone, flavonols and isoflavone glycosides), saponins, alkaloids, resins, naringin and naringenin 7-O-glucoside (Benhammou et al., 2009; Emam, 2011). The previous studies of Kabbash & Shoeib (2012) and Al-Senosy et al. (2018) have demonstrated its antioxidant, antimicrobial, antileishmanial, anti-inflammatory, antiproliferative and antidiabetic effects.

Furthermore, *Bunium incrassatum* Amo is indicated to treat allergy, asthma, cough, cysts, tonsillitis and thyroid disorders. According to Benarba et al. (2015), this species is used in the treatment of allergy, bronchitis and cough. The powder of dried tubers of this species was used for bronchitis, cough, inflammatory hemorrhoids and as astringent and anti-diarrheal agent (Bousetla et al., 2015). The phytochemical analyses have demonstrated its richness in several active compounds such as scopoletin, coumarins, scoparone, β-sitosterol, caryophyllene, germacrene and farnesene (Bousetla et al., 2014; Bousetla et al., 2015; El Kolli et al., 2017). In addition, the tested activity of its essential oil has shown antioxidant, anti-hemolytic, anti-inflammatory, antibacterial and antimicrobial properties (Bousetla et al., 2014; El Kolli et al., 2017).

All plant parts of *Foeniculum vulgare* Mill are used for the treatment of digestive, reproductive, respiratory and endocrine disorders. In general, this plant constitutes a common remedy for gastrointestinal disorders including bloating, indigestion (Kaur & Arora, 2009).

Ouelbani et al. (2016) stated that it is used in the treatment of rheumatism, muscular problems, lactation, weight loss as it possesses an antispasmodic activity. Its seeds are known to improve the unpleasant odor of the mouth (Badgujar et al., 2014). They are consumed either raw or as a tea made by adding boiling water to a teaspoon of seeds. Its extracts are also useful in the treatment of hypertension and glaucoma (Rather et al., 2016). This plant is a rich source of polyphenols, flavonoids, terpenoids, carotenoids, coumarins, curcumin, fenchone, estragole, phenolic glycosides and trans-anethole (Rather et al., 2016; Zellagui et al., 2011).

Besides, *Matricaria chamomilla* L. was recommended for gastric, respiratory, neurologic and inflammatory problems. Bigagli et al. (2017) reported the use of chamomile to treat ulcers, stomachache, inflammations, wounds, skin irritation, gastrointestinal disorders, pharyngitis and rheumatic pain. The popular uses of this plant are infusion, tea and capsules (Petruľová-Poracká et al., 2013; Tolouee et al., 2010). Singh et al. (2011) described infusion of chamomile for urinary inflammation, digestive and menstruation disorders, and powder for external use for wounds and hemorrhoids. However, Rebbas et al. (2012) stated that oily maceration of leaves is useful for rheumatic and migraine pain. Phytochemical analyses have shown its richness in terpenoids, luteolin, apigenin, α-bisabolol, caffeic acid, matricin, coumarins, α-bisabolol oxides A and B, chlorogenic acid, quercetin and naringenin (Bigagli et al., 2017; Singh et al., 2011).

As well, *Rubia tinctorum* L. is reported in this study to treat anemia. Baghalian et al. (2010) have cited that its roots are useful for the treatment of kidney and bladder stones due to the presence of 1-hydroxyanthraquinone which is a laxative and sedative agent. In addition, Esalat Nejad & Esalat Nejad (2013) have indicated it to treat urinary diseases and menstruation pain. This plant is also indicated against cancer, inflammation, tuberculosis, wounds, rheumatism and metrorrhagia (Nejat et al., 2017). Ford et al. (2015) and Nejat et al. (2017) have attributed the biological properties of this species mainly to the anthraquinones along with other bioactive phytochemical compounds such as polyphenols, flavonoids, alkaloids, terpenes, tannins, cardiac glycosides, coumarins and iridoid asperuloside.

However, a large number of species has been reported just once such as *Thapsia garganica* L., *Vicia faba* L., *Tilia cordata* Mill. and *Ricinus communis* L. which may translate the lack of knowledge about their uses and their beneficial effects.

4.7. New therapeutic uses and new ethnomedicinal plant species

Throughout the current study, 246 new therapeutic uses belonging to 55 known medicinal plant species and 29 botanical families have been reported for the first time in the north Africa. These species belong mainly to the Apiaceae, Asteraceae, Lamiaceae, Fabaceae, and Rosaceae families. These findings consolidate the importance of the cited botanical families as effective source of bioactive molecules holding potential therapeutic effects (Benarba et al., 2015; Meddour & Meddour-Sahar, 2016; Sarri et al., 2015; Sarri et al., 2014).

Moreover, five plant species have been reported for the first time as medicinal plants in the north Africa and Algeria throughout the present study namely *Bunium incrassatum* Amo, *Echinops spinosus* L., *Cucurbita moschata* Duchesne, *Pennisetum glaucum* (L.) R.Br and *Malus domestica* Borkh.

Interestingly, *Bunium incrassatum* Amo was indicated to treat asthma, cysts, thyroid disorders and tonsillitis. However, *Echinops spinosus* L. was indicated for cough, influenza, inflammation and it is widely used to clean the female genital apparatus after childbirth. In addition, *Cucurbita moschata* Duchesne was designated for renal lithiasis while *Pennisetum glaucum* (L.) R.Br. was recommended for anorexia, breastfeeding and osteoarthritis. Besides, *Malus domestica* Borkh was mentioned to normalize cholesterol and high blood pressure.

4.8. Use value

The use value index (UV) of the reported medicinal plant species ranged from 1.5 to 0.016. This quantitative index is used in order to prove the relative importance of the plant species known locally. The highest values were reported, respectively, for *Nigella sativa* L. (UV=1.5), *Trigonella foenum-graecum* L. (UV=1.38), *Thymus serpyllum* L. (UV=1.2), *Ziziphus lotus* (L.) Lam. (UV=1.14), *Urtica dioica* L. (UV=1.13), *Senna alexandrina* Mill. (UV=0.52), *Atriplex halimus* L. (UV=0.5), *Matricaria chamomilla* L. (UV=0.48), *Bunium incrassatum* Amo and *Foeniculum vulgare* Mill. (UV=0.45 each), respectively. These results corroborate the previous findings of Benarba *et al*. (2014), Ouelbani et al. (2016) and Eddouks et al. (2017) which demonstrated also higher use values for *Trigonella foenum-graecum* L. and *Nigella sativa* L. The traditional indication of *N. sativa* L. to treat anemia and inflammation has been proven and attributed mainly to its thymoquinone and nigellone molecules which can act as inhibitors of the generation of eicosanoids, leukotrienes and histamine (Al-Saleh et al., 2006; Tayman et al., 2013). As well, the antioxidant activity of *N. sativa* L. was also determined (Bouasla et al., 2014). In addition, *T. foenum-graecum* has also a long history of use in the treatment of respiratory infections, reproductive disorders, treating hormonal disorders, increasing milk supply, reducing menstrual pain and reducing fever. This species has been shown to possess antiviral, antimicrobial, hypotensive, antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic and antitumor activity (Al-Oqail et al., 2013).

However, Bouasla & Bouasla (2017) have mentioned *Thymus vulgaris* L. and *Mentha* × *piperita* L. with highest use values. *Thymus* spp. have been one of plants having the highest use values in Portugal (Neves et al., 2009) and Italy (Idolo et al., 2010) to treat different respiratory ailments such as bronchitis, allergy, cold, flu and cough. *Thymus* spp. are rich in several active compounds such as thymol, carvacrol, p-cymene, eugenol, and luteolin that may explain its remedial potential (Monira & Naima, 2012). These compounds are known to have antiviral, anti-inflammatory, antioxidant, anti-nociceptive, anti-anaphylactic and antibacterial properties (Javed et al., 2013).

4.9. Informant consensus factor

The informant consensus factor (FIC) indicates that the highest FIC value was reported for digestive diseases (0.81), cardiovascular diseases and urogenital diseases (0.73 each). The higher values of the index indicate higher homogeneity of knowledge among informants. Similar results have been reported by Benarba et al. (2015) in Mascara (north west of Algeria), Bouasla & Bouasla (2017) in Skikda (north east of Algeria), Fakchich & Elachouri (2014) in Morocco and Tuttolomondo et al. (2014) in Italy.

The high F_{IC} value reported for digestive diseases may be explained by its high incidence in the region and/or the ability of the traditional healers to diagnose easily these pathologies (Punnam Chander et al., 2014). The high incidence of digestive disorders might inform probably an unhealthy lifestyle. Interestingly, cancer is reported to have the 5_{th} highest F_{IC} value (0.66) which could be attributed mainly to the high incidence of cancers in the region.

5. Conclusion

The obtained results reveal the importance of local knowledge throughout the variety and the large number of reported aromatic and medicinal plants used in traditional medicines to treat various ailments among local populations in the region of Tiaret.

Overall, informants have described the use of 107 medicinal plants belonging to 45 families and 97 genera for the treatment of various ailments. Lamiaceae, Apiaceae and Asteraceae were the most represented families. Besides, the most frequently cited species are *Senna alexandrina* Mill., *Atriplex halimus* L., *Bunium incrassatum* Amo, *Foeniculum vulgare* Mill., *Matricaria chamomilla* L., *Rubia tinctorum* L., *Artemisia herba-alba* Asso and *Juniperus phoenicea* L. However, the higher use values were reported for *Nigella sativa* L., *Trigonella foenum-graecum* L., *Thymus serpyllum* L., *Ziziphus lotus* (L.) Lam., *Urtica dioica* L., *Senna alexandrina* Mill., *Atriplex halimus* L., *Matricaria chamomilla* L., *Bunium incrassatum* Amo and *Foeniculum vulgare* Mill. respectively.

Interestingly, *Bunium incrassatum* Amo, *Echinops spinosus* L., *Cucurbita moschata* Duchesne, *Pennisetum glaucum* (L.) R.Br and *Malus domestica* Borkh. were reported for the first time in this study as medicinal plants in the north Africa and Algeria. Moreover, 246 new therapeutic uses were described.

It should be noted that *Pistacia atlantica* Desf., *Tetraclinus articulata* (Vahl) Mast., *Oudneya africana* R. Br., *Euphorbia guyoniana* Boiss. & Reut, *Teucrium polium* L. and *Marrubium deserti* (Noë) Coss. are endemic to North Africa-Algeria, Northern and Central Sahara. Furthermore, *Artemisia herba-alba* Asso, *Anacyclus pyrethrum* (L.) Lag., *Cuminum cyminum* L., *Saussurea costus* (Falc.) Lipsch., *Boswellia sacra* Flueck. and *Pistacia atlantica* Desf. are considered threatened, rare or endangered species. Therefore, an urgent intervention is required to protect these genetic resources from the abusive use by local population which might lead to their loss and extinction.

Evidently, it is the time to increase effective scientific studies on the determination of the nature and mechanisms of action of bioactive compounds included in these medicinal plants in order to produce effective and safe drugs.

Chapter II

Chapter 2: Phytochemistry and biological activities

1. Introduction

For centuries, people have used medicinal plants as treatments for various illnesses due to their richness in substances with therapeutic potential (Adegbola et al., 2017). In fact, medicinal plants constitute an immense reservoir of primary and secondary metabolites widely used in developing and synthesizing new drugs (Dar et al., 2017). Primary metabolites represent molecules essential for plant species' development and growth, including carbohydrates, lipids, amino acids, fatty acids, and steroids. However, secondary metabolites are bioactive compounds such as phenolic compounds, alkaloids, and terpenoids holding several therapeutic properties (Singh, 2015).

Interestingly, secondary metabolites, especially phenolic compounds, possess interesting biological activities such as antioxidant, anticancer, antimicrobial, antiviral, and anti-inflammatory activities among others (Vuolo et al., 2019). According to Hussein and El-Anssary (2019), and Ganaie (2021), phenolic compounds alike polyphenols, flavonoids, and tannins act as effective antioxidants by scavenging free radicals and preventing cells from oxidative stress, including lipid peroxidation and DNA single-strand breaks.

The present study aims to examine the phytochemical profile and the corresponding biological activities of some selected aromatic and medicinal plants that have been reported in our previous study being used in traditional Algerian medicine. Interestingly, the selected plant species have not been previously studied, namely *Atriplex halimus* L., *Bunium incrassatum* Amo, and *Echinops spinosus* L.

2. Presentation of the selected medicinal plants used in Algerian traditional medicine

2.1. *Atriplex halimus* L.

- **Characterization and geographic distribution**

Atriplex halimus L., commonly called "Guetaf," is one of the perennial halophytic shrubs belonging to the Amaranthaceae family (Al-Senosy et al., 2018; Kabbash and Shoeib, 2012). It is native to the Mediterranean basin, which includes North Africa and it is widely widespread in arid and semi-arid areas, in high plateaus at elevations below 900 m, as well as on the littoral. It has a height of 1 to 3 m and 3 m in diameter (Belouadah et al., 2021; Benhammou et al., 2009; El-Aasr et al., 2016; Ortiz-Dorda et al., 2005) (Fig. 1).

In Algeria, it is classified among the spontaneous plants of the salt steppes and it is recognized by its high tolerance to salinity and drought (Nedjimi et al., 2013). It grows on a wide range of soils at more than 1100 m of altitude (Zeghib, 2020), with rainfall ranging from 100–400 mm/year and average minimum temperatures ranging from –10°C to –12°C, especially in the coldest months (Nedjimi, 2012). Most of their populations that grow naturally belong to the schweinfurthii subspecies (Nedjimi et al., 2013).

Figure 1. *Atriplex halimus* ssp. (Nedjimi, 2012).

- **Ethno-medicinal uses**

Traditionally, it has been widely used for thousands of years. It is indicated to treat several ailments such as thyroid (Ouelbani et al., 2016), heart disease, syphilis (Zeghib, 2020), as well as chest problems, muscular pain, and intestinal diseases in animals (Al-Senosy et al., 2018). In the Arab world, it is used for stomach pain, intestinal worms, inflammation of the urinary tract, urolithiasis, as it regulates gallbladder excretion (Messaoudi et al., 2020). Whereas in Algeria, it treats cancer, thyroid disorders, diabetes mellitus, anemia and different types of cysts such as ovarian, uterine and breast cysts (Chikhi et al., 2014; Mohammedi, 2016; Ounaissia et al., 2020; Taïbi et al., 2021; Zeghib, 2020).

Their aerial parts and roots in decoction, infusion, and powder are mentioned for cysts, urinary problems, and joint pain (Farah et al., 2015), while their leaves are recommended to treat cardiovascular diseases, diabetes, rheumatism (Slama et al., 2020), and even hypercholesterolemia (Benarba, 2016). Furhermore, Their decoctions, especially leaves and aerial parts, are used for fever, jaundice, blood purification, liver diseases, and all types of skin edema (Ali et al., 2021; Volpato et al., 2012), while the decoction of seeds is mentioned to treat cancer (Benarba, 2016) and the ash from burnt plants is used as an alkali (Walker et al., 2014).

In addition to its ethnomedicinal uses, A. halimus has remarkable energy and nutritional value (Zeghib, 2020). It is integrated into the diets of nomads and the local population of the steppes (Ounaissia et al., 2020) as it is used for vegetables and salads in many regions (Nedjimi, 2012), for feeding sheep and goats, and to treat intestinal diseases in animals (Chikhi et al., 2014).

- **Phytochemical composition**

Based on the literature, *A. halimus* is an excellent source of bioactive compounds. Several phytochemical screenings have reported that it contains 10% sodium chloride along with a large number of active compounds such as phenolic acids, flavonoids, alkaloids, tannins, saponins, resins, terpenoids, and carotenoids acting as powerful reducing agents and singlet oxygen quenchers (Benhammou et al., 2009; Khaldi et al., 2015; Souad et al., 2019; Taïbi et al., 2020).

Its tender leaves are rich in dietary fibers, cardinolites, proteins, vitamins (B and C), organic acids, phosphatidylglycerol and various mineral salts such as sodium, magnesium, phosphorus, calcium and potassium (Gattouche et al., 2020; Ounaissia et al., 2020), which facilitates the digestion of food, increases gastric repletion and hydrates the contents of the faecal bolus (Nedjimi et al., 2013).

Table 1. Chemical composition and dry matter of *A. halimus* leaves (Nedjimi et al., 2013).

MS (%)	MAT (MS%)	CB (MS%)	Na (MS%)	Ca (MS%)	K (MS%)	P (MS%)	Mg (MS%)
34.2	15.1	15.4	4.41	1.77	2.59	0.21	0.32

MS: dry matter, MAT: total nitrogenous matter, CB: crude fiber

Chromatographic investigation of ethyl acetate extract has revealed the presence of flavonol, flavanone, flavone and isoflavone glycosides as well as fatty acids, sterols, alkaloids, amino acids and combined sugars that possess various biological activities (Emam, 2011).

Moreover, another phytochemical study performed by Kabbash and Shoeib (2012) on extracts of aerial parts allowed the isolation of two flavonol glycosides, which are atriplexoside A and atriplexoside B with six other compounds, including two methoxylated flavonoid glycosides, an ecdysteroid, two phenolic glycosides, and a megastigmane.

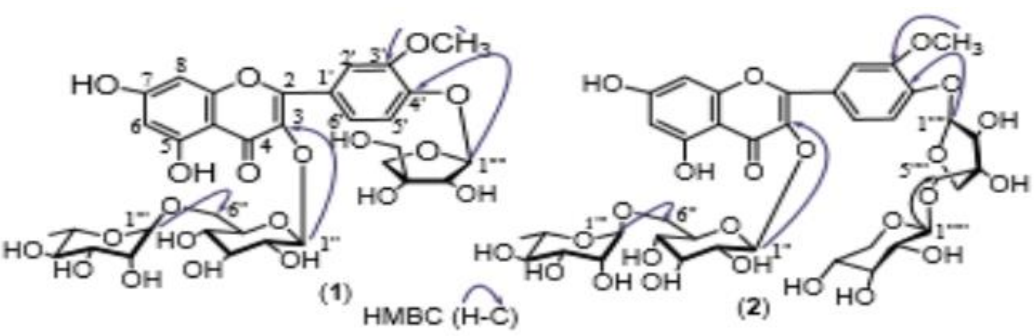


Figure 2. Chemical structure of atriplexoside A and atriplexoside B (Kabbash and Shoeib, 2012).

In addition to four flavonol glycosides designated as artiplexoside A, syringetin 3-O-β-D-rutinoside, isorhamnetin 3-O-β-D-rutinoside and syringetin 3-O-β-D-glucopyranoside have been isolated from their aerial parts, wich possess a powerful antibacterial activity (El-Aasr et al., 2016).

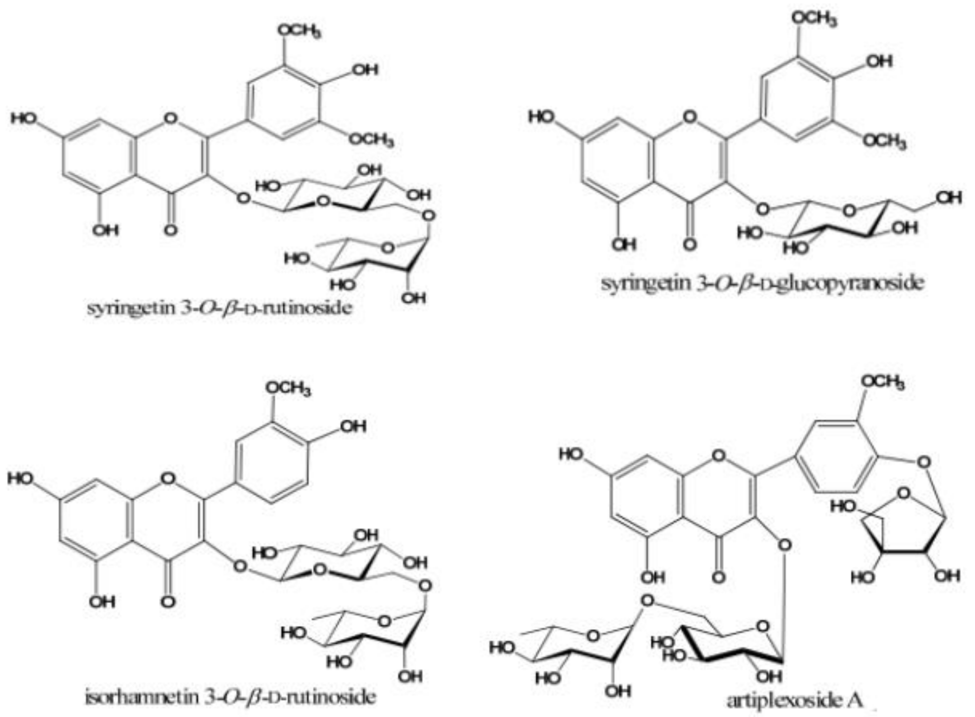


Figure 3. Chemical structure of flavonol glycosides isolated from *A. halimus* (El-Aasr et al., 2016).

- **Therapeutic properties**

In addition to its diverse phytochemical composition, previous investigations conducted on A. halimus have reported their various pharmacological properties, including antidiuretic, antidiabetic, antioxidant, laxative, and anti-inflammatory (Azzi et al., 2012; Gattouche et al., 2020; Ounaissia et al., 2020; Slama et al., 2020; Souad et al., 2019) as well as anti-multidrug and antileishmanial effects (Kabbash and Shoeib, 2012). These activities are mainly due to its richness in secondary metabolites such as flavonoids, which may be responsible for antioxidant activity, and flavonoid glycosides, which have an antidiabetic property and reduce blood glucose levels (Ali et al., 2021).

Furthermore, other studies on this plant's extracts have found that its crude extract has an antiproliferative effect in a wide range of tumors, including lung cancer (A549), hepatocellular and prostate cancers (HepG2, PC3), with no toxicity to normal or healthy cells (Al-Senosy et al., 2018; El-Aasr et al., 2016). Moreover, extracts of the aerial parts, especially obtained with methanol or hexane, showed anti-bacterial activity against some pathogenic microorganisms, including gram-positive and negative pathogenic bacteria (Walker et al., 2014).

Besides, extracts obtained with butanolic and ethyl-acetate have antioxidant activity (Ali et al., 2021). Although chloroform and ethyl acetate fractions obtained from the crude root extract show inhibitory activity against acetylcholinesterase (ACe) with an inhibition rate of (74.60%, 65.08%) at a dose of 125 µg mL–1 (Mohammedi, 2016). In addition, flavonoid glycosides found in various extracts have anti-hyperthyroid activity due to their ability to inhibit thyroid hormone synthesis by acting as alternative substrates for thyroperoxidase, a key enzyme in thyroid hormone biosynthesis (Taïbi et al., 2020).

2.2. *Bunium incrassatum* Amo.

- **Characterization and geographic distribution**

Bunium incrassatum, commonly called "Talghouda", is one of the aromatic medicinal plants distributed in the north and the east of Algeria (Bousetla et al., 2015; Chentouh et al., 2017). It is a geophyte belonging to Apiaceae family present as tubers with black, scaly bark (Battandier and Trabut, 1888).

Figure 4. *Bunium incrassatum* (Aiouaz et al., 2022).

- **Ethno-medicinal uses**

This species is an important economic source widely used in food and traditional medicine, whose roots have great nutritional value as it is usually consumed as a potato or eaten raw (Bousetla et al., 2015). For a long time, it has been used as a galactagogue to promote breast milk production and increase farm animal weight (Chentouh et al., 2017; Hammoudi et al., 2020).

In indigenous medicine, their dried and powdered tubers are recommended to treat various diseases such as inflammatory hemorrhoids, coughs, bronchitis as well as astringent and antidiarrheic (Bousetla et al., 2015; Chentouh et al., 2017). Whereas, essential oils and seeds are used in food and medicine all over the world (Jassbi et al., 2005). In Algeria, especially during French colonization, it was consumed as a flour and couscous by drying and grinding the harvested tubers to avoid starvation. Curently, several traditional healers claim that this plant treats hypo and hyperthyroidism (Taïbi et al., 2021).

- **Phytochemical composition**

Until this day, data on secondary metabolites of B. incrassatum and its therapeutic uses are still insufficient in Algeria and worldwide, except for a few studies that have explored the chemical compositions and phytochemical compounds of this species. These studies include an investigation performed by Bousetla et al. (2015) on the roots of *B. incrassatum* that demonstrated the presence of several bioactive components such as sucrose, oleic acid, scopoletin, scoparone, and β –sitosterol.

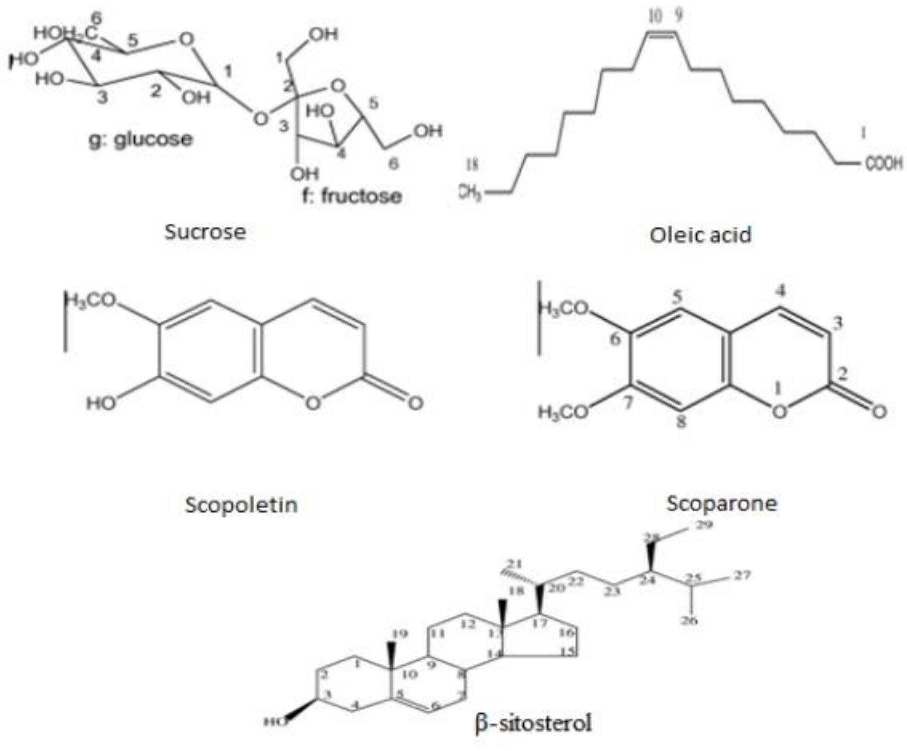


Figure 5. Chemical structure of compounds isolated from *B. incrassatum* roots (Bousetla et al., 2015).

Moreover, another work conducted on the evaluation of the chemical composition of essential oils obtained by the hydrodistilation of different parts of this species, whose analysis using GC and GC/MS revealed the presence of 40 constituents (85.2%) in fruit-bearing branches, 28 components (81.4%) in ground fruit oil, 24 compounds (75.4%) in thickened branches

(Bousetla et al., 2014), and 31 constituents (97.19%) in aerial parts where the abundant elements were terpens and their derivatives, and the main component was palmitic acid (18.39%) (El Kolli et al., 2017).

Table 2. Composition of the main constituents of essential oils in the fruits and branches of *B. incrassatum* (Bousetla et al., 2014).

Plant parts	Composition	Amount (%)
Ground fruit	Caryophyllene oxide	31.0
	(Z)-β –farnesene	8.7
	β-caryophyllene	7.2
	Germacrene B	5.8
Fruit-bearing branches	Caryophyllene oxide	26.8
	Nonacosane	11.6
	Germacrene B	7.7
	β-caryophyllene	5.8
	(Z)-β –farnesene	5.1
	Caryophyllenol II	4.8
	Spathulenol	2.5
	Nonacosane	44.7
	Spathulenol	5.3
	Eudesm-4(15),7-dien-1 β-ol	4.4
Thickened branches	Caryophyllenol II	4.1
	(Z)-β-farnesene	2.3
	Germacrene B	1.2
	β-caryophyllene	1.0

In addition to studies where phytochemical screening is also conducted on different extracts, whose results have shown that this species contains several bioactive substances such as flavonoids, tannins, terpenoids, and quinones (Dehimi et al., 2021).

- **Therapeutic properties**

Based on the literature, this plant is very rich in bioactive substances including essential oils. This richness is responsible for their various therapeutic purposes including antimicrobial activity present in their crude extract (Bousetla et al., 2015). Besides, antibacterial, anti-hemolytic, anti-inflammatory, and antioxidant effects found in essential oils and methanolic extracts of its aerial parts (El Kolli et al., 2017).

Moreover, estrogenic and hypoglycemic properties offered by organic extract prepared from its roots, which can be used for both nutritional and therapeutic purposes with a daily intake of up to 100 mg/kg (Chentouh et al., 2017; Hammoudi et al., 2020).

Furthermore, anti-radical and anti-hemolytic agents exhibited by acetonic and ethanolic extracts from tubers. these latter could be due to the presence of different classes of phenolic compounds like antihemolytic properties, which have returned to tannins and flavonoids, which stabilize red blood cell membrane lysis in hypotonic medium, and antioxidant activity, which is due to the presence of certain components such as carvacrol and thymol (Berroukeche et al., 2022).

2.3. *Echinops spinosus* L.

- **Characterization and geographic distribution**

Echinops spinosus L., commonly known as 'Taskra', is a medicinal plant with variable morphology belonging to the Astraceae family. It is a perennial herb, that can reach 1 m or more, widely distributed in the Mediterranean basin and North Africa (ressources, 2005; Sanchez-Jimenez et al., 2012). In Algeria, it is very popular in the Algerian Sahara and it grows in desert conditions where rainfall ranges from 20 to 100 mm/year. In general, it is characterized by its high tolerance to drought. Besides, it has a wide ecological range for the soil as it is divided into two subspecies: ssp. bovei (Boiss.) Mayorand and ssp. EU. Spinosus (Bouzabata et al., 2018; Helal et al., 2020; Ozenda, 1991).

Figure 6. *Echinops spinosus* L. (Ressources, 2005).

- **Ethno-medicinal uses**

This species is a popular medicinal plant whose roots, stems, and leaves are widely used as diuretics (Hegazy et al., 2019). For thousands of years, it has been used to treat several ailments such as migraines, diarrhea, cardiovascular disorders, intestinal worms (Khedher et al., 2021), spleen disease, and sore throats (Bouattour et al., 2016; Tsafantakis et al., 2019). In folk medicine, it is indicated for diabetes, indigestion, gastric disorders, sposmolytic problems, and even as an abortifacient (Khedher et al., 2014).

Traditionally, their leaves are recommended to treat respiratory disorders (Abdallah Emad et al., 2013), dermal problems, inflammation of the urinary tract and as an antifungal (Mothana et al., 2011). Their flowers are mentioned for chest pain, infections, intestinal worms, and hemorrhoids (Bouattour et al., 2017). Moreover, in Algeria, their roots and their flowers treat prostatism and dysmenorrhea (Bouzabata et al., 2018).

- **Phytochemical composition**

Based on the literature, *E. spinosus* is considered as a great source of bioactive substances. Qualitative phytochemical screening carried out on its extracts demonstrated the presence of alkaloids, reducing sugars, flavonoids, tannins and other phenolic compounds (Gheffour et al., 2015). Besides that, other investigations from North Africa have reported that this species contains 11.3% alkaloids along with a large number of active compounds such as thiophenes and terpenes, among them taraxasterile acetate, echinopins A and B, lupeol, stigmasterol-β-D-glucoside and β-sitosterol-β-D-glucoside (Bouattour et al., 2016; Khedher et al., 2021).

Moreover, nine triterpenoids have also been revealed from their aerial parts, including four types of taraxastane, three types of lupane, one type of oleanane, and one phytosterol, whose structures were clarified using NMR and HRMS spectra data analysis (Tsafantakis et al., 2019).

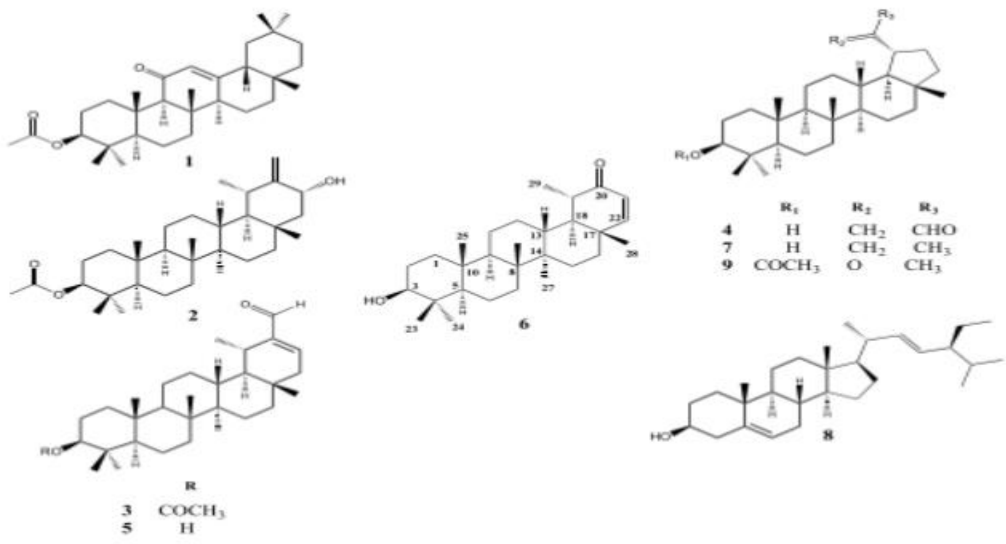


Figure 7. Triterpenoids isolated from *E. spinosus* (Tsafantakis et al., 2019).

In addition, twenty-two different types of flavonoids, including hespirtin and hespiridine, were found in the aerial parts of *E. spinosus* from Algeria and Egypt, along with 42 other compounds that were recovered from this species (Bouzabata et al., 2018; Othman et al., 2022).

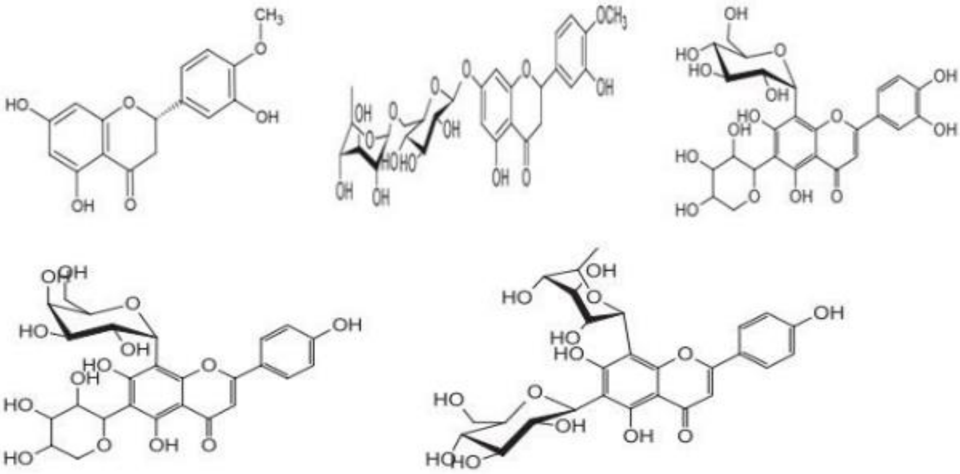


Figure 8. Chemical structure of the major elements isolated from the flavonoids of *E. spinosus* (Bouzabata et al., 2018).

Furthermore, twenty compounds (97.47%) present in essential oils extracted from their roots were also identified using GC-MS, GC-FID methods, whose major elements are reported in the following table (Yahyaoui et al., 2018).

Table 3. Composition of the main essential oil constituents present in the roots of *E. spinosus*.

Plant parts	Composition	Amount (%)
Roots	**Sesquiterpenoids**	**42.245**
	γ-Cadinene	27.224
	Caryophyllene oxide	5.217
	β-caryophyllene	2.736
	Thiophenes	**39.358**
	5-(3-buten-1-ynyl)-2,2’-bithienyl	21.334
	2,2’,5’,2’’-Terthiophene	18.024
	Monoterpenoids	**4.005**
	α- Pinene	1.532
	Camphor	0.862
	Others	**11.862**

- **Therapeutic properties**

This great source of organic compounds covers a large number of pharmacological properties which have health benefits such as antioxidant, hypoglycemic, anti-inflammatory, and antiapoptotic activities present in its methanolic extracts. These activities can protect cells from oxidative stress, regulate blood glucose levels, decrease inflammation, and inhibit the apoptotic cascade (Othman et al., 2022).

Other properties have also been demonstrated, like the antibacterial effect of acetylated terpenoids and sterols found in hexane extracts of its flowers, which are very effective against bacteria (Bouattour et al., 2016).

In addition to antioxidants and antimicrobial agents exhibited by organic extracts and essential oils of its roots (Khedher et al., 2021; Yahyaoui et al., 2018), as well as cholesterol-lowering activity offered by different extracts prepared from its flowers, which is generally due to the antioxidant effect and its different bioactive molecules (Frikha-Dammak et al., 2020).

3. Methodology

3.1. Plant material

The medicinal plants used in this study were purchased from an herbalist in the region of Tiaret in December 2020. The botanical identification was performed by Prof. TAIBI Khaled from Ibn Khaldoun University, Tiaret. The choice of plant parts used in this study was based on our previous finding regarding their uses in traditional medicines in the region of Tiaret (Algeria), i.e., the aerial parts of *Atriplex halimus* L., tubers of *Bunium incrassatum* Amo, and roots of *Echinops spinosus* L.

3.2. Preparation of extracts

The plants are first cleared from all impurities, cleaned and washed with tap water then with distilled water, and finally left to dry in shade at room temperature. Dried plants are ground in an electric mill until obtaining a fine powder, which is stored in clean glass jars and kept away from light. Later, 30 g of the resulting plant powder is placed in a glass flask containing 300 ml of distilled water.

The mixture is left to macerate with stirring, at room temperature, and in the dark. After 24 hours, the extract is filtered using Whatman paper and the obtained filtrate is dehydrated in an incubator at 40°C to obtain a dry residue, which is kept in clean boxes and stored in a refrigerator at 4°C until use (Berrabah et al., 2019).

3.3. Extraction yield

Extraction yield (EY) is estimated by calculating the ratio between the obtained and the initial mass used for the extraction in grams (Meharie and Tunta, 2020). It is expressed as a percentage according to the equation:

$$EY(\%) = \frac{\text{Obtained mass}}{\text{Initial mass used}} \text{ x } 100$$

3.4. Antioxidant activity

3.4.1. DPPH free radical scavenging activity

DPPH (2,2-diphenyl-1-picrylhydrazyl) is a purple stable free radical with an absorbance maximum of 517. This DPPH radical may receive electrons from compounds that are antioxidants. In this case, the radical solution in the presence of an electron donor loses its intensity and turns yellow, depending on the number of electrons obtained (Moon and Shibamoto, 2009).

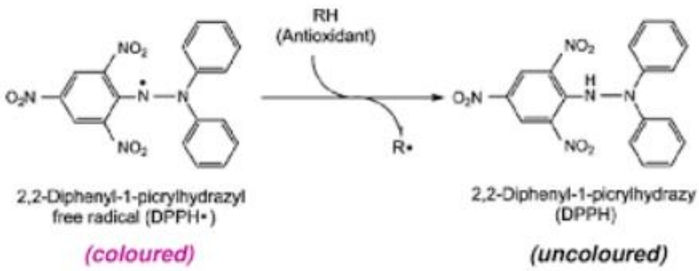


Figure 9. Reaction between an antioxidant and the DPPH free radical (Moon and Shibamoto, 2009).

Therefore, radical scavenging activity was assessed by measuring the antioxidants' reducing capacity toward DPPH radical (Ait Abderrahim et al., 2019). Briefly, 1 mL of aqueous extracts at different concentrations was added to 5 mL of a methanolic solution of DPPH (4 mg/L). The mixture was incubated for 30 minutes at room temperature, and the absorbance was measured spectrophotometrically at 517 nm. Ascorbic acid was used as a positive control.

The determination of radical scavenging activity of the tested extracts is evaluated in two ways:

The first step entails creating a calibration curve using ascorbic acid as a reference antioxidant. The results are expressed in mg of equivalent ascorbic acid per gram of extracts (AAE/g).

The second step entails calculating the IC50 (concentration inhibiting 50%), which refers to the amount of an antioxidant necessary to reduce 50% of the free radicals DPPH (Benhammou et al., 2009). The obtained results for each of the tested extracts are compared with those obtained for ascorbic acid, which is a standard antioxidant. Radical scavenging activity is calculated using the formula described below. The IC50 is determined by plotting the concentrations of the tested extracts and ascorbic acid according to the percentages of inhibited DPPH.

$$RSA\ (\%) = [(Control\ abs - Extract\ abs)\ /Control\ abs]\ X\ 100$$

Where:

RSA (%) : radical scavenging activity percentage

Control abs: absorbance of the control (DPPH solution without extract).

Extract abs: absorbance of the tested extract.

3.4.2. Ferric Reducing Antioxidant Potency (FRAP)

The FRAP is a method based on the reduction of ferric ions Fe^{+3}into ferrous ions Fe^{+2} by an antioxidant in an acidic environment, resulting in a blue color detected at 593 nm (Moon and Shibamoto, 2009).

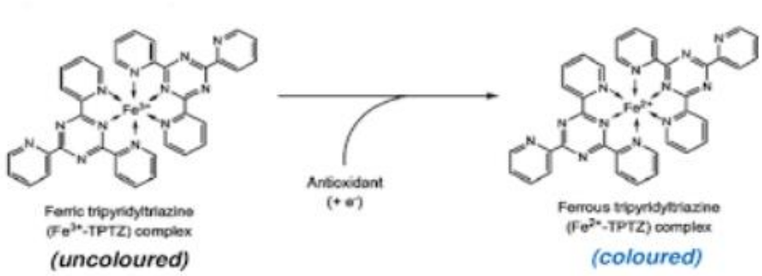


Figure 10. Reduction of Fe3+ into Fe2+ by an antioxidant (Moon and Shibamoto, 2009).

The reducing power was determined following the method described by Benhammou et al. (2009). Briefly, Briefly, 0.5 ml of aqueous extracts were mixed with 1.25 ml of each phosphate buffer solution (0.2 M, pH 6.6) and potassium ferricyanide (1%). The obtained mixture was incubated for 20 minutes at 50°C and 1.25 ml of 10% trichloroacetic acid was added followed by centrifugation at 3000 rpm for 10 minutes.

Afterward, 1.25 ml of the supernatant was added to 1.25 ml of distilled water and 250 µL of ferric chloride ($FeCl_3$, 6 H_2O, 0.1%), and the absorbance was measured against a blank at 700 nm. Each experiment was performed in triplicate. Ascorbic acid prepared under the same conditions was used as a positive control. Increased absorbance values indicate potent reducing power.

3.5. Phytochemical analysis

The choice of phytochemicals to be analysed is based on their predominance in aromatic and medicinal plants.

3.5.1. Phytochemical screening of the tested plant extracts

The aqueous extracts of the studied plants were tested for the presence of bioactive compounds and the results are expressed as (+) for their presence and (-) for their absence.

- **Tannins**

1 ml of aqueous extract was added to 1 ml of ferric chloride reagent ($FeCl_3$, 1%). The formation of a blueish-black or brownish-green color indicated the presence of tannins (Gheffour et al., 2015).

- **Flavonoids**

On a steam bath, 0.5 g of extracts were added to 10 mL distilled water. The filtrate was treated with a few drops of sodium hydroxide solution (20%). The appearance of a yellow coloration indicated the presence of flavonoids (Meharie and Tunta, 2020).

- **Steroids**

0.5 g of the extracts were mixed with 3 ml of chloroform. After filtration, 2 ml of concentrated H_2SO_4 was carefully added to form the lower layer. The appearance of a reddish-brown ring indicates the presence of terpenoids and steroids (Aiyegoro and Okoh, 2010).

- **Alkaloids**

0.5 g of extracts were mixed with 5 ml of HCl (1%) in a steam bath. After 5 minutes, 1 ml of the filtrate was treated with a few drops of Wagner's reagent. The formation of an orange-brown precipitate indicates the presence of alkaloids (Ghosh et al., 2018).

- **Saponins**

The extract was diluted with 3 ml of distilled water. The mixtures were shaken vigorously in a water bath. The formation of a persistent stable foam indicated the presence of saponins (Kalita et al., 2011).

- **Terpenoids**

0.5 g of extract was added to 2 ml of chloroform, followed by 2 ml of concentrated H_2SO_4. The formation of a reddish-brown color indicates the presence of terpenoids (Iqbal et al., 2015).

3.5.2. Quantification of total phenolic content

The dosage of polyphenols was determined according to the method described by Ait Abderrahim et al. (2019) using the Folin-Ciocalteu reagent, which is a yellow mixture composed of two acids phosphor-tungstic acid and phosphomolybdic acid. This reagent is reduced during the oxidation of phenols into a mixture of blue oxides, where the colour intensity is proportionally linked to the quantity of polyphenols present in the extract (Singleton et al., 1965)

This method consists of mixing 100 µl of the aqueous extract (1 mg/ml) with 1,5 ml of Folin-Ciocalteu reagent diluted 14 times in distilled water (1:14). After 3 minutes, 0.4 ml of 20%

sodium carbonate solution (Na_2CO_3) was added. The mixture obtained was kept in the dark for 30 minutes at room temperature.

The absorbance was then measured using a UV-Visible spectrophotometer at 760 nm against a blank already prepared beforehand by replacing the tested extract with distilled water. A standard calibration curve is produced in parallel under the same operating conditions using gallic acid as a positive control at different concentrations (12.5 to 400 ug/ml). Each measurement is performed in triplicate. The obtained results are expressed as mg of gallic acid equivalent per gram of extracts (mg GAE/g).

3.5.3. Quantification of total flavonoid content

Total flavonoid content was determined using the aluminium chloride colorimetric method described by Berrabah et al. (2019). Briefly, 1 mL of the aqueous extract at a concentration (1 mg/mL) was added to 1 mL of 2% methanol $AlCl_3$. The obtained mixture was kept in the dark for 15 minutes at room temperature. The absorbance was read using a UV-Visible spectrophotometer at 430 nm against a blank already prepared beforehand by replacing the tested extract with distilled water.

A standard calibration curve is produced under the same conditions using quercetin as a positive control at different concentrations. Each measurement is performed in triplicate. The total flavonoid content is calculated from the calibration curve and the results are expressed as mg quercetin equivalent per gram of weight of extracts (mg QE/g).

3.5.4. Quantification of total tannins content

The total tannins content was evaluated following the method used by (Meharie and Tunta, 2020). Briefly, 0.1 mL of the aqueous extracts were mixed with of Folin-Ciocalteu reagent (0.5 mL). Then, 1 ml of 35% of sodium carbonate solution was added. The obtained mixture was diluted to 10 ml and kept in the dark for 30 minutes.

The absorbance was then measured at 700 nm against a blank. A calibration curve using tannic acid as a standard is plotted. Each measurement is performed in triplicate. The tannin content is expressed in mg of tannic acid equivalent per gram of extracts (mg TAE/g).

3.6. Statistical analysis

The experiments were repeated at least three times. The collected data were subjected to a one-way analysis of variance in order to determine the variation between the different tested extracts. The comparison between the samples was performed using Duncan's test. The correlation based on the coefficient of Pearson has also been applied to establish possible links between the antioxidant activity of the tested plant extracts and their content in phenolic compounds. Significant differences between all means were determined on the scale of $P<0.05$. Results were plotted as the mean ± standard deviation.

4. Results

4.1. Extraction yield

The yield of extracts (Fig. 11) from the studied plants is presented in table 4. The higher yield is observed in *A. halimus* extract (25.13%), while the lowest is reported in *E. spinosus* extract (5.46%).

Table 4. Yield of the tested plants extracts.

Extracts	**Yield %**
A. halimus	25.13
B. incrassatum	13.33
E. spinosus	5.46

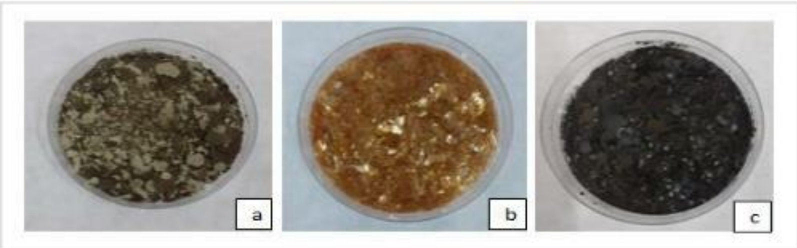


Figure 11. Extracts of tested plants: (a) *A. halimus*, (b) *B. incrassatum*, (c) *E. spinosus*.

4.2. Evaluation of the antioxidant activity

4.2.1. DPPH free radical scavenging activity

The anti-radical activity reflected by the reduction of DPPH free radicals is expressed both in concentration inhibiting 50% of the radicals (IC_{50}) as well as in mg equivalent of ascorbic acid.

- **DPPH IC_{50}**

The reducing ability was evaluated by measuring the loss of the purple-colored solution of DPPH radical. The color intensity and the antioxidant concentration are inversely correlated. The results are expressed in IC_{50}, which is the sample concentration that causes 50% inhibition of the DPPH radicals.

The difference in the inhibition concentration (IC_{50}) of DPPH radicals is highly significant between all the investigated samples ($P<0.001$**).

Table 5. One-way analysis of variance of variability of DPPH IC_{50} variation of tested plants.

Source of variation	SS	df	MS	F	Significance
Corrected model	83.721	3	27.907	16.471	0.001**
Error	13.554	8	1.694		
Total	287.649	12			

The asterisks (*) indicate significant differences while ns: non-significant differences.

In this context, the antioxidant activity of a compound is considered even higher when its IC_{50} is low. As a result, ascorbic acid demonstrates the highest antiradical activity with the lower IC_{50} (0.25±0.013 mg/ml). Moreover, the aqueous extract of *B. incrassatum* shows high antiradical activity ($P<0.001$***) with an IC_{50} value of 2.73±0.15 mg/ml when compared with the aqueous extracts of *A. halimus* and *E. spinosus* that show no significant difference between their IC_{50}s (6.24±0.74 and 6.69±2.48, respectively).

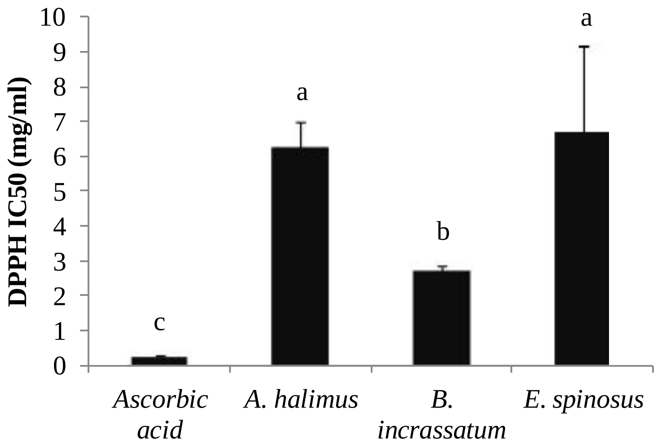


Figure 12. Inhibition concentrations (IC_{50}) of the DPPH radicals of the tested plant extracts.

- **Ascorbic acid equivalent**

Data analysis regarding the ascorbic acid equivalent of the tested plant extracts reveals that there is no significant difference ($P>0.05$) between them (Fig. 13).

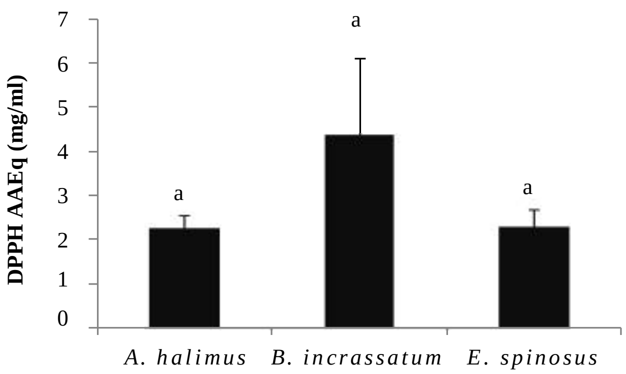


Figure 13. The variation in the content expressed in ascorbic acid equivalent of plant extracts.

Table 6. One-way analysis of variance of the variation of the contents of the examined samples expressed as ascorbic acid equivalents.

Source of variation	SS	df	MS	F	Significance
Corrected model	8,647	2	4.324	3.789	0.086ns
Error	6.847	6	1.141		
Total	95.120	9			

The asterisks (*) indicate significant differences while ns: non-significant differences.

4.2.2. Ferric Reducing Antioxidant Potency (FRAP)

- **FRAP EC_{50}**

The FRAP method is a simple test that makes it possible to evaluate the reducing power of a sample by causing the reduction of ferric iron to ferrous iron. This reducing power is expressed by EC_{50} (effective concentration 50%), which designates the effective concentration of a sample necessary to reduce 50% of the ions.

There is a substantial difference (P<0.0***) between all tested samples in the effective concentration (EC_{50}) of the reducing power of the tested plant extracts.

Table 7. One-way analysis of the variance of the effective concentration difference (EC_{50}) of the reducing power.

Source of variation	SS	df	MS	F	Significance
Corrected model	60.588	3	20.196	113.812	0.0***
Error	1.420	8	0.177		
Total	176.795	12			

The asterisks (*) indicate significant differences while ns: non-significant differences.

The reducing capacity of a sample is considered very important when its EC_{50} is lower. As a result, ascorbic acid has the highest power-reducing with an EC_{50} of 0.162±0.003 mg/ml. The extract of *E. spinosus* exhibited the highest reducing capacity when compared to the other extracts, with an EC_{50} of 2.18±0.13 mg/ml followed by *B. incrassatum* extract with an EC_{50} of 3.70±0.18 mg/ml and *A. halimus* extract showing the lower ferric reducing power (EC_{50}=6.31±0.81 mg/ml).

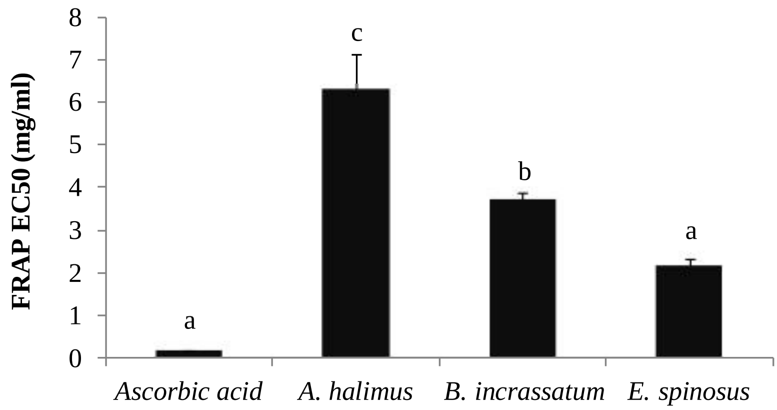


Figure 14. Effective concentration (EC_{50}) of the reducing power of the tested extracts.

4.3. Phytochemical screening of the tested plant extracts

The aqueous extracts of different parts of the studied plants were tested for the presence of bioactive molecules. As shown in Table 8, all the tested plant extracts were rich for tannins, flavonoids, steroids, alkaloids, and terpenoids but without saponins.

Table 8. Phytochemical screening of the tested plants extracts.

Active compounds	*A. halimus*	*B. incrassatum*	*E. spinosus*
Tannins	+	+	+
Flavonoids	+	+	+
Steroids	+	+	+
Alkaloids	+	+	+
Terpenoids	+	+	+
Saponins	-	-	-

(+): presence, (-): absence.

4.4. Quantification of secondary metabolites

4.4.1. Total phenolic content

Statistical analysis of the data shows that there is a significant difference in the total phenolic content among the examined plants extracts (P<0.0***) (Table 9).

Table 9. One-way analysis of variance of variability of polyphenol content among the tested extracts.

Source of variation	SS	df	MS	F	Significance
Corrected model	2847.056	2	1423.528	254.012	0.0***
Error	33.625	6	5.604		
Total	17300.688	9			

The asterisks (*) indicate significant differences while ns: non-significant differences.

The higher value is recorded by *E. spinosus* extract with a content of 65.08±1.44 (mg GAE/g), whereas the lower values are recorded by *B. incrassatum* and *A. halimus* extracts with respective contents of 29.41±3.76 and 25.58±0.76 mg GAE/g (P > 0.05).

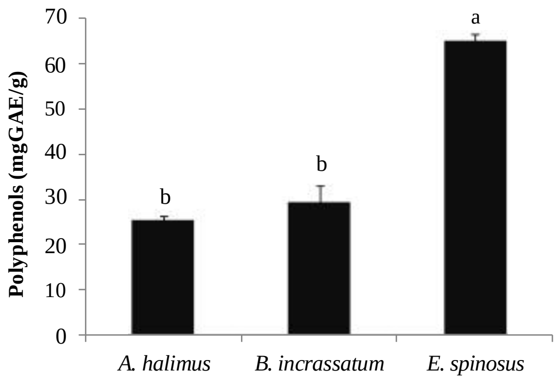


Figure 15. Total polyphenol content of the tested plants extracts.

4.4.2. Total flavonoid content

The analysis of variance indicates significant difference regarding the flavonoid contents between the tested extracts (P<0.0***).

Table 10. One-way analysis of variance of variability of flavonoid content among the tested extracts.

Source of variation	SS	Df	MS	F	Significance
Corrected model	637.407	2	318.704	672.986	0.0***
Error	2.841	6	0.474		
Total	1380.996	9			

The asterisks (*) indicate significant differences, while ns: non-significant differences.

The obtained results demonstrate that the extract of *E. spinosus* presents the highest content (20.97±0.84 mg QE/g), which differs significantly (P<0.001) from the extracts of *A. halimus* and *B. incrassatum* (3.2±0.47 mg QE/g and 3.03±0.68 mg QE/g, respectively (P>0.05)).

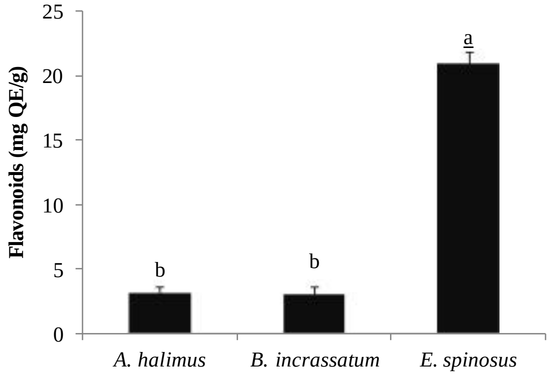


Figure 16. Flavonoid content of the tested plants extracts.

4.4.3. Total tannins content

The analysis of variance of total tannins content reveals that there is a significant difference between the tested extracts (P<0.0***).

Table 11. One-way analysis of variance of variability of tannins content among the tested extracts.

Source of variation	SS	Df	MS	F	Significance
Corrected model	2502.889	2	1251.444	139.049	0.0***
Error	54.000	6	9.000		
Total	5844.000	9			

The asterisks (*) indicate significant differences while ns: non-significant differences.

The extract of *E. spinosus* has the highest total tannins content (42.66±4.93 mg TAE/g) compared with *A. halimus* and *B. incrassatum* (6.33±0.57 and 8.33±1.52 mg TAE/g respectively (P>0.05)).

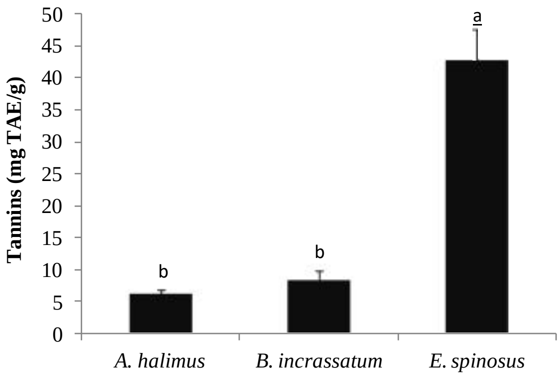


Figure 17. Total tannins content of the tested extracts.

5. Discussion

Since antiquity, people have used plants worldwide for various purposes, particularly as food for nutrition and as medicine for the prevention and treatment of various diseases in both humans and animals (Mensah et al., 2019). Due to their potential use as a source of biologically active substances and potential role in the prevention and treatment of diseases, natural products, and healthy foods are receiving more attention in research (Berrabah et al., 2019). For this reason, this study aims to evaluate the antioxidant activity as well as to quantify the secondary metabolites of interest i.e., polyphenols, flavonoids, and tannins of *A. halimus*, *B. incrassatum,* and *E. spinosus* in order to valorise the use of these plants in the traditional medicine and the development and synthesis of new drugs.

The extraction of metabolites was carried out using distilled water. This choice is justified by the fact that the aqueous extract is the most used by the local population in its traditional practices due to its safety and usefulness (Pastori et al., 2013). The highest yield was obtained from *A. halimus* followed by *B. incrassatum* then *E. spinosus*. Unfortunately, it is difficult to compare the obtained results with those in the literature since the yield depends on the chemical composition of the plants, the extraction processes applied such as the temperature, the extraction time, and pH, as well as the polarity of the solvents used (Toul et al., 2022).

Regarding the antioxidant activity of the investigated plant extracts, it should be noted that the measurement of the potent antioxidants of the plant extracts must be carried out using several tests based on different mechanisms in order to avoid the test can reveal chemical reactivity only under the particular conditions applied to it (Dehimi et al., 2021). Therefore, two methods were used DPPH and FRAP assays.

The DPPH assay is a popular test due to its ease, high sensitivity, reproducibility, and simplicity. The obtained results revealed that all the tested extracts have potential antioxidant activity which is significantly high in *B. incrassatum* extract. According to Benrahou et al. (2022), the interaction between the antioxidants and DPPH radical is mainly related to the hydroxyl group responsible for this activity, which suggests that the antiradical activity of the tested extracts can be attributed to its abundance in molecules containing a hydroxyl group. These findings have already been confirmed by Dehimi et al. (2021) who reported that the aqueous extract of *A. halimus* has an antioxidant activity with an IC_{50} value of 22.11 mg/ml. Additionally, Benhammou et al. (2009) mentioned that methanolic extract of *A. halimus* has an antiradical activity with IC_{50} of 31.83 and 20.58 mg/ml, respectively.

Likewise, Benrahou et al. (2022) reported high antiradical activity of the aqueous and ethanolic extracts of *E. spinosus* roots compared to the obtained results in our study, with a lower IC_{50} of (25±10.69 and 13±0.25 µg/mL, respectively). Furthermore, Khedher et al. (2014) reported that the ethanolic extract of *E. spinosus* offers a good ability to reduce DPPH radicals, whose IC_{50} value is 147 µg/mL.

Besides, Aiouaz et al. (2022) demonstrated that methanolic extract of *B. incrassatum* tubers exhibits potent antioxidant activity with a low IC_{50} value that does not exceed 1.60±0.002 mg/mL. In addition, Toul et al. (2022) demonstrated that the aqueous extract of *B. incrassatum* seeds has strong antiradical activity with an IC_{50} of 0.29±0.02 mg/ml.

The FRAP assay is a more accurate method to evaluate the antioxidant potential of plant foods. Results show that all the tested plant extracts have significant reducing effects. The highest reducing power is observed in the extract of *E. spinosus*. The extract of *B. incrassatum* has a moderate reducing capacity, while the extract of *A. halimus* offers a weak reducing capacity which is consistent with other studies.

Yahyaoui et al. (2018) demonstrated that the essential oil of *E. spinosus* roots exhibits a good reducing power with a value of 2.81 mg BHT/E. In addition, Benrahou et al. (2022) indicated that the aqueous and methanolic extracts of the roots of *E. spinosus* possess a reducing power (20.61±2.72 and 51.1±1.2 mg AAE/g, respectively). Furthermore, Slama et al. (2020) reported in their studies that the aqueous extract of *A. halimus* has a lower reducing power with an EC_{50} of 4.40±0.076 mg/ml, which was observed in our study. Moreover, the study conducted by Dehimi et al. (2021) stated that the reducing power of *A. halimus* and *B. incrassatum* extracts is linked to their content of polyphenols and their ability to donate electrons. Thus, the primary causes of this reducing power are flavonoids and phenolic compounds (Vuolo et al., 2019).

Benrahou et al. (2022) claim that several flavonoids acting as antioxidants have the ability to degrade deoxyribose, when reducing Fe^{+3} to Fe^{+2}. In general, the antioxidant activity is related to the presence of phenolic compounds, which are contained in plants extracts. According to Zeghib and Boutlelis (2021), polyphenols and flavonoids represent the most powerful antioxidants as they are considered good indicators of the antioxidant properties of plants. They serve as hydrogen or electron donors, absorb and neutralize free radicals, quench singlet and triplet oxygen, and chelate metal ions or break down peroxides (Berrabah et al., 2019).

In addition to the examined biological activities, a phytochemical screening with a quantification of the contents of secondary metabolites including polyphenols, flavonoids, and tannins was also performed. The phytochemical study revealed the presence of a wide range of bioactive compounds, namely flavonoids, tannins, terpenoids, alkaloids, and steroids. These findings supported studies performed by Zeghib and Boutlelis (2021) and

Chikhi et al. (2014), which reported the abundance of these bioactive compounds in *A. halimus* aqueous extracts. In addition, the study of Benhammou et al. (2009) demonstrated the richness of *A. halimus* methanolic extracts in secondary metabolites. Besides, only a few phytochemical investigations on *B. incrassatum* tubers have been conducted. Dehimi et al. (2021) reported the presence of phenolic compounds, alkaloids, terpenoids, and quinones, whereas Bousetla et al. (2015) reported the abundance of coumarins, β-sitosterol, sucrose, and oleic acid. In contrast, Gheffour et al. (2015) and Othman et al. (2022) reported the presence of these active substances in both the aqueous extract and the methanolic extract of *E. spinosus*. The absence of saponins in all tested aqueous extracts in this study corroborates some studies (Hegazy et al., 2019; Dehimi et al., 2021).

The obtained results show that there is a significant difference in polyphenol content between all the tested extracts. The highest content is recorded by the aqueous extract of *E. spinosus* roots, with appreciable amounts of 65.08±1.44 mg GAE/g.

This finding is consistent with previous studies of Benrahou et al. (2022) noting the richness of the aqueous and ethanolic extracts of *E. spinosus* roots in polyphenols with a content of 34±0.58 and 77.01±2.25 mg GEA/g, respectively. Dehimi et al. (2021) reported considerable amounts of polyphenols in the aqueous extract of *A. halimus* (28.10±9.66 µg GAE/mg E) and their low contents in the aqueous extract of *B. incrassatum* (06.92±0.00 µg GAE/mg E).

Furthermore, Zeghib and Boutlelis (2021) demonstrated that the polyphenol content found in *A. halimus* is close to that obtained in our study, with an amount of 17.183±0.06 mg GAE eq/g. Besides, Benhammou et al. (2009),Chikhi et al. (2014), and Slama et al. (2020) indicated the presence of polyphenols in *A. halimus* extract at different concentrations. Moreover, et al. (2017) revealed that the polyphenol content present in the methanolic extract prepared from the aerial part of *B. incrassatum* are higher than those found in roots, reaching up to 236.6 µg EQ/mg. In the same way, Toul et al. (2022) mentioned higher phenolic content in different extracts prepared from the seeds of *B. incrassatum*.

Flavonoids content was high in the extract of *E. spinosus* roots measuring 20.97±0.84 mg QE/g. This finding has been reported by Benrahou et al. (2022) signalling the presence of flavonoids in both aqueous and ethanolic extracts of *E. spinosus* roots with of 10.33±4.2 and 544.33±26.33 mg RE/g, respectively. Aiouaz et al. (2022) mentioned that the methanolic extracts of *B. incrassatum* contain a low content of flavonoids (2.36 ± 0.06 mg QE/g). Dehimi et al. (2021) reported high amounts of flavonoids compared to our results in both *A. halimus* and *B. incrassatum*, with 17.70±0.65 and 06.91±0.01 µg QE/mg, respectively. Furthermore, Zeghib and Boutlelis (2021) demonstrated that flavonoids content in *A. halimus* was 4.02±0.001 mg Qeq/g, which was close to the value recorded in our study.

E. spinosus root extract presented high amounts of tannins (42.66±4.93 mg TAE/g) comparing to *B. incrassatum* and *A. halimus*.

Tannins content present in the aqueous extract of *E. spinosus* roots and *A. halimus* reported by Benrahou et al. (2022) and Slama et al. (2020) are close to the obtained values of our study, with concentrations of 42±13.3 mg CE/g and 7.56±0.21 mg EC/g, respectively. However, Dehimi et al. (2021) reported higher amount of tannins in *A. halimus* extract (32.30±0.97 µg TAE/mg) and lower amount in *B. incrassatum* (04.72±0.00 µg TAE/mg). Similarly, Toul et al. (2022) reported high condensed tannins content in the aqueous extract of *B. incrassatum* seeds with 30.24±1.83 mg TAE.

The difference in the concentration of phenolic compounds of the same species may be due to several factors, including climate, plant parts used, ecological conditions in which the plants grow, extraction methods, and agricultural practices (Bouaziz et al., 2021). According to Benhammou et al. (2009), genotypic factors that regulate partially the accumulation of these compounds in the plant may also have a role in the variations in phenol content within the same species. Hence, these factors also influence the distribution of secondary metabolites in the plant. In fact, our research demonstrates that the tested plants extracts are rich in polyphenols, flavonoids, and tannins.

General discussion

General discussion

Aromatic and medicinal plants are rich in various secondary metabolites with therapeutic potential such as alkaloids, phenolic compounds, and terpenoids, which can act individually, additively, or synergistically to reduce an effect and can have beneficial or toxic effects on human health (Mensah et al., 2019).

Since time immemorial, people have used them to treat a variety of ailments. Several plant parts have been reported to be useful in treating a variety of ailments, including parasite infections, sleeping sickness, wounds, diarrhea, reproductive and liver issues, circulatory disorders, respiratory problems, and reproductive disorders (Owolarafe et al., 2020). This herbal medicine, which is used in all cultures worldwide, constitutes an integral part of the population's information that has evolved over millions of years and is passed down from one generation to another (Subramanian et al., 2018).

Algeria is home to thousands of interesting plant species. Their history spans several centuries and includes wars and colonization that led to the merging of several different civilizations, including Berber, Greco-Roman, Arab, Ottoman, and French (Taïbi et al., 2020). Additionally, Algerian people hold valuable knowledge on aromatic and medicinal plants uses in traditional practices for the treatment and management of various ailments (Azzi et al., 2012). This precious knowledge concerning the preparations and uses of medicinal plants differs significantly from one region to another within the same country (Taïbi et al., 2020). The present study has discovered 246 novel therapeutic uses and 107 plant species belonging to 45 families and 97 genera for the treatment of various diseases in the region of Tiaret, some of which are endemic, threatened, rare, or endangered. The most represented families are Lamiaceae, Apiaceae, and Asteraceae, and the most frequently cited species are *Senna alexandrina* Mill. (FC=27), *Atriplex halimus* L. and *Bunium incrassatum* Amo (FC=23 each), *Foeniculum vulgare* Mill. (FC=22), and *Matricaria chamomilla* L. (FC=21).

Interestingly, *Bunium incrassatum* Amo and *Echinops spinosus* L. are among the plants cited for the first time as medicinal plants in Algeria. This potential use of medicinal plants is mainly in national primary health care programs due to several factors, namely their accessibility, availability, and reasonable prices, as they are considered to be much safer than modern synthetic drugs (Dar et al., 2017).

It should be noted that the choice of plant species, to be studied for their antioxidant activity and phytochemical contents along with the study of their toxicity at the cellular and genetic levels, is based on the ethnopharmacological studies conducted in the region of Tiaret, which reported that *A. halimus* and *B. incrassatum* are among the most cited species, as well as that *E. spinosus* and *B. incrassatum* are reported for the first time as medicinal plants in Algeria, which requires more studies to identify their active compounds responsible for their biological activities, including antioxidant activity.

Our previous studies on medicinal plants have shown that biological activities are significantly related to their bioactive substances (Aït Abderrahim et al., 2019; Berrabah et al., 2019). The present study reported the antioxidant activity and the total polyphenol, flavonoid, and tannin content of the aqueous extracts of *A. halimus*, *B. incrassatum*, and *E. spinosus*, and the results show that *B. incrassatum* and *E. spinosus* extracts have stronger antioxidant activities compared to *A. halimus* extracts. Due to their chemical diversity, diverse biological activities, and medicinal properties, they will be used indefinitely to meet primary health needs and develop candidate drugs for the treatment of human diseases, particularly difficult-to-treat diseases (Yuan et al., 2016). This is why their importance has increased significantly, and they have become one of the most important resources in the healthcare system (Jain et al., 2019). Likewise, *E. spinosus* has high content of phenolic compounds when compared with the other extracts. This finding corroborates those of previous research of Benrahou et al. (2022), Dehimi et al. (2021), and Zeghib and Boutlelis (2021).

Despite all the beneficial effects of aromatic and medicinal plants, their use can be harmful due to their constituents, which can be toxic, causing adverse effects and threatening human health, resulting in acute toxicity and the death of patients (Anywar et al., 2021). Various problems, such as gastrointestinal disorders, allergic reactions, organ damage, hemolysis, and carcinogenicity, have been associated with plant toxicity (Ihegboro et al., 2020). Additionally, it is noted that the absence of clear toxic effects when using medicinal plants does not mean that they are totally safe because only acute and serious adverse effects can be recognized (Aydın et al., 2016). Moreover, it is through traditional medicine that we can discover toxic medicinal herbs because it helps to assess the risks of possible systemic toxicity (Mensah et al., 2019). Numerous investigations have demonstrated the mutagenic, cytotoxic, and genotoxic effects of several plants used as food or in traditional medicine when tested *in vitro* and *in vivo,* where several of their substances are found to be toxic and have been linked to a high rate of tumor development in some human populations (Okorie Asita et al., 2017). Therefore, it is necessary to evaluate the cytotoxic effect of traditional medicinal plants using cytotoxic and genotoxic studies, which constitute a crucial means used in drug synthesis and development for the evaluation of the biosafety characteristics of medicinal plants and their bioactive compounds (Ihegboro et al., 2020).

In the present studies, the cytotoxic and genotoxic effects of aqueous extracts of some aromatic and medicinal plants commonly used in Algerian traditional medicine, namely *A. halimus*, *B. incrassatum*, and *E. spinosus*, are tested using both hemolytic activity and the *Allium cepa* test, which are considered excellent *in vitro* and *in vivo* models. The first is based on the use of erythrocytes, which are the main medium because their membrane has similarities with other cell membranes (Wadhwa et al., 2019) and the second allows for the prediction of potential DNA damage to eukaryotes because the roots grow in close contact with the tested substance (Owolarafe et al., 2020).

The results show that all the tested plant extracts exhibited low hemolytic activity but accompanied by a mitodepressive and genotoxic effects. Several chromosomal aberrations have been identified, namely disturbances, stickiness, c-metaphase, vagrant chromosomes, bridges, micronuclei, polyploidy, micronuclei, binucleate. The percentage of chromosomal aberrations increases slightly when the concentration increases, and *A. halimus* extract exhibited a sublethal effect at concentrations equal or above 1 mg/ml compared to the other extracts. These cyto-genotoxic effects may be due to their richness in some molecules such as alkaloids, polyphenols, tannins, and sesquiterpenes, which can interfere with cell cycle components, leading to chromosomal damage.

Consequently, medicinal and aromatic plants used in traditional medicines could be toxic due to their inherent substances through inappropriate dosage and method of administration (Taïbi et al., 2020; Subramanian et al., 2018). Patients must have sufficient information about the use of medicinal plants, their traditional formulation, mode of administration, the appropriate dosage, and side effects (Mensah et al., 2019). Besides, the use of medicinal and aromatic plants must be recommended by professional and experienced healers; thus, care must be taken when consuming them; a suitable dosage must be used; the duration of treatment must be respected; and the best method of administration must be chosen (Aftab and Hakeem, 2021).

In this sense, toxicity testing at the cellular and molecular levels is more than necessary to evaluate the efficacy and safety of medicinal plants and their bioactive molecules. This will provide information on molecular bioactivity and their interactions with various target groups (Gurib-Fakim, 2006). Several parameters can be assessed to avoid any kind of toxicity, such as cell death, cell growth, proliferation, and replication as cytotoxicity endpoints, and chromosomal damage, gene mutations, and DNA strand breaks as genotoxicity endpoints (Liu et al., 2018; Aydın et al., 2016).

In general, ethnomedicine is of great interest as a natural therapeutic approach. Local pharmacopeia with national standardized guidelines for collection and use must be developed (Taïbi et al., 2020). More studies are necessary to safeguard the Algerian local pharmacopeia, to conserve cultural heritage, preserve biodiversity, respond to population health care needs, and provide a scientific basis for developing novel drugs (Djahafi et al., 2021). Besides, *in vitro* and *in vivo* studies are also essential to validate the popular uses of the cited medicinal and aromatic plant species and their preparations (Taïbi et al., 2021).

General conclusion

General conclusion

Algeria has a considerable and diverse floral wealth with many endemic and vulnerable species due to its geographical and climatic diversity. This flora is widely used in traditional medicine by local population and occupies a very important place from a socio-cultural and socio-economic point of view. Many local traditional practices have been developed due to the diverse civilizations, cultures, languages, and religious beliefs of this country, providing a great library of precious knowledge that has been passed down from generation to generation through millions of years. The use of aromatic and medicinal plants in phytotherapy has become so important in daily practices as well as receiving great interest in biomedical research since they constitute an inexhaustible source of secondary metabolites with a wide range of biological activities, making them the ideal candidates for the synthesis of novel all-natural medicines with no adverse effects.

Despite all the therapeutic benefits that aromatic and medicinal plants provide, some of them have been found to be toxic, endangering human health and potentially causing a number of ailments. The toxicity, mutagenicity, and carcinogenicity of medicinal plants need more toxicological research and exploration.

The present study aims to (i) identify aromatic and medicinal plants used in Algerian traditional medicine, in the region of Tiaret (northwest Algeria), in order to safeguard the local cultural heritage and national pharmacopoeia, then to (ii) assess the antioxidant activity, phytochemical profile, and safety of use of the main cited plants throughout cyto-genotoxicity analyses.

The ethnopharmacological study revealed the use of 107 plant species belonging to 45 families and 97 genera for the treatment of various diseases in the region of Tiaret, whose most represented families are the Lamiaceae, Apiaceae, and Asteraceae. Moreover, the most frequently cited species are *Senna alexandrina* Mill., *Atriplex halimus* L., *Bunium incrassatum* Amo, *Foeniculum vulgare* Mill. and *Matricaria chamomilla* L. However, the highest usage values are reported for *Nigella sativa* L., *Trigonella foenum-graecum* L., *Thymus serpyllum* L., *Ziziphus lotus* (L.) Lam., *Urtica dioica* L., and *Senna alexandrina* Mill. respectively. Interestingly, 246 new therapeutic uses have been reported.

It has been shown that *Pistacia atlantica* Desf., *Tetraclinis articulata* (Vahl) Mast., *Oudneya africana* R. Br., *Euphorbia guyoniana* Boiss. & Reut, *Teucrium polium* L., and *Marrubium deserti* (Noë) Coss. are endemic to North Africa-Algeria, Northern and Central Sahara. However, *Artemisia herba-alba* Asso, *Anacyclus pyrethrum* (L.) Lag., *Cuminum cyminum* L., *Saussurea costus* (Falc.) Lipsch., *Boswellia sacra* Flueck. and *P. atlantica* Desf. are threatened, rare, or endangered plant species, while, *B. incrassatum*, *Echinops spinosus*, *Cucurbita moschata* Duchesne, *Pennisetum glaucum* (L.) R.Br. are cited for the first time as medicinal plants in Algeria.

Subsequently, *A. halimus*, *B. incrassatum*, and *E. spinosus* were selected for the evaluation of antioxidant activity, phytochemical profile, and cyto-genotoxicity studies. The antioxidant activity was high in *B. incrassatum* and *E. spinosus* extracts than *A. halimus* extract. Nevertheless, the three tested plants constitute a rich source of secondary metabolites. Moreover, the tested plants extracts exhibited a low *in vitro* hemolytic activity. Analysis of the mitotic index demonstrated that the tested plants extracts do not exhibit lethal or sublethal effects at the studied concentrations, except for the aqueous extract of *A. halimus* at concentrations above 1 mg/ml. Besides, various chromosomal aberrations have been identified, including stickiness, C-metaphase, disturbances, chromosomal bridges, vagrant chromosomes, polyploidy, binucleate and micronuclei. However, although the tested plants extracts presented a mito-depressive effect, the number of the observed aberrations remained remains below the danger threshold at the recommended traditional dosage.

Our findings promote the value of local knowledge in terms of the variety and number of reported aromatic and medicinal plants used in traditional remedies to treat a wide range of illnesses. However, the use of aromatic and medicinal plants in traditional medicine should be directed very carefully to avoid any kind of toxicity.

Further studies on the separation and characterization of bioactive compounds and the elucidation of their mechanisms of action and toxicity, separately, are recommended. Furthermore, additional research *in vivo* and *in vitro* to determine the optimal dosage are necessary assure the production of safe, marketed, and accessible products with the best therapeutic effects.

References

References

Abdallah Emad, M., & El-Ghazali Gamal, E. (2013). Screening for antimicrobial activity of some plants from Saudi folk medicine. *Global journal of research on medicinal plants and indigenous*, *2*(4), 210-218.

Achir, M. (2016). Etude de l'impact des changements climatiques sur la dynamique de l'alfa (*Stipa tenacissima L.*) dans la région steppique de Tiaret (Algérie occidentale). Thèse de doctorat, Université de Sidi Bel Abbès, Algérie, p. 96.

Adegbola, P., Aderibigbe, I., Hammed, W., & Omotayo, T. (2017). Antioxidant and anti-inflammatory medicinal plants have potential role in the treatment of cardiovascular disease: A review. *American Journal of Cardiovascular Disease*, *7*(2), 19–32.

Adnan, M., Ullah, I., Tariq, A., Murad, W., Azizullah, A., Khan, A. L., & Ali, N. (2014). Ethnomedicine use in the war affected region of northwest Pakistan. *Journal of Ethnobiology and Ethnomedicine*, *10*(1), 1-16.

Aftab, T., & Hakeem, K. R. (2021). *Medicinal and Aromatic Plants: Healthcare and Industrial Applications*. Springer Nature.

Ahmad, M., Sultana, S., Fazl-i-Hadi, S., Ben Hadda, T., Rashid, S., Zafar, M., Khan, M. A., Khan, M. P. Z., & Yaseen, G. (2014). An ethnobotanical study of medicinal plants in high mountainous region of Chail valley (District Swat-Pakistan). *Journal of Ethnobiology and Ethnomedicine*, *10*, 1-18. https://doi.org/10.1186/1746-4269-10-36

Ahmad, R., Ahmad, N., Naqvi, A. A., Shehzad, A., & Al-Ghamdi, M. S. (2017). Role of traditional Islamic and Arabic plants in cancer therapy. *Journal* of *Traditional* and *Complementary Medicine*, *7*(2), 195-204. https://doi.org/10.1016/j.jtcme.2016.05.002

Ahmed, E., Arshad, M., Khan, M. Z., Amjad, M. S., Sadaf, H. M., Riaz, I., Riaz, I., Sabir, S., & Ahmad, N. (2017). Secondary metabolites and their multidimensional prospective in plant life. *Journal of Pharmacognosy and Phytochemistry*, *6*(2), 205-214.

Aiouaz, M., & Bitam, A. (2022). *Bunium incrassatum* Bois. Batt. Trab.(Talghouda) in the improvement of thyroid tissue damages in female rats. *Journal of Fundamental and Applied Pharmaceutical Science*, *2*(2), 92-108.

Ait Abderrahim, L., Taïbi, K., & Ait Abderrahim, C. (2019). Assessment of the antimicrobial and antioxidant activities of *Ziziphus lotus* and *Peganum harmala*. *Iranian Journal of*

Science and Technology, Transactions A: Science, *43*(2), 409-414. doi:10.1007/s40995-017-0411-x

Ait Abderrahim, L., Taïbi, K., Ait Abderrahim, N., Boussaid, M., Rios-Navarro, C., & Ruiz-Saurí, A. (2019). Euphorbia honey and garlic: Biological activity and burn wound recovery. *Burns*, *45*(7), 1695-1706. doi: 10.1016/j.burns.2019.05.002

Aiyegoro, O. A., & Okoh, A. I. (2010). Preliminary phytochemical screening and *in vitro* antioxidant activities of the aqueous extract of *Helichrysum longifolium* DC. *BMC Complementary and Alternative Medicine*, *10*(1), 1-8. https://doi.org/10.1186/1472-6882-10-21

Akinboro, A., & Bakare, A. (2007). Cytotoxic and genotoxic effects of aqueous extracts of five medicinal plants on *Allium cepa* Linn. *Journal of Ethnopharmacology*, *112*(3), 470-475. doi: 10.1016/j.jep.2007.04.014

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). An overview of the cell cycle. In *Molecular Biology of the Cell. 4th edition*.

Albuquerque, U. P., Ramos, M. A., de Lucena, R. F. P., & Alencar, N. L. (2014). Methods and techniques used to collect ethnobiological data. *Methods and Techniques in Ethnobiology and Ethnoecology*, 15-37.

Ali, B., Musaddiq, S., Iqbal, S., Rehman, T., Shafiq, N., & Hussain, A. (2021). The therapeutic properties, ethno pharmacology and phytochemistry of Atriplex species: A review. *Pakistan Journal of Biochemistry and Biotechnology*, *2*(1), 49-64.

Alonso, M. R., Anesini, C. A., & Martino, R. F. (2018). Anti-inflammatory activity. *J Sesquiterpene Lactones: Advances in their Chemistry and Biological Aspects*, 325-346.

Al-Oqail, M. M., Farshori, N. N., Al-Sheddi, E. S., Musarrat, J., Al-Khedhairy, A. A., & Siddiqui, M. A. (2013). *In vitro* cytotoxic activity of seed oil of fenugreek against various cancer cell lines. *Asian Pacific Journal of Cancer Prevention*, *14*(3), 1829-1832. doi: 10.7314/apjcp.2013.14.3.1829

Al-Saleh, I. A., Billedo, G., & El-Doush, I. I. (2006). Levels of selenium, dl-α-tocopherol, dl-γ-tocopherol, all-trans-retinol, thymoquinone and thymol in different brands of *Nigella sativa* seeds. *Journal of Food Composition and Analysis*, *19*(2), 167-175.

Al-Senosy, N. K., Abou-Eisha, A., & Ahmad, E. S. (2018). *In vitro* antiproliferation effect of *Atriplex halimus* L. crude extract on human cell lines by induction of apoptosis and G2/M phase arrest. *Egyptian Academic Journal of Biological Sciences. C, Physiology and Molecular Biology*, *10*(1), 115-126.

Andrade-Cetto, A., & Heinrich, M. (2011). From the field into the lab: Useful approaches to selecting species based on local knowledge. *Frontiers in Pharmacology*, *2*, 20. doi: 10.3389/fphar.2011.00020

Anywar, G., Kakudidi, E., Byamukama, R., Mukonzo, J., Schubert, A., Oryem-Origa, H., & Jassoy, C. (2021). A review of the toxicity and phytochemistry of medicinal plant species used by herbalists in treating people living with HIV/AIDS in Uganda. *Frontiers in Pharmacology*, *12*, 615147. doi: 10.3389/fphar.2021.615147

Aşkin Çelik, T., & Aslantürk, Ö. (2007). Cytotoxic and genotoxic effects of *Lavandula stoechas* aqueous extracts. *Biologia*, *62*(3), 292-296. https://doi.org/10.2478/s11756-007-0051-2

Aşkin Çelik, T., & Aslantürk, Ö. S. (2006). Anti-mitotic and anti-genotoxic effects of *Plantago lanceolata* aqueous extract on *Allium cepa* root tip meristem cells. *Biologia*, *61*(6), 693-697. https://doi.org/10.2478/s11756-006-0142-5

Aşkin Çelik, T., & Aslantürk, Ö. S. (2010). Evaluation of cytotoxicity and genotoxicity of *Inula viscosa* leaf extracts with *Allium test*. *Journal of Biomedicine and Biotechnology*, *2010*, 189252. https://doi.org/10.1155/2010/189252

Aydın, A., Aktay, G., & Yesilada, E. (2016). A guidance manual for the toxicity assessment of traditional herbal medicines. *Natural Product Communications*, *11*(11), 1763 - 1773.

Azzi, R., Djaziri, R., Lahfa, F., Sekkal, F. Z., Benmehdi, H., & Belkacem, N. (2012). Ethnopharmacological survey of medicinal plants used in the traditional treatment of diabetes mellitus in the North Western and South Western Algeria. *Journal of Medicinal Plants Research*, *6*(10), 2041-2050.

Babaei, G., Aliarab, A., Abroon, S., Rasmi, Y., & Aziz, S. G. G. (2018). Application of sesquiterpene lactone: A new promising way for cancer therapy based on anticancer activity. *Biomedicine and Pharmacotherapy*, *106*, 239-246. doi: 10.1016/j.biopha.2018.06.131

Badgujar, S. B., Patel, V. V., & Bandivdekar, A. H. (2014). *Foeniculum vulgare* Mill: A review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. *BioMed Research International*, *2014*, 842674. doi: 10.1155/2014/842674

Baghalian, K., Maghsodi, M., & Naghavi, M. (2010). Genetic diversity of Iranian madder (*Rubia tinctorum*) populations based on agro-morphological traits, phytochemical content and RAPD markers. *Industrial Crops and Products*, *31*(3), 557-562.

Ballout, F., Habli, Z., Monzer, A., Rahal, O. N., Fatfat, M., & Gali-Muhtasib, H. (2019). Anticancer alkaloids: Molecular mechanisms and clinical manifestations. *Bioactive Natural Products for the Management of Cancer: from Bench to Bedside*, 1-35.

Battandier, J. A., & Trabut, L. (1888). *Flore de l'Algérie*.

Belouadah, Z., Belhaneche-Bensemra, N., & Ati, A. (2021). Characterization of ligno-cellulosic fiber extracted from *Atriplex halimus* L. plant. *International Journal of Biological Macromolecules*, *168*, 806-815. doi: 10.1016/j.ijbiomac.2020.11.142

Benarba, B. (2015). Use of medicinal plants by breast cancer patients in Algeria. *EXCLI Journal*, *14*, 1164-1166. doi: 10.17179/excli2015-571

Benarba, B. (2016). Medicinal plants used by traditional healers from South-West Algeria: An ethnobotanical study. *Journal of Intercultural Ethnopharmacology*, *5*(4), 320–330. doi: 10.5455/jice.20160814115725

Benarba, B., Belabid, L., Righi, K., amine Bekkar, A., Elouissi, M., Khaldi, A., & Hamimed, A. (2015). Ethnobotanical study of medicinal plants used by traditional healers in Mascara (North West of Algeria). *Journal of Ethnopharmacology*, *175*, 626-637. doi: 10.1016/j.jep.2015.09.030

Benarba, B., Meddah, B., & Hamdani, H. (2014). Cancer incidence in North West Algeria (Mascara) 2000-2010: Results from a population-based cancer registry. *EXCLI Journal*, *13*, 709-723.

Benderradji, L., Rebbas, K., Ghadbane, M., Bounar, R., Brini, F., & Bouzerzour, H. (2014). Ethnobotanical study of medicinal plants in Djebel messaad region (M'sila, Algeria). *Global journal* of research on *medicinal plants* and *indigenous medicine*, *3*(12), 445-459.

Benhammou, N., Bekkara, F. A., & Panovska, T. K. (2009). Antioxidant activity of methanolic extracts and some bioactive compounds of *Atriplex halimus*. *Comptes Rendus Chimie*, *12*(12), 1259-1266.

Benrahou, K., Doudach, L., Mrabti, H. N., EL Guourrami, O., Zengin, G., Bouyahya, A., Cherrah, Y., & Faouzi, M. E. A. (2022). Acute toxicity, phenol content, antioxidant and postprandial anti-diabetic activity of *Echinops spinosus* extracts. *International Journal of Secondary Metabolite*, *9*(1), 91-102. https://doi.org/10.21448/ijsm.1031208

Berrabah, H., Taïbi, K., Ait Abderrahim, L., & Boussaid, M. (2019). Phytochemical composition and antioxidant properties of prickly pear (*Opuntia ficus-indica* L.) flowers from the Algerian germplasm. *Journal of Food Measurement and Characterization*, *13*(2), 1166-1174. https://doi.org/10.1007/s11694-019-00032-8

Berroukeche, F., Attoui, N., Toul, F., Ziane, M., Soulimane, N. M., & Merzouk, H. (2022). Investigation of antioxidant and anti-hemolytic properties of Algerian *Bunium incrassatum* tubers and their effects as diet on histological and biochemical parameters of normal Wistar rats. *Asian Journal of Agriculture* and *Biology*, (1).

Bigagli, E., Cinci, L., D'Ambrosio, M., & Luceri, C. (2017). Pharmacological activities of an eye drop containing *Matricaria chamomilla* and *Euphrasia officinalis* extracts in UVB-induced oxidative stress and inflammation of human corneal cells. *Journal of Photochemistry and Photobiology B: Biology*, *173*, 618-625. doi: 10.1016/j.jphotobiol.2017.06.031

Bonciu, E., Firbas, P., Fontanetti, C. S., Wusheng, J., Karaismailoğlu, M. C., Liu, D., Menicucci, F., Pesnya, D., Popescu, A., & Romanovsky, A. V. (2018). An evaluation for the standardization of the *Allium cepa* test as cytotoxicity and genotoxicity assay. *Caryologia*, *71*(3), 191-209. https://doi.org/10.1080/00087114.2018.1503496

Bouasla, A., & Bouasla, I. (2017). Ethnobotanical survey of medicinal plants in northeastern of Algeria. *Phytomedicine*, *36*, 68-81. doi: 10.1016/j.phymed.2017.09.007

Bouasla, I., Bouasla, A., Boumendjel, A., Messarah, M., Abdennour, C., Boulakoud, M. S., & El Feki, A. (2014). *Nigella sativa* oil reduces aluminium chloride-induced oxidative injury in liver and erythrocytes of rats. *Biological trace element research*, *162*, 252-261. doi: 10.1007/s12011-014-0114-5

Bouattour, E., Fakhfakh, J., Affes, M., Chawech, R., Damak, M., & Jarraya, R. (2017). Chemical constituents of *Echinops spinosus* from Tunisia. *Chemistry of Natural Compounds*, *53*(5), 984-987. doi:10.1007/s10600-017-2179-9

Bouattour, E., Fakhfakh, J., Frikha Dammak, D., Jabou, K., Damak, M., & Mezghani Jarraya, R. (2016). Hexane extract of *Echinops spinosissimus* Turra subsp. spinosus from tunisia: A potential source of acetylated sterols–investigation of its biological activities. *Chemistry and Biodiversity*, *13*(12), 1674-1684. doi: 10.1002/cbdv.201600118

Bouaziz, S., Amri, M., Taibi, N., Zeghir-Bouteldja, R., Benkhaled, A., Mezioug, D., & Touil-Boukoffa, C. (2021). Protoscolicidal activity of *Atriplex halimus* leaves extract against *Echinococcus granulosus* protoscoleces. *Experimental Parasitology*, *229*, 108155. https://doi.org/10.1016/j.exppara.2021.108155

Bouchikh, Y., Labani, A., Abbad, A., Bouhelouane, S., Lakhdari, W., & Dahliz, A. (2016). Ethnobotanical study of medicinal flora in the Atriplexaies plantation of Saida-a high land stepic city of Algeria. *Bangladesh Journal of Botany*, *45*(1), 233-238.

Boudjelal, A., Henchiri, C., Sari, M., Sarri, D., Hendel, N., Benkhaled, A., & Ruberto, G. (2013). Herbalists and wild medicinal plants in M'Sila (North Algeria): An ethnopharmacology survey. *Journal of Ethnopharmacology*, *148*(2), 395-402. doi: 10.1016/j.jep.2013.03.082

Boughrara, B., & Belgacem, L. (2016). Ethnobotanical study close to the population of the extreme north east of Algeria: The municipalities of El Kala National Park (EKNP). *Industrial Crops and Products*, *88*, 2-7. doi:10.1016/j.indcrop.2016.03.009

Bousetla, A., Kurkcuoglu, M., Konuklugil, B., Baser, K., & Rhouati, S. (2014). Composition of essential oil from *Bunium incrassatum* from Algeria. *Chemistry of Natural Compounds*, *50*(4), 753-755. https://doi.org/10.1007/s10600-014-1074-x

Bousetla, A., Zellagui, A., Derouiche, K., & Rhouati, S. (2015). Chemical constituents of the roots of Algerian *Bunium incrassatum* and evaluation of its antimicrobial activity. *Arabian Journal of Chemistry*, *8*(3), 313-316. doi:10.1016/j.arabjc.2011.01.022

Boussaid, M., Taïbi, K., Ait Abderrahim, L., & Ennajah, A. (2018). Genetic diversity of *Ziziphus lotus* natural populations from Algeria based on fruit morphological markers. *Arid Land Research and Management*, *32*(2), 184-197. doi:10.1080/15324982.2018.1424742

Bouzabata, A. (2013). Traditional treatment of high blood pressure and diabetes in Souk Ahras District. *Journal of Pharmacognosy and Phytotherapy* *5*(1), 12-20. doi:10.5897/JPP11.065

Bouzabata, A., & Mahomoodally, M. F. (2019). A quantitative documentation of traditionally-used medicinal plants from Northeastern Algeria: Interactions of beliefs among healers and diabetic patients. *Journal of Herbal Medicine*, *22*, 100318. doi:10.1016/j.hermed.2019.100318

Bouzabata, A., Mahomoodally, F., & Tuberoso, C. (2018). Ethnopharmacognosy of *Echinops spinosus* L. in North Africa: A mini review. *Journal of Complementary Medicine Research*, *8*(1), 40-52.

Cabuga Jr, C. C. (2017). *Allium cepa* test: An evaluation of genotoxicity. *Proceedings of the International Academy of Ecology and Environmental Sciences*, *7*(1), 12.

Chakraborty, R., Mukherjee, A. K., & Mukherjee, A. (2009). Evaluation of genotoxicity of coal fly ash in *Allium cepa* root cells by combining comet assay with the *Allium* test. *Environmental Monitoring and Assessment*, *153*(1), 351-357. https://doi.org/10.1007/s10661-008-0361-z

Chatterjee, N., & Walker, G. C. (2017). Mechanisms of DNA damage, repair, and mutagenesis. *Environmental and Molecular Mutagenesis*, *58*(5), 235-263. doi: 10.1002/em.22087

Chentouh, S., Boulahbel, S., Ouldjaoui, A., Hammoudi, N., Djebaili, H., & Adjal, F. (2017). Effect of organic extracts of *Bunium incrassatum* on the hematological, ovarian and uterine parameters of mature female rabbit. *Journal of Fundamental and Applied Sciences*, *9*(3), 1618-1633.

Chermat, S., & Gharzouli, R. (2015). Ethnobotanical study of medicinal flora in the North East of Algeria-An empirical knowledge in Djebel Zdimm (Setif). *Journal of Materials Science and Engineering A, (1-2)*, 50-59. doi:10.17265/2161-6213/2015.1-2.007

Chikhi, I., Allali, H., Dib, M. E. A., Medjdoub, H., & Tabti, B. (2014). Antidiabetic activity of aqueous leaf extract of *Atriplex halimus* L.(Chenopodiaceae) in streptozotocin–induced diabetic rats. *Asian Pacific journal of Tropical Disease*, *4*(3), 181-184. doi: 10.1016/S2222-1808(14)60501-6

Chua, L. S. (2013). A review on plant-based rutin extraction methods and its pharmacological activities. *Journal of Ethnopharmacology*, *150*(3), 805-817. doi: 10.1016/j.jep.2013.10.036

Chukwujekwu, J. C., & Van Staden, J. (2014). Cytotoxic and genotoxic effects of water extract of *Distephanus angulifolius* on *Allium cepa* Linn. *South African Journal of Botany*, *92*, 147-150. https://doi.org/https://doi.org/10.1016/j.sajb.2014.03.001

Convention of Biological Diversity (C.B.D). (2020). Algeria – Overview: Biodiversity facts. https://www.cbd.int/countries/profile/?country=dz

da Silva, V. A., do Nascimento, V. T., Soldati, G. T., Medeiros, M. F. T., & Albuquerque, U. P. (2014). Techniques for analysis of quantitative ethnobiological data: Use of indices. *Methods and Techniques in Ethnobiology and Ethnoecology*, 379-395.

Dar, R. A., Shahnawaz, M., & Qazi, P. H. (2017). General overview of medicinal plants: A review. *Journal of Phytopharmacology*, *6*(6), 349-351.

das Gracas Medeiros, M., & Takahashi, C. S. (1987). Effects of *Luffa operculata* on *Allium cepa* root-tip cells. *Cytologia*, *52*(2), 255-259.

Dehimi, K., Djoudi, Z., Dahamna, S., Boulaouad, A., Maadadi, A., & Khennouf, S. (2020). A contribution to the valorization of two medicinal plants: *Atriplex halimus* Sub. Sp. Schweinfurthii and *Bunium incrassatum*, growing in the region of M'sila (North-East Algeria). *Indian Journal of Novel Drug Delivery*, *12*(4), 208-216.

Djahafi, A., Taïbi, K., & Ait Abderrahim, L. (2021). Aromatic and medicinal plants used in traditional medicine in the region of Tiaret, North West of Algeria. *Mediterranean Botany*, *42*, e71465. doi:10.5209/mbot.71465

Eddouks, M., Ajebli, M., & Hebi, M. (2017). Ethnopharmacological survey of medicinal plants used in Daraa-Tafilalet region (Province of Errachidia), Morocco. *Journal of Ethnopharmacology*, *198*, 516-530. doi: 10.1016/j.jep.2016.12.017

El Kolli, H., Laouer, H., & El Kolli, M. (2017). Chemical composition and biological activities of the essential oils and the methanolic extracts of *Bunium incrassatum* and *Bunium alpinum* from Algeria. *Journal of the Chilean Chemical Society*, *62*(1), 3335-3341. doi:10.4067/S0717-97072017000100006

El-Aasr, M., Kabbash, A., El-Seoud, K. A. A., Al-Madboly, L. A., & Ikeda, T. (2016). Antimicrobial and immunomodulatory activities of flavonol glycosides isolated from *Atriplex halimus* L. herb. *Journal of Pharmaceutical Sciences and Research*, *8*(10), 1159.

Elansary, H. O., Szopa, A., Kubica, P., Ekiert, H., Ali, H. M., Elshikh, M. S., Abdel-Salam, E. M., El-Esawi, M., & El-Ansary, D. O. (2018). Bioactivities of traditional medicinal plants in Alexandria. *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1463579-1463579. https://doi.org/10.1155/2018/1463579

El-Ghamery, A., El-Kholy, M., & Abou El-Yousser, M. (2003). Evaluation of cytological effects of Zn2+ in relation to germination and root growth of *Nigella sativa* L. and *Triticum aestivum* L. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *537*(1), 29-41. doi: 10.1016/s1383-5718(03)00052-4

El-Ghamery, A., El-Nahas, A., & Mansour, M. (2000). The action of atrazine herbicide as an inhibitor of cell division on chromosomes and nucleic acids content in root meristems of *Allium cepa* and *Vicia faba*. *Cytologia*, *65*(3), 277-287.

Emam, S. S. (2011). Bioactive constituents of *Atriplex halimus* plant. *Journal of Natural Products*, *4*, 25-41.

Esalat Nejad, H., & Esalat Nejad, A. (2013). *Rubia tinctorum* L.(Rubiaceae) or Madder as one of the living color to dyeing wool. *International Journal of Advanced Biological and Biomedical Research*, *1*(11), 1315-1319.

Fakchich, J., & Elachouri, M. (2014). Ethnobotanical survey of medicinal plants used by people in Oriental Morocco to manage various ailments. *Journal of Ethnopharmacology*, *154*(1), 76-87. doi: 10.1016/j.jep.2014.03.016

Feretti, D., Zerbini, I., Zani, C., Ceretti, E., Moretti, M., & Monarca, S. (2007). *Allium cepa* chromosome aberration and micronucleus tests applied to study genotoxicity of extracts from pesticide-treated vegetables and grapes. *Food Additives and Contaminants*, *24*(6), 561-572. doi: 10.1080/02652030601113602

Fiskesjö, G. (1985). The *Allium* test as a standard in environmental monitoring. *Hereditas*, *102*(1), 99-112. doi: 10.1111/j.1601-5223.1985.tb00471.x

Ford, L., Rayner, C. M., & Blackburn, R. S. (2015). Isolation and extraction of ruberythric acid from *Rubia tinctorum* L. and crystal structure elucidation. *Phytochemistry*, *117*, 168-173. doi: 10.1016/j.phytochem.2015.06.015

Frikha-Dammak, D., Saad, H., Bouattour, E., Boudaouara, O., & Jarraya, R. (2020). *Improvement on high-cholesterol diet induced atherosclerosis, lipid profile, oxidative stress and genotoxicity in the liver of mice by Echinops spinosissimus Turra subsp. spinosus*. https://doi.org/10.21203/rs.3.rs-18432/v1

Gajbhiye, R. L., Mahato, S. K., Achari, A., Jaisankar, P., & Ravichandiran, V. (2019). Cancer chemoprevention by dietary polyphenols, flavonoids, terpenoids, and saponins. *Bioactive Natural Products for the Management of Cancer: from Bench to Bedside*, 91-109

Ganaie, H. A. (2021). Review of the active principles of medicinal and aromatic plants and their disease fighting properties. *Medicinal and Aromatic Plants*, 1-36.

Gattouche, S., Zenkhri, L., Belfar, M. L., & Tabchouche, A. (2020). Phytochemical screening, anti-bacterial and anti-oxidant activities of some aerial parts extracts in *Atriplex halimus* L., from Ouargla (Algeria). *Asian Journal of Research in Chemistry*, *13*(5), 365-372. doi:10.5958/0974-4150.2020.00069.3

Gheffour, K. (2018). *In vitro* antihemolytic activity of *Echinops spinosus* tannins extracts against human erythrocytes. *Asian Journal of Pharmaceutics*, *12*(03). https://doi.org/10.22377/ajp.v12i03.2647

Gheffour, K., Boucherit, K., & Boucherit-Otmani, Z. (2015). Étude phytochimique et évaluation de l'activité antioxydante des extraits *d'Echinops spinosus*. *Phytothérapie*, *13*(5), 288-294. https://doi.org/10.1007/s10298-015-0917-8

Ghosh, T., Biswas, M. K., Chatterjee, S., & Roy, P. (2018). *In-vitro* study on the hemolytic activity of different extracts of Indian medicinal plant Croton bonplandianum with phytochemical estimation: A new era in drug development. *Journal of Drug Delivery and Therapeutics*, *8*(4), 155-160.

Ghramh, H. A., Khan, K. A., & Ibrahim, E. H. (2019). Biological activities of *Euphorbia peplus* leaves ethanolic extract and the extract fabricated gold nanoparticles (AuNPs). *Molecules*, *24*(7), 1431. https://doi.org/10.3390/molecules24071431

Giada, M. (2013). Food phenolic compounds: Main classes, sources and their antioxidant power. *Oxidative stress and chronic degenerative diseases-A role for antioxidants*, *2013*, 87-112. doi:10.5772/51687

González-Tejero, M., Casares-Porcel, M., Sánchez-Rojas, C., Ramiro-Gutiérrez, J., Molero-Mesa, J., Pieroni, A., Giusti, M.E., Censorii, E., De Pasquale, C., & Della, A. (2008). Medicinal plants in the Mediterranean area: Synthesis of the results of the project Rubia. *Journal of Ethnopharmacology*, *116*(2), 341-357. doi: 10.1016/j.jep.2007.11.045

Grant, W. F. (1978). Chromosome aberrations in plants as a monitoring system. *Environmental Health Perspectives*, *27*, 37-43.

Gurib-Fakim, A. (2006). Medicinal plants: Traditions of yesterday and drugs of tomorrow. *Molecular Aspects of Medicine*, *27*(1), 1-93. doi: 10.1016/j.mam.2005.07.008

Hamburger, M., & Hostettmann, K. (1991). Bioactivity in plants: The link between phytochemistry and medicine. *Phytochemistry*, *30*(12), 3864-3874.

Hammiche, V., & Maiza, K. (2006). Traditional medicine in Central Sahara: Pharmacopoeia of Tassili N'ajjer. *Journal of Ethnopharmacology*, *105*(3), 358-367. doi: 10.1016/j.jep.2005.11.028

Hammoudi, N., Hafid, H., Moumen, Y., Chentouh, S., Djebaili, H., & Boulahbel, S. (2020). Effect of organic materials extract from *Bunium incrassatum* (Talghouda) roots on hematological and histological parameters of the adrenal glands in the pregnant rabbits, Oryctolaguscuniculus. *Journal of New Technology and Materials*, *10*(1), 38-43.

Hassanpour, S., MaheriSis, N., & Eshratkhah, B. (2011). Plants and secondary metabolites (Tannins): A Review. *International Journal of Forest, Soil and Erosion*, *1*(1), 47-53.

Hayakawa, F., Kimura, T., Hoshino, N., & Ando, T. (1999). DNA cleavage activities of (-)-epigallocatechin,(-)-epicatechin,(+)-catechin, and (-)-epigallocatechin gallate with various kind of metal ions. *Bioscience, Biotechnology, and Biochemistry*, *63*(9), 1654-1656. doi: 10.1271/bbb.63.1654

Hegazy, M. G., Emam, M. A., Khattab, H. I., & Helal, N. M. (2019). Biological activity of *Echinops spinosus* on inhibition of paracetamol-induced renal inflammation. *Biochemistry and Cell Biology*, *97*(2), 176-186. doi: 10.1139/bcb-2018-0212

Helal, N. M., Alharby, H. F., Alharbi, B. M., Bamagoos, A. A., & Hashim, A. M. (2020). *Thymelaea hirsuta* and *Echinops spinosus*: Xerophytic plants with high potential for first-generation biodiesel production. *Sustainability*, *12*(3), 1137. https://doi.org/10.3390/su12031137

Herdiana, Y., Wathoni, N., Shamsuddin, S., & Muchtaridi, M. (2021). α-Mangostin nanoparticles cytotoxicity and cell death modalities in breast cancer cell lines. *Molecules*, *26*(17), 5119. https://doi.org/10.3390/molecules26175119

Herrero, O., Martín, J. P., Freire, P. F., López, L. C., Peropadre, A., & Hazen, M. (2012). Toxicological evaluation of three contaminants of emerging concern by use of the *Allium cepa* test. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *743*(1-2), 20-24. doi: 10.1016/j.mrgentox.2011.12.028

Hsiao, A.-S & Hung, J.-Y. (2023). Microtubule Regulation in Plants: From Morphological Development to Stress Adaptation. *Biomolecules*, *13(14)*, 627. https://doi.org/10.3390/biom13040627

Hussein, R. A., & El-Anssary, A. A. (2019). Plants secondary metabolites: The key drivers of the pharmacological actions of medicinal plants. *Herbal Medicine*, *1*(3).

Idolo, M., Motti, R., & Mazzoleni, S. (2010). Ethnobotanical and phytomedicinal knowledge in a long-history protected area, the Abruzzo, Lazio and Molise National Park (Italian Apennines). *Journal of Ethnopharmacology*, *127*(2), 379-395. https://doi.org/10.1016/j.jep.2009.10.027

Ihegboro, G. O., Alhassan, A. J., Ononamadu, C. J., Owolarafe, T. A., & Sule, M. S. (2020). Evaluation of the biosafety potentials of methanol extracts/fractions of *Tapinanthus bangwensis* and *Moringa oleifera* leaves using *Allium cepa* model. *Toxicology Reports*, *7*, 671-679. doi: 10.1016/j.toxrep.2020.05.001

Iqbal, E., Kamariah, A. S., & Lim, L. (2015). Phytochemical screening, total phenolics and antioxidant activities of bark and leaf extracts of *Goniothalamus velutinus* (Airy Shaw) from Brunei Darussalam. *Journal of King Saud University-Science*, *4*(3), 224-232. https://doi.org/10.1016/j.jksus.2015.02.003

Istifli, E. S., Hüsunet, M. T., & Ila, H. B. (2019). Cell division, cytotoxicity, and the assays used in the detection of cytotoxicity. *Cytotoxicity-Definition, Identification, and Cytotoxic Compounds*, *1*.

Jahier, J., Chevre, A., Eber, F., Delourme, R., & Tanguy, A. (1992). Techniques de cytogénétique végétale. INRA. In: Springer, Paris.

Jain, C., Khatana, S., & Vijayvergia, R. (2019). Bioactivity of secondary metabolites of various plants: A review. *International Journal of Pharmaceutical Sciences* and *Research*, *10*(2), 494-504.

Jamshidi-Kia, F., Lorigooini, Z., & Amini-Khoei, H. (2018). Medicinal plants: Past history and future perspective. *Journal of Herbmed Pharmacology*, *7*(1), 1-7. doi: 10.15171/jhp.2018.01

Jamshidi-Kia, F., Wibowo, J. P., Elachouri, M., Masumi, R., Salehifard-Jouneghani, A., Abolhasanzadeh, Z., & Lorigooini, Z. (2020). Battle between plants as antioxidants with free radicals in human body. *Journal of Herbmed Pharmacology*, *9*(3), 191-199. doi: 10.34172/jhp.2020.25

Jamwal, K., Bhattacharya, S., & Puri, S. (2018). Plant growth regulator mediated consequences of secondary metabolites in medicinal plants. *Journal of Applied Research on Medicinal and Aromatic Plants*, *9*, 26-38. https://doi.org/10.1016/j.jarmap.2017.12.003

Jaradat, N. A., Al-Ramahi, R., Zaid, A. N., Ayesh, O. I., & Eid, A. M. (2016). Ethnopharmacological survey of herbal remedies used for treatment of various types of cancer and their methods of preparations in the West Bank-Palestine. *BMC Complementary Alternative Medicine*, *16*(1), 1-12. doi: 10.1186/s12906-016-1070-8

Jassbi, A. R., Mehrdad, M., Soleimani, M., Mirzaeian, M., & Sonboli, A. (2005). Chemical Composition of the Essential Oils of Bunium elegans and Bunium caroides. *Chemistry of Natural Compounds*, *41*(4), 415-417. https://doi.org/10.1007/s10600-005-0165-0

Javed, H., Erum, S., Tabassum, S., & Ameen, F. (2013). An overview on medicinal importance of *Thymus vulgaris*. *Journal of Asian Scientific Research*, *3*(10), 974-982.

Kabbash, A., & Shoeib, N. (2012). Chemical and biological investigation of some secondary metabolites in *Atriplex halimus* growing in Egypt. *Natural Product Communications*, *7*(11), 1465 - 1468.

Kabera, J. N., Semana, E., Mussa, A. R., & He, X. (2014). Plant secondary metabolites: Biosynthesis, classification, function and pharmacological properties. *Journal* of *Pharmacy* and *Pharmacology*, *2*(7), 377-392.

Kalita, S., Kumar, G., Karthik, L., & Rao, K. V. B. (2011). Phytochemical composition and *in vitro* hemolytic activity of *Lantana camara* L.(Verbenaceae) leaves. *Pharmacologyonline Online*, *1*, 59-67.

Kaur, G. J., & Arora, D. S. (2009). Antibacterial and phytochemical screening of *Anethum graveolens*, *Foeniculum vulgare* and *Trachyspermum ammi*. *BMC Complementary Alternative Medicine*, *9*(1), 1-10. https://doi.org/10.1186/1472-6882-9-30

Khaldi, A., Amamra, D., Maghdouri, N., & Tir Touil, A. (2015). Assessment of *Atriplex halimus* extracts activity against multidrug resistant bacteria isolated from different environments. *Journal of Chemical and Pharmaceutical Research*, *7*(6), 543-549.

Khallef, M., Liman, R., Konuk, M., Ciğerci, İ. H., Benouareth, D., Tabet, M., & Abda, A. (2015). Genotoxicity of drinking water disinfection by-products (bromoform and chloroform) by using both *Allium* anaphase-telophase and comet tests. *Cytotechnology*, *67*(2), 207-213. doi: 10.1007/s10616-013-9675-y

Khameneh, B., Iranshahy, M., Soheili, V., & Fazly Bazzaz, B. S. (2019). Review on plant antimicrobials: A mechanistic viewpoint. *Antimicrobial Resistance and Infection Control*, *8*(1), 118. https://doi.org/10.1186/s13756-019-0559-6

Khedher, O., Moussaoui, Y., & Salem, R. B. (2014). Solvent effects on phenolic contents and antioxidant activities of the *Echinops spinosus* and the *Limoniastrum monopetalum*. *Research Journal* of *Pharmaceutical*, *Biological* and *Chemical* Sciences, *5*, 66-76.

Khedher, O., Rigane, G., Riguene, H., Ben Salem, R., & Moussaoui, Y. (2021). Phenolic profile (HPLC-UV) analysis and biological activities of two organic extracts from *Echinops spinosissimus* Turra roots growing in Tunisia. *Natural Product Research, 35*(24), 5786-5793. doi: 10.1080/14786419.2020.1837812

Kouzmine, Y., Fontaine, J., Yousfi, B. E., & Otmane, T. (2009). Étapes de la structuration d'un désert: L'espace saharien algérien entre convoitises économiques, projets politiques et aménagement du territoire. *Annales de géographie 670(6)*, 659-685.

Kumar, G., Karthik, L., & Rao, K. V. B. (2011). Hemolytic activity of Indian medicinal plants towards human erythrocytes: An *in vitro* study. *Elixir Appl Botany*, *40*(5534), e5537.

Kumar, N., & Goel, N. (2019). Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnology Reports*, *24*, e00370. doi: 10.1016/j.btre.2019.e00370

Lakhdari, W., Dehliz, A., Acheuk, F., Mlik, R., Hammi, H., Doumandji-Mitiche, B., Gheriani, S., Berrekbia, M., Guermit, K., & Chergui, S. (2016). Ethnobotanical study of some plants used in traditional medicine in the region of Oued Righ (Algerian Sahara). *Journal of Medicinal Plants Studies, 4(2)*, 204-211.

Laura, A., Moreno-Escamilla, J. O., Rodrigo-García, J., & Alvarez-Parrilla, E. (2019). Phenolic compounds. *Postharvest Physiology and Biochemistry of Fruits and Vegetables*, 253-271.

Lee, K.-H., Yeh, M.-H., Kao, S. T., Hung, C.-M., Liu, C.-J., Huang, Y. Y., & Yeh, C. C. (2010). The inhibitory effect of hesperidin on tumor cell invasiveness occurs via suppression of activator protein 1 and nuclear factor-kappaB in human hepatocellular carcinoma cells. *Toxicology Letters*, *194*(1-2), 42-49. doi: 10.1016/j.toxlet.2010.01.021

Leme, D. M., & Marin-Morales, M. A. (2009). *Allium cepa* test in environmental monitoring: A review on its application. *Mutation Research/Reviews in Mutation Research*, *682*(1), 71-81. https://doi.org/10.1016/j.mrrev.2009.06.002

Liu, X., Rodeheaver, D. P., White, J. C., Wright, A. M., Walker, L. M., Zhang, F., & Shannon, S. (2018). A comparison of *in vitro* cytotoxicity assays in medical device regulatory studies. *Regulatory Toxicology and Pharmacology*, *97*, 24-32. doi: 10.1016/j.yrtph.2018.06.003

López-Lázaro, M. (2009). Distribution and biological activities of the flavonoid luteolin. *Mini Reviews in Medicinal Chemistry*, *9*(1), 31-59. doi: 10.2174/138955709787001712

López-Romero, D., Izquierdo-Vega, J. A., Morales-González, J. A., Madrigal-Bujaidar, E., Chamorro-Cevallos, G., Sánchez-Gutiérrez, M., Betanzos-Cabrera, G., Alvarez-Gonzalez, I., Morales-González, Á., & Madrigal-Santillán, E. (2018). Evidence of some natural products with antigenotoxic effects. Part 2: Plants, vegetables, and natural resin. *Nutrients*, *10*(12), 1954. doi: 10.3390/nu10121954

Lovkova, M.Y., Buzuk, G.N., Sokolova, S.M., & Kliment'eva, N. I. (2001). Chemical features of medicinal plants. *Applied Biochemistry and Microbiology*, *37*, 229-237. https://doi.org/10.1023/A:1010254131166

Magdolenova, Z., Collins, A., Kumar, A., Dhawan, A., Stone, V., & Dusinska, M. (2014). Mechanisms of genotoxicity. A review of *in vitro* and *in vivo* studies with engineered nanoparticles. *Nanotoxicology*, *8*(3), 233-278. doi: 10.3109/17435390.2013.773464

Mahomoodally, M. F. (2013). Traditional medicines in Africa: An appraisal of ten potent African medicinal plants. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 617459. doi: 10.1155/2013/617459

Majewska, A., Furmanowa, M., Śliwińska, E., Głowniak, K., Guzewska, J., Kuraś, M., & Zobel, A. (2000). Influence of extract from shoots of *Taxus baccata* var.'Elegantissima'on mitotic activity of meristematic cells of *Allium cepa* L. roots. *Acta Societatis Botanicorum Poloniae*, *69*(3), 185-192.

Martin, G. (1995). Ethnobotany—A manual of methods. *London: Chapman et Hall.*

Meddour, R., & Meddour-Sahar, O. (2015). Medicinal plants and their traditional uses in Kabylia (Tizi Ouzou, Algeria). *Arabian Journal of Medicinal and Aromatic Plants*, *1*(2), 137-151. doi:10.48347/IMIST.PRSM/ajmap-v1i2.4331

Meharie, B. G., & Tunta, T. A. (2020). Evaluation of diuretic activity and phytochemical contents of aqueous extract of the shoot apex of *Podocarpus falcactus*. *Journal of Experimental Pharmacology*, *12*, 629-641. https://doi.org/10.2147/JEP.S287277

Mensah, M., Komlaga, G., Forkuo, A. D., Firempong, C., Anning, A. K., & Dickson, R. A. (2019). Toxicity and safety implications of herbal medicines used in Africa. *Herbal Medicine*, *63*, 1992-0849.

Mesi, A., & Kopliku, D. (2013). Cytotoxic and genotoxic potency screening of two pesticides on *Allium cepa* L. *Procedia Technology*, *8*, 19-26. https://doi.org/10.1016/j.protcy.2013.11.005

Messaoudi, Z. A., Messaoudi, M., Benreguieg, M., & Merah, M. (2020). Phytochemical screening of Algerian medicinal plants and their antimicrobial effects. *Mycoppath*, *16*(2).

Mishra, P., Shukla, A. K., & Sundaresan, V. (2018). Candidate DNA barcode tags combined with high resolution melting (Bar-HRM) curve analysis for authentication of *Senna alexandrina* Mill. with validation in crude drugs. *Frontiers in Plant Science*, *9*, 283.

Moazzami, F., Seyed Hamed , Ghorbani, A., Ajani, Y., Sadr, M., & Mozaffarian, V. (2018). Ethnobotanical applications and their correspondence with phylogeny in Apiaceae-Apioideae. *Research Journal of Pharmacognosy*, *5*(3), 79-97.

Mohammedi, Z. (2016). Resistance, pharmacology properties and nutritional value of a shrub from arid environments *Atriplex halimus*. *Research Journal* of *Medicinal Plant*, *10*(1), 10-18.

Mohammedi, Z., & Atik, F. (2014). Hemolytic activity of different herbal extracts used in Algeria. *International Journal of Pharmaceutical Sciences* and *Research*, *5*(8), 495-500.

Monira, A. K. A., & Naima, M., Z. (2012). Evaluation of protective and antioxidant activity of thyme (Thymus vulgaris) extract on paracetamol-induced toxicity in rats. *Australian Journal of Basic and Applied Sciences*, *6*(7), 467-474.

Moon, J.-K., & Shibamoto, T. (2009). Antioxidant assays for plant and food components. *Journal of Agricultural and Food Chemistry*, *57*(5), 1655-1666. https://doi.org/10.1021/jf803537k

Mota, T. F. M., Sampaio, A. R., Vasconcelos, M. W., & de Castilhos Ghisi, N. (2022). *Allium cepa* test vs. insecticides: A scientometric and meta-analytical review. *Environmental Science and Pollution Research*, *29*(28), 42678-42691. doi: 10.1007/s11356-021-15953-5

Mothana, R. A., Kriegisch, S., Harms, M., Wende, K., & Lindequist, U. (2011). Assessment of selected Yemeni medicinal plants for their *in vitro* antimicrobial, anticancer, and antioxidant activities. *Pharmaceutical Biology*, *49*(2), 200-210. doi: 10.3109/13880209.2010.512295

Nagarathna, P. K. M., Wesley, M., Reddy, P., & Reena, K. (2013). Review on genotoxicity, its molecular mechanisms and prevention. *International Journal of Pharmaceutical Sciences Review and Research*, *22*, 236-243.

Nedjimi, B. (2012). Seasonal variation in productivity, water relations and ion contents of *Atriplex halimus* spp. schweinfurthii grown in Chott Zehrez wetland, Algeria. *Journal of the Saudi Society of Agricultural Sciences*, *11*(1), 43-49. https://doi.org/10.1016/j.jssas.2011.08.002

Nedjimi, B., Guit, B., Toumi, M., Beladel, B., Akam, A., & Daoud, Y. (2013). *Atriplex halimus* subsp. schweinfurthii (Chenopodiaceae): Description, écologie et utilisations pastorales et thérapeutiques. *Fourrages*, *216*, 333-338.

Nejat, H., Sedaghat, K., Vakili, A., Jarrahi, M., & Khorasani, M. Z. (2017). The Contractive effect of *Rubia tinctorum* L. extract on the isolated aorta smooth muscle and its protective effect against the damage caused by hyperglycemic solution in Rat. *Jundishapur Journal of Natural Pharmaceutical Products*, *12*(3), e64319. doi:10.5812/jjnpp.64319

Neves, J. M., Matos, C., Moutinho, C., Queiroz, G., & Gomes, L. R. (2009). Ethnopharmacological notes about ancient uses of medicinal plants in Trás-os-Montes (northern of Portugal). *Journal of Ethnopharmacology*, *124*(2), 270-283. doi: 10.1016/j.jep.2009.04.041

Noudeh, G. D., Sharififar, F., Khatib, M., Behravan, E., & Afzadi, M. A. (2010). Study of aqueous extract of three medicinal plants on cell membrane–permeabilizing and their surface properties. *African Journal of Biotechnology*, *9*(1).

Oh, H. H., Surapaneni, S., & Hui, J. Y. (2017). Preclinical development of oncology drugs. *A Comprehensive Guide to Toxicology in Nonclinical Drug Development*, 685-707. https://doi.org/10.1016/B978-0-12-803620-4.00026-8

Okorie Asita, A., Moramang, S., Rants'o, T., & Magama, S. (2017). Modulation of mutagen-induced genotoxicity by vitamin C and medicinal plants in *Allium cepa* L. *Caryologia*, *70*(2), 151-165. https://doi.org/10.1080/00087114.2017.1311166

Orhan, I. E. (2014). Pharmacognosy: Science of natural products in drug discovery. *BioImpacts: BI*, *4*(3), 109-110. doi: 10.15171/bi.2014.001

Ortiz-Dorda, J., Martínez-Mora, C., Correal, E., Simón, B., & Cenis, J. (2005). Genetic structure of *Atriplex halimus* populations in the Mediterranean Basin. *Annals of Botany*, *95*(5), 827-834. doi: 10.1093/aob/mci086

Othman, M. S., Khaled, A. M., Al-Bagawi, A. H., Fareid, M. A., Hameed, R. A., Zahra, F. A. A., & Moneim, A. E. A. (2022). *Echinops spinosus* effect against diabetes and its hepatorenal complications: Total extract and flavonoids fraction. *Environmental Science and Pollution Research*, *29*(25), 38606-38617. doi: 10.1007/s11356-022-18824-9

Ouelbani, R., Bensari, S., Mouas, T. N., & Khelifi, D. (2016). Ethnobotanical investigations on plants used in folk medicine in the regions of Constantine and Mila (North-East of Algeria). *Journal of Ethnopharmacology*, *194*, 196-218. doi: 10.1016/j.jep.2016.08.016

Ould Kaddour, A. S., Bouzouina, M., & Lotmani, B. (2019). Phenolics contents and *in vitro* evaluation of the antioxidant effects of the aerial parts of three Algerian *Atriplex halimus* L. Ecotypes. *Plant Archives*, *19*(1), 1583-1592.

Ounaissia, K., Bennadja, S., Aliane, L., & Djahoudi, A. (2020). Phytochemical screening and anti-bacterial activity of methanolic extracts of the aerial parts of *Atriplex halimus* L., from Biskra (Algeria). *International Journal of Agricultural and Natural Sciences*, *13*(1), 26-33.

Owolarafe, T. A., Salawu, K., Ihegboro, G. O., Ononamadu, C. J., Alhassan, A. J., & Wudil, A. M. (2020). Investigation of cytotoxicity potential of different extracts of *Ziziphus mauritiana* (Lam) leaf *Allium cepa* model. *Toxicology Reports*, *7*, 816-821. https://doi.org/10.1016/j.toxrep.2020.06.010

Oyedare, B. M., Bakare, A. A., & Akinboro, A. (2009). Genotoxicity assessment of water extracts of *Ocimum gratissimum*, *Morinda lucida* and *Citrus medica* using the *Allium cepa* assay. *Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas*, *8*(2), 97-103.

Oyeyemi, I. T., & Bakare, A. A. (2013). Genotoxic and anti-genotoxic effect of aqueous extracts of *Spondias mombin* L., *Nymphea lotus* L. and *Luffa cylindrica* L. on *Allium cepa* root tip cells. *Caryologia*, *66*(4), 360-367. https://doi.org/10.1080/00087114.2013.857829

Oyeyemi, I. T., Yekeen, O. M., Odusina, P. O., Ologun, T. M., Ogbaide, O. M., Olaleye, O. I., & Bakare, A. A. (2015). Genotoxicity and antigenotoxicity study of aqueous and hydro-methanol extracts of *Spondias mombin* L., *Nymphaea lotus* L. and *Luffa* *cylindrical* L. using animal bioassays. *Interdisciplinary Toxicology*, *8*(4), 184-192. doi: 10.1515/intox-2015-0028

Ozenda, P. (1991). *Flora and vegetation of the Sahara*. CNRS.

Pagano, M., & Faggio, C. (2015). The use of erythrocyte fragility to assess xenobiotic cytotoxicity. *Cell Biochemistry and Function*, *33*(6), 351-355. doi: 10.1002/cbf.3135

Pagare, S., Bhatia, M., Tripathi, N., Pagare, S., & Bansal, Y. (2015). Secondary metabolites of plants and their role: Overview. *Current Trends in Biotechnology and Pharmacy*, *9*(3), 293-304.

Pastori, T., Flores, F. C., Boligon, A. A., Athayde, M. L., da Silva, C. d. B., do Canto-Dorow, T. S., & Tedesco, S. B. (2013). Genotoxic effects of *Campomanesia xanthocarpa* extracts on *Allium cepa* vegetal system. *Pharmaceutical Biology*, *51*(10), 1249-1255. doi: 10.3109/13880209.2013.786097

Perez-Carreon, J., Cruz-Jiménez, G., Licea-Vega, J., Popoca, E. A., Fazenda, S. F., & Villa-Treviño, S. (2002). Genotoxic and anti-genotoxic properties of *Calendula officinalis* extracts in rat liver cell cultures treated with diethylnitrosamine. *Toxicology in Vitro*, *16*(3), 253-258. doi: 10.1016/s0887-2333(02)00005-x

Petruľová-Poracká, V., Repčák, M., Vilková, M., & Imrich, J. (2013). Coumarins of *Matricaria chamomilla* L.: Aglycones and glycosides. *Food Chemistry*, *141*(1), 54-59. doi: 10.1016/j.foodchem.2013.03.004

Prajitha, V., & Thoppil, J. (2016). Genotoxic and antigenotoxic potential of the aqueous leaf extracts of *Amaranthus spinosus* Linn. using *Allium cepa* assay. *South African Journal of Botany*, *102*, 18-25. https://doi.org/10.1016/j.sajb.2015.06.018

Prance, G. T., Baleé, W., Boom, B., & Carneiro, R. L. (1987). Quantitative ethnobotany and the case for conservation in Ammonia. *Conservation Biology*, *1*(4), 296-310. doi:10.1111/j.1523-1739.1987.tb00050.x

Punnam Chander, M., Kartick, C., Gangadhar, J., & Vijayachari, P. (2014). Ethno medicine and healthcare practices among Nicobarese of Car Nicobar–An indigenous tribe of Andaman and Nicobar Islands. *Journal of Ethnopharmacology*, *158*, 18-24. doi: 10.1016/j.jep.2014.09.046

Radhika, P., & Jyothi, Y. (2019). A review on genotoxicity, its molecular mechanisms, regulatory testing in drug development process. *International Journal of Pharmaceutical Sciences and Research*, *10*(9), 4054-4069.

Ramdane, F., Hadj Mahammed, M., Didi Ould Hadj, M., Hammoudi, R., Hillali, N., Mesrouk, H., Bouafia,N., & Bahaz, C. (2015). Ethnobotanical study of some medicinal plants from Hoggar, Algeria. *Journal of Medicinal Plants Research*, *9*(30), 820-827. doi:10.5897/JMPR2015.5805

Rapido, F., Brittenham, G. M., Bandyopadhyay, S., La Carpia, F., L'Acqua, C., McMahon, D. J., Rebbaa, A., Wojczyk, B., Netterwald, J., & Wang, H. (2017). Prolonged red cell storage before transfusion increases extravascular hemolysis. *Journal of Clinical Investigation*, *127*(1), 375-382. doi: 10.1172/JCI90837

Rashid, S., Ahmad, M., Zafar, M., Sultana, S., Ayub, M., Khan, M. A., & Yaseen, G. (2015). Ethnobotanical survey of medicinally important shrubs and trees of Himalayan region of Azad Jammu and Kashmir, Pakistan. *Journal of Ethnopharmacology*, *166*, 340-351. doi: 10.1016/j.jep.2015.03.042

Rasool Hassan, B. (2012). Medicinal plants (importance and uses). *Pharmaceut Anal Acta*, *3*(10), 2153-2435.

Rather, M. A., Dar, B. A., Sofi, S. N., Bhat, B. A., & Qurishi, M. A. (2016). *Foeniculum vulgare*: A comprehensive review of its traditional use, phytochemistry, pharmacology, and safety. *Arabian Journal of Chemistry*, *9*, S1574-S1583.

Rebbas, K., Bounar, R., Gharzouli, R., Ramdani, M., Djellouli, Y., & Alatou, D. (2012). Plants of interest medicinal and ecological in the area of Ouanougha (M'sila, Algeria). *Phytothérapie*, *10*(2), 131-142. https://doi.org/10.1007/s10298-012-0701-6

Rehman, K., Khan, M. A., Ullah, Z., & Chaudhary, H. J. (2015). An ethnobotanical perspective of traditional medicinal plants from the Khattak tribe of Chonthra Karak, Pakistan. *Journal of Ethnopharmacology*, *165*, 251-259. https://doi.org/10.1016/j.jep.2015.02.035

Ren, N., Atyah, M., Chen, W.-Y., & Zhou, C.-H. (2017). The various aspects of genetic and epigenetic toxicology: Testing methods and clinical applications. *Journal of Translational Medicine*, *15*(1), 1-13. https://doi.org/10.1186/s12967-017-1218-4

Ren-Ren, B., Xiao-Ming, W., & Jin-Yi, X. (2015). Current natural products with antihypertensive activity. *Chinese journal of natural medicines*, *13*(10), 721-729. doi: 10.1016/S1875-5364(15)30072-8

Ressources. (2005). *A guide to medicinal plants in North Africa*.

Rosculete, C. A., Bonciu, E., Rosculete, E., & Olaru, L. A. (2019). Determination of the environmental pollution potential of some herbicides by the assessment of cytotoxic and genotoxic effects on *Allium cepa*. *International Journal of Environmental Research and Public Health*, *16*(1), 75. https://doi.org/10.3390/ijerph16010075

Roy, A. J. I. (2017). A review on the alkaloids an important therapeutic compound from plants. *International Journal of Plant Biotechnology*, *3*(2), 1-9.

Russell, W., & Duthie, G. (2011). Plant secondary metabolites and gut health: The case for phenolic acids. *Proceedings of the Nutrition Society*, *70*(3), 389-396. https://doi.org/10.1017/s0029665111000152

Rychlinska, I., & Nowak, S. (2012). Quantitative determination of arbutin and hydroquinone in different plant materials by HPLC. *Notulae Botanicae Horti Agrobotanici Cluj-Napoca*, *40*(2), 109-113.

Saad, B., & Said, O. (2011). *Greco-Arab and Islamic herbal medicine: Traditional system, ethics, safety, efficacy, and regulatory issues*. John Wiley and Sons.

Sabeen, M., Mahmood, Q., Bhatti, Z. A., Irshad, M., Bilal, M., Hayat, M. T., Irshad, U., Akbar, T. A., Arslan, M., & Shahid, N. (2020). *Allium cepa* assay based comparative study of selected vegetables and the chromosomal aberrations due to heavy metal accumulation. *Saudi Journal of Biological Sciences*, *27*(5), 1368-1374. https://doi.org/10.1016/j.sjbs.2019.12.011

Sanchez-Jimenez, I., Hidalgo, O., & Garnatje, T. (2012). *Echinops spinosissimus* Turra subsp. neumayeri (Vis.) Kožuharov (Asteraceae, Cardueae): A new record for the flora of Greece. *Adansonia*, *34*(1), 129-132.

Sargin, S. A., Selvi, S., & Büyükcengiz, M. (2015). Ethnomedicinal plants of Aydıncık district of Mersin, Turkey. *Journal of Ethnopharmacology*, *174*, 200-216. https://doi.org/10.1016/j.jep.2015.08.008

Sari, M., Sarri, D., Hendel, N., & Boudjelal, A. (2012). Ethnobotanical study of therapeutic plants used to treat arterial hypertension in the Hodna region of Algeria. *Global Journal of Research on Medicinal Plants and Indigenous Medicine*, *1*(9), 411-417.

Sarri, M., Boudjelal, A., Hendel, N., Sarri, D., & Benkhaled, A. (2015). Flora and ethnobotany of medicinal plants in the southeast of the capital of Hodna (Algeria). *Arabian Journal of Medicinal and Aromatic Plants*, *1*(1), 24-30.

Sarri, M., Mouyet, F. Z., Benziane, M., & Cheriet, A. (2014). Traditional use of medicinal plants in a city at steppic character (M'sila, Algeria). *Journal of Pharmacy and Pharmacognosy Research*, *2*(2), 31-35.

Schafer, K. (1998). The cell cycle: A review. *Veterinary pathology*, *35*(6), 461-478.

Sher, H., Aldosari, A., Ali, A., & de Boer, H. J. (2015). Indigenous knowledge of folk medicines among tribal minorities in Khyber Pakhtunkhwa, northwestern Pakistan.

Journal of Ethnopharmacology, *166*, 157-167. https://doi.org/10.1016/j.jep.2015.03.022

Shoaib, M., Shah, I., Ali, N., Adhikari, A., Tahir, M. N., Shah, S. W. A., Ishtiaq, S., Khan, J., Khan, S., & Umer, M. N. (2017). Sesquiterpene lactone! a promising antioxidant, anticancer and moderate antinociceptive agent from *Artemisia macrocephala* jacquem. *BMC Complementary Alternative Medicine*, *17*(1), 1-11. https://doi.org/10.1186/s12906-016-1517-y

Singh, O., Khanam, Z., Misra, N., & Srivastava, M. K. (2011). Chamomile (*Matricaria chamomilla* L.): An overview. *Pharmacognosy Reviews*, *5*(9), 82-95. https://doi.org/10.4103%2F0973-7847.79103

Singh, R. (2015). Medicinal plants: A review. *Journal of Plant Sciences*, *3*(1-1), 50-55.

Singleton, V. L., & Rossi, J. A. (1965). Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents. *American Journal of Enology and Viticulture*, *16*(3), 144-158.

Slama, K., Boumendjel, M., Taibi, F., Boumendjel, A., & Messarah, M. (2020). *Atriplex halimus* aqueous extract abrogates carbon tetrachloride-induced hepatotoxicity by modulating biochemical and histological changes in rats. *Archives of Physiology and Biochemistry*, *126*(1), 49-60. https://doi.org/10.1080/13813455.2018.1489852

Slimani, I., Najem, M., Belaidi, R., Bachiri, L., Bouiamrine, E. H., Nassiri, L., & Ibijbijen, J. (2016). Étude ethnobotanique des plantes médicinales utilisées dans la région de Zerhoun-Maroc. *International Journal of Innovation and Applied Studies*, *15*(4), 846-863.

Słoczyńska, K., Powroźnik, B., Pękala, E., & Waszkielewicz, A. M. (2014). Antimutagenic compounds and their possible mechanisms of action. *Journal of Applied Genetics*, *55*(2), 273-285. https://doi.org/10.1007%2Fs13353-014-0198-9

Sohani, S. (2019). Herbal plants used to treat diseases in India: A review. *International Journal of Pharmacy and Life Sciences*, *10*(9-10), 6385-6387.

Stacks, N. M. (2015). *Apigenin and Naringenin: Natural Sources, Pharmacology and Role in Cancer Prevention*. Nova Science Publishers, Incorporated.

Subramanian, K., Sankaramourthy, D., & Gunasekaran, M. (2018). Toxicity studies related to medicinal plants. *Natural Products and Drug Discovery*, 491-505.

Tabassum, S., Ahmad, S., Rehman Khan, K. R., Tabassum, F., Khursheed, A., Zaman, Q. U., Bukhari, N. A., Alfagham, A., Hatamleh, A. A., & Chen, Y. (2022). Phytochemical profiling, antioxidant, anti-Inflammatory, thrombolytic, hemolytic Activity *in vitro* and in silico potential of *Portulacaria afra*. *Molecules*, *27*(8), 2377. doi: 10.3390/molecules27082377

Taïbi, K. (2009). Détection du changement et de la variabilité climatique en Algérie et étude de leurs impacts sur les agro-écosystèmes. Mémoire de Magister, University of Djelfa, Algérie. pp 156.

Taibi, K., Ait Abderrahim, L., Boussaid, M., Taibi, F., Achir, M., Souana, K., Benaissa, T., Farhi, K. H., Naamani, F. Z., & Said, K. N. (2021). Unraveling the ethnopharmacological potential of medicinal plants used in Algerian traditional medicine for urinary diseases. *European Journal of Integrative Medicine*, *44*, 101339. doi:10.1016/j.eujim.2021.101339

Taïbi, K., Ait Abderrahim, L., Ferhat, K., Betta, S., Taïbi, F., Bouraada, F., & Boussaid, M. (2020). Ethnopharmacological study of natural products used for traditional cancer therapy in Algeria. *Saudi Pharmaceutical Journal*, *28*(11), 1451-1465. https://doi.org/10.1016/j.jsps.2020.09.011

Taïbi, K., Ait Abderrahim, L., Helal, F., & Hadji, K. (2021). Ethnopharmacological study of herbal remedies used for the management of thyroid disorders in Algeria. *Saudi Pharmaceutical Journal*, *29*(1), 43-52. https://doi.org/10.1016/j.jsps.2020.12.004

Takahashi, N., & Umeda, M. (2013). Cell Cycle. In S. Assmann and B. Liu (Eds.), *Cell Biology* (pp. 1-19). Springer New York. https://doi.org/10.1007/978-1-4614-7881-2_11-1

Tayman, C., Cekmez, F., Kafa, I. M., Canpolat, F. E., Cetinkaya, M., Tonbul, A., Uysal, S., Tunc, T., & Sarici, S. U. (2013). Protective effects of *Nigella sativa* oil in hyperoxia-induced lung injury. *Archivos de Bronconeumología*, *49*(1), 15-21. https://doi.org/10.1016/j.arbres.2012.03.013

Telli, A., Esnault, M. A., & Ould El Hadj Khelil, A. (2016). An ethnopharmacological survey of plants used in traditional diabetes treatment in south-eastern Algeria (Ouargla province). *Journal of Arid Environments*, *127*, 82-92. https://doi.org/10.1016/j.jaridenv.2015.11.005

Teoh, E. S. (2016). Secondary metabolites of plants. *Medicinal orchids of Asia*, *5*, 59-73. https://doi.org/10.1007%2F978-3-319-24274-3_5

Timothy, O., Idu, M., Olorunfemi, D., & Ovuakporie-Uvo, O. (2014). Cytotoxic and genotoxic properties of leaf extract of *Icacina trichantha* Oliv. *South African Journal of Botany*, *91*, 71-74. https://doi.org/10.1016/j.sajb.2013.11.008

Tolouee, M., Alinezhad, S., Saberi, R., Eslamifar, A., Zad, S. J., Jaimand, K., Taeb, J., Rezaee, M. B., Kawachi, M., & Shams-Ghahfarokhi, M. (2010). Effect of *Matricaria chamomilla* L. flower essential oil on the growth and ultrastructure of Aspergillus niger van Tieghem. *International journal of Food Microbiology*, *139*(3), 127-133. https://doi.org/10.1016/j.ijfoodmicro.2010.03.032

Toul, F., Djendar, A., Seladji, M., & Berroukeche, F. (2022). Algerian *Bunium incrassatum* Seeds: Effects of extraction solvent polarity on phenolic profile and antioxidant activity. *Journal of The Turkish Chemical Society Section A: Chemistry*, *9*(2), 475-482. https://doi.org/10.18596/jotcsa.1058060

Tsafantakis, N., Zelianeos, K., Termentzi, A., Vontzalidou, A., Aligiannis, N., & Fokialakis, N. (2019). Triterpenes from *Echinops spinosissimus* Turra subsp. spinosissimus. *Phytochemistry Letters*, *30*, 273-277. https://doi.org/10.1016/j.phytol.2019.02.005

Tülay Aşkin, Ç. (2018). Introductory Chapter: Cytotoxicity. In Ç. Tülay Aşkin (Ed.), *Cytotoxicity* (pp. Ch. 1). IntechOpen. https://doi.org/10.5772/intechopen.77244

Tuttolomondo, T., Licata, M., Leto, C., Savo, V., Bonsangue, G., Gargano, M. L., Venturella, G., & La Bella, S. (2014). Ethnobotanical investigation on wild medicinal plants in the Monti Sicani Regional Park (Sicily, Italy). *Journal of Ethnopharmacology*, *153*(3), 568-586. https://doi.org/10.1016/j.jep.2014.02.032

Umair, M., Altaf, M., & Abbasi, A. M. (2017). An ethnobotanical survey of indigenous medicinal plants in Hafizabad district, Punjab-Pakistan. *Plos One*, *12*(6), e0177912. https://doi.org/10.1371/journal.pone.0177912

VC, M., & Stephen, J. (1980). Adriamycin induced genetic toxicity as demonstrated by the *Allium* test. *Cytologia*, *45*(4), 769-777.

Villagómez-Rodríguez, A., Pérez-Ramos, J., Esquivel-Campos, A. L., Pérez-González, C., Soto-Peredo, C. A., & Pérez-Gutiérrez, S. (2019). Anti-inflammatory activity of *Jefea gnaphalioides* (a. gray), Astereaceae. *BMC Complementary and Alternative Medicine*, *19*(1), 263. https://doi.org/10.1186/s12906-019-2654-x

Volpato, G., Kourková, P., & Zelený, V. (2012). Healing war wounds and perfuming exile: The use of vegetal, animal, and mineral products for perfumes, cosmetics, and skin healing among Sahrawi refugees of Western Sahara. *Journal of Ethnobiology and Ethnomedicine*, *8*(1), 1-20. https://doi.org/10.1186/1746-4269-8-49

Vuolo, M. M., Lima, V. S., & Junior, M. R. M. (2019). Phenolic compounds: Structure, classification, and antioxidant power. *Bioactive Compounds*, 33-50. https://doi.org/10.1016/B978-0-12-814774-0.00002-5

Walker, D., Lutts, S., Sánchez-García, M., & Correal, E. (2014). *Atriplex halimus* L.: Its biology and uses. *Journal of Arid Environments, 100*, 111-121. https://doi.org/10.1016/j.jaridenv.2013.09.004

Wang, T.-y., Li, Q., & Bi, K.-s. (2018). Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. *Asian Journal of Pharmaceutical Sciences, 13*(1), 12-23. https://doi.org/10.1016/j.ajps.2017.08.004

Wang, X., Wang, T., Pan, T., Huang, M., Ren, W., Xu, G., Amin, H. K., Kassab, R. B., & Abdel Moneim, A. E. (2020). *Senna alexandrina* extract supplementation reverses hepatic oxidative, inflammatory, and apoptotic effects of cadmium chloride administration in rats. *Environmental Science and Pollution Research, 27*, 5981-5992. https://doi.org/10.1007/s11356-019-07117-3

WHO. (2004). *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems*. World Health Organization.

WHO. (2018). *Global Health Observatory. who.int/gho/database/en/.* World Health Organization.

Yahyaoui, A., Khedher, O., Rigane, G., Salem, R., & Moussaoui, Y. (2018). Chemical analysis of essential oil from *Echinops spinosus* L. roots: Antimicrobial and antioxidant activities. *Revue Roumaine de Chimie*, *63*(3), 199-204.

Yang, L., & Stöckigt, J. (2010). Trends for diverse production strategies of plant medicinal alkaloids. *Natural Product Reports, 27*(10), 1469-1479. https://doi.org/10.1039/c005378c

Yuan, H., Ma, Q., Ye, L., & Piao, G. (2016). The traditional medicine and modern medicine from natural products. *Molecules, 21*(5), 559. https://doi.org/10.3390/molecules21050559

Ždralović, A., Mesic, A., Eminović, I., & Parić, A. (2019). Cytotoxic and genotoxic activity of *Plantago major* L. extracts. *Caryologia*, *72*(3), 35-40. doi:10.13128/caryologia-759

Zeghib, K. (2020). *Evaluation of the pharmacological effects of Atriplex halimus L. aqueous extract against pathophysiological alterations induced by Benzene and Sodium benzoate (food additive): Experimental study in rats*. Thèse de doctorat, University of Eloued, Algérie.

Zeghib, K., & Boutlelis, D. A. (2021). Food additive (sodium benzoate)-induced damage on renal function and glomerular cells in rats; modulating effect of aqueous extract of *Atriplex halimus* L. *Iranian Journal of Pharmceutical Research, 20*(1), 296-306. https://doi.org/10.22037/ijpr.2020.111634.13272

Zellagui, A., Gherraf, N., Elkhateeb, A., Hegazy, M.-E. F., Mohamed, T. A., Touil, A., Shahat, A., & Rhouati, S. (2011). Chemical constituents from Algerian *Foeniculum vulgare* aerial parts and evaluation of antimicrobial activity. *Journal of the Chilean Chemical Society*, *56*(3), 759-763. doi:10.4067/S0717-97072011000300008

Zhang, H., & Dawe, R. K. (2011). Mechanisms of plant spindle formation. *Chromosome Research*, *19*(3), 335-344. https://doi.org/10.1007/s10577-011-9190-y

Zougagh, S., Belghiti, A., Rochd, T., Zerdani, I., & Mouslim, J. (2019). Medicinal and aromatic plants used in traditional treatment of the oral pathology: The ethnobotanical survey in the economic capital Casablanca, Morocco (North Africa). *Natural products and bioprospecting*, *9*(1), 35-48. doi: 10.1007/s13659-018-0194-6 .