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PHYTOCHEMICAL SCREENING, ELEMENTAL COMPOSITION AND IN VITRO ANTIOXIDANT ASSESSMENT OF SELECTED UAE MEDICINAL PLANTS

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PHYTOCHEMICAL SCREENING, ELEMENTAL COMPOSITION AND *IN VITRO* ANTIOXIDANT ASSESSMENT OF SELECTED UAE MEDICINAL PLANTS

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This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Science in Environmental Sciences

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Declaration of Original Work

I, Amina Mukhtar Dirir, the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this thesis entitled "*Phytochemical Screening, Elemental Composition and In Vitro Antioxidant Assessment of Selected UAE Medicinal Plants*", hereby, solemnly declare that this thesis is my own original research work that has been done and prepared by me under the supervision of Professor Taoufik Ksiksi in the College of Science at UAEU. This work has not previously been presented or published, or formed the basis for the award of any academic degree, diploma or a similar title at this or any other university. Any materials borrowed from other sources (whether published or unpublished) and relied upon or included in my thesis have been properly cited and acknowledged in accordance with appropriate academic conventions. I further declare that there is no potential conflict of interest with respect to the research, data collection, authorship, presentation and/or publication of this thesis.

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Abstract

Medicinal herbs have been used since prehistoric times to alleviate pain and to treat many different diseases. In recent decades, there has been a growing interest on natural product research, particularly on herbal plants and their bioactive constituents. The resurgence of interest in medicinal plants is primarily attributed to the inefficacy of synthetic medicines in combating many diseases as well as to their toxic and side effects. The flora of the UAE is rich with various medicinal plants that were utilized by the indigenous people for different therapeutic purposes. Unfortunately, there are still gaps of knowledge, research and development on the phytochemical and pharmacological aspects of the UAE medicinal plants. Therefore, this thesis is aimed to perform phytochemical screening, to determine the content of phenolic and flavonoid compounds, to determine the content of thirteen chemical elements and to evaluate the *in vitro* antioxidant activities of the crude extracts of six UAE medicinal plants. The medicinal plants examined in this work were: *Acridocarpus orientalis, Leptadenia pyrotechnica, Calotropis procera, Tecomella undulata, Euphorbia larica* and *Cyperus conglomeratus*. The phytochemical screening was performed using preliminary chemical tests. The total phenolic and flavonoid contents were determined by Folin Ciocalteau and aluminum chloride colorimetric methods, respectively. The elemental analysis was performed using inductively coupled plasma-optical emission spectrometry (ICP-OES). The DPPH, ABTS and FRAP assays were used to assess the antioxidant activities of the selected medicinal plants. Results revealed the presence of phenols, flavonoids and terpenoids in all six medicinal plants. Different amounts of phenolic and flavonoid contents were recorded in the different plant extracts. The phenolic content was found to be highest in *Acridocarpus orientalis* extract (506.42 mg GAE/g DE) and the lowest in *Cyperus conglomeratus* extract (61 mg GAE/g DE). Similarly, the highest total flavonoid content was revealed in *Acridocarpus orientalis* (454.37 mg QE/g DE), while *Cyperus conglomeratus* had the least total flavonoid content (9.54 mg QE/g DE). The average concentrations of macro-elements were ranged from 3175 to 37,596; 567.49 to 13,472; 4452.16 to 15,562 and 205.31 to 6837.46 mg/kg for Ca, Mg, K and Na, respectively. All the plants crossed the allowable levels set for iron, manganese, copper, chromium and aluminum.

Acridocarpus orientalis showed the highest antioxidant activity with an IC_{50} of 34 µg/mL and 45 µg/mL for the DPPH and ABTS radical scavenging assays, respectively. The reducing power of *Acridocarpus orientalis* was found to be dose dependent. The chemical content and the biological properties of the majority of the plants were studied for the first time in the UAE and therefore their uses in the traditional medicine against different diseases were scientifically validated.

Keywords: Phytochemicals, chemical elements, antioxidants, *Acridocarpus orientalis, Leptadenia pyrotechnica, Calotropis procera, Tecomella undulata, Euphorbia larica, Cyperus conglomeratus.*

Title and Abstract (in Arabic)

مسح للمواد الكيميائية النباتية وتحديد محتوى العناصر الكيميائية لنباتات طبية مختارة من بيئة الإمارات مع تقييم قدرتها على مقاومة الأكسدة

الملخص

إستخدمت النباتات الطبية منذ العصور القديمة لتخفيف الآلام ولعلاج العديد من الأمراض المختلفة. في العقود الأخيرة، كان هناك اهتمام متزايد بأبحاث المنتجات الطبيعية، لا سيما بالنباتات الطبية ومركباتها النشطة بيولوجياً. يعزى عودة الإهتمام بالنباتات الطبية في المقام الأول إلى عدم كفاءة العقاقير الصناعية في مكافحة العديد من الأمراض فضلاً عن آثارها السامة والجانبية. تزخر بيئة الإمارات بالعديد من النباتات الطبية المختلفة التي استخدمها السكان الأصليون لأغراض علاجية مختلفة. لسوء الحظ، لا تزال هناك فجوات في المعرفة والبحث والتطوير على الجوانب الأحيائية والكيميائية للنباتات الطبية في دولة الإمارات. لذلك، تهدف هذه الأطروحة إلى إجراء فحص أولي للمواد الكيميائية النباتية، تحديد محتوى مركبات الفينول والفلافونويد، تحديد محتوى ثلاثة عشر عنصراً كيميائياً بالإضافة إلى تقييم القدرة على مقاومة الأكسدة مخبرياُ للمستخلصات الخام لستةٍ من النباتات الطبية الإماراتية. النباتات الطبية التي تم فحصها في هذه الدراسة هي: *Acridocarpus orientalis, Leptadenia pyrotechnica, Calotropis procera, Tecomella undulata, Euphorbia larica and Cyperus conglomeratus*. تم إجراء الفحص الكيميائي النباتي باستخدام إختبارات كيميائية أولية. تم تحديد محتوى مركبات الفينول والفلافونويد الكلية باستخدام منهجية ال Folin–Ciocalteau و aluminum chloride، على التوالي. تم إجراء تحليل العناصر الكيميائية باستخدام الأداة التحليلية (ICP-OES). كما وقد تم استخدام منهجية ال DPPH, ABTS و FRAP لتقييم الأنشطة المضادة للأكسدة مخبرياً للنباتات الطبية المختارة.

كشفت النتائج عن وجود الفينولات والفلافونويد والتربينويدات في جميع النباتات الطبية الستة. تم العثور على كميات مختلفه من المحتويات الفينوليه والفلافونويديه في المستخلصات النباتية. وجد أن المحتوى الفينولي هو الأعلى في مستخلص نبتة القفص بينما هو الأدنى في مستخلص نبتة التندا. بالمثل، فإن أعلى محتوى للفلافونويد وجد في نبتة القفص بينما أدنى محتوى وجد في نبتة التندا. احتوت النباتات على عناصر مختلفة من المعادن الكبرى والصغرى والخطيرة. أظهرت نبتة القفص أعلى نشاط مضاد للأكسدة من بين جميع النباتات. تمت دراسة غالبية النباتات لأول مرة في دولة وتم التحقق من صحة استخداماتها في الطب التقليدي ضد الأمراض المختلفة.

مفاهيم البحث الرئيسية: المواد الكيميائية النباتية، العناصر الكيميائية، مضادات الأكسده، القفص، المرخ، العُشر، فارفار، العسبق، الثندا.

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Dedication

To my father "Mukhtar":

A great man

To my mother "Farhiya":

A strong women

To my sisters:

My best friends

To my brothers:

My real supporters

To all the Somali people:

Who strive for excellence

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List of Abbreviations

ALT	Alanine AminoTransferase
ALP	Alkaline Phosphatase
AST	Aspartate AminoTransferase
Bcl-2	B-cell Leukemia 2
CuZnSOD	Copper Zinc Superoxide Dismutase
DDB	4,4'-Dimethoxy-5,6,5',6'- Dimethylene-Dioxy-2,2'-Dicarboxylate Biphenyl
DNA	Deoxyribonucleic Acid
EPA	Environmental Protection Agency
FAO/WHO	Food and Agriculture Organization/World Health
FeSOD	Iron Superoxide Dismutase
FRAP	Ferric Reducing Antioxidant Power
GC-MS	Gas Chromatography Mass Spectrometry
GSH	Glutathione
GSSG	Glutathione Disulfide
HDL	High Density Lipoproteins
HPLC ESIMS/ MS	High-Performance Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry
IC_{50}	Half Maximal Inhibitory Concentration
LOX	Lipoxygenase
MnSOD	Manganese Superoxide Dismutase
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromidefor
NADPH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen

NDGA	Nordihydroguaiaretic Acid
NFκB	Nuclear Factor Kappa Beta
NiSOD	Nickel Superoxide Dismutase
pH	Potential of Hydrogen
PPM	Parts Per Million
ROS	Reactive Oxygen Species
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TBARS	Thiobarbituric Acid Reactive Substances
UV	Ultraviolet
WHO	World Health Organization

Chapter 1: Introduction

1.1 Medicinal plants

Medicinal plants have been used since ancient times to alleviate pain and to treat many different diseases. Some of the earliest evidence of plant utilization for therapeutic purposes can be found in the Mesopotamian clay tablets, Artharvaveda and in the Eber Papyrus in Egypt [1]. Medicinal plants have contributed to the establishment of complex traditional medicine systems in many countries around the world such as China and India [2]. Currently, there are still many people rely on medicinal plants as a primary mean to improve health and to treat many different ailments. According to available statistics, 80% of the world population, particularly those settle the developing countries, utilize herbal medicines and plant-based natural products for healing purposes [3]. As stated by WHO, medicinal plant is any plant that possesses therapeutically valuable chemicals, which can act as a starting material for the partial chemical synthesis of novel chemical compounds with diverse pharmacological actions [4].

In recent decades, there has been a growing interest in the investigation of herbal plants and their bioactive compounds. In a global scale, the trend of using medicinal plants is evident from the rise in research studies carried out by scientists from various fields of study [5]. Many plants provide a wide array of diverse chemical compounds that can be utilized for different pharmaceutical and commercial purposes [6]. One of the most important factors that has contributed in shifting the attention towards the alternative medicine, is the inefficiency of synthetic drugs in combating many diseases. Furthermore, plant chemical compounds exhibited a lesser toxicity and collateral effects than most synthetic medicines [7].

1.2 Phytochemicals

Phytochemicals are a group of natural organic chemicals that are involved in the plant metabolic processes [8]. On the basis of their role in plant metabolism, plant chemical compounds have been classified into primary and secondary metabolites [9]. Primary metabolites play a fundamental role in plant growth, development and reproduction. Examples of primary metabolites include lipids, proteins and carbohydrates [10]. In contrast, secondary metabolites have no direct role in the plant physiological and metabolic processes. They are biosynthesized from primary metabolites and considered as an end products of the primary metabolism [11]. Another profound difference between primary metabolites and secondary metabolites, is that secondary metabolites are species-specific. Certain secondary metabolites exist solely in taxonomically related groups of plant species, while primary metabolites are found in all plant kingdom [12].

According to their biosynthetic origin, plant secondary metabolites have been classified into three distinct groups: terpenes, phenolics and nitrogen containing compounds [13]. Terpenoids are diverse chemical group that contain highly valuable bioactive compounds such as phytol, tocopherol and sterols [14]. Phenolics are chemical compounds that are ubiquitously found in nature and possess many health beneficial effects. Phenolics contain different chemical classes such as anthocyanins, cinnamic acids, lignin and flavonoids [15]. Alkaloids are nitrogen containing chemical compounds that are biosynthesized by many living organisms such as animals, fungi, plants and bacteria. Several biological activities have been attributed to alkaloids such as antimalarial and anticancer activities [16].

The biotic and abiotic stresses trigger the expression of certain genes that encode enzymes responsible of the production of certain secondary metabolites [17]. This is broadly supported by many studies that demonstrated the accumulation of phytochemicals in plants during the time that they were subjected to different environmental stimuli. Numerous crop plants such as lettuce [18], tomato [19] and potato [20] have accumulated antioxidants and medicinally valuable secondary metabolites when they exposed to stresses imposed by the surrounding environment. It s noteworthy to mention that these group of chemical compounds perform a myriad of crucial functions in plants such as the protection against UV radiation and the attraction of the insect pollinators [21].

Beside their valuable roles in plants, many secondary metabolites possess distinct pharmacological actions beneficial for humans. Several epidemiological studies and meta-analyses have shown an inverse correlation between the consumption of plant-based foods and the incidence of chronic diseases such as stroke [22], diabetes [23] and cancer [24]. Plant-bioactive compounds act as a cofactors and inhibitors of enzyme-catalyzed reactions, substrates for biochemical reactions and scavengers of free radicals and toxic compounds [25]. Among the health promoting phytochemicals that have been widely studied are carotenoids and phenolic compounds. Carotenoids are members of the tetraterpenes family and are biosynthesized by plants, fungi and algae [26]. Carotenoids have received a great attention because of their pivotal role in the prevention of chronic diseases such as cancer and cardiovascular diseases [27 29]. Moreover, considerable pool of evidence has pointed to the healthful benefits that are associated with phenolic compounds. Phytophenols are known to possess anticancer, antiaging and antidiabetic effects [30]. Table 1 illustrates other examples of phytochemicals and their biological properties.

Table 1: Examples of some phytochemicals and their biological properties

Phytochemicals	Examples	Biological properties	References
Diterpenes	Clerodanes	Antiulcer, cytotoxic and antiinflammatory activities	[31]
	Marrubiin	Cardioprotective and antidiabetic activities	[32]
	Diisocyanoadociane	Antimalarial activity	[33]
Tannins	Corilagin	Antiinflammatory and antiapoptotic activities	[34]
Quinones	Reserpine	Antibacterial and antioxidant activities	[35]
	Vinblastine	Anticancer activity	[36]
Phenylpropanoids	Genistein	Anticancer activity	[37]
	Quercetin	Antioxidant activity	[38]
	Galangin	Antitumor and antimutagenic activities	[39]

1.2.1 The antimicrobial action of phytochemicals

The discovery of antibiotics is one of the salient medical discoveries that has contributed to the eradication of several pathogenic microbes such as bacteria and viruses. However, the extensive and indiscriminate use of antibiotics has led to microbial resistance to antibiotics and to the inefficiency of antibiotics in hampering microbial growth [40]. Microbial strains take several resistance mechanisms through which they avoid the fatal effect of antibiotics. These mechanisms include antibiotic inactivation, modification of the antibiotic target site and the expression of efflux pump genes [41].

There are a current efforts and attempts to address this challenge by looking for other novel antimicrobial drugs, particularly those derived from plant species. Numerous plant secondary metabolites such as quinones, alkaloids, tannins, lignans and terpenoids showed toxicity against miscellaneous groups of pathogenic microorganisms [42]. These metabolites exert their antimicrobial action via a variety of mechanisms such as the prevention of biofilm formation and the suppression of efflux pumps function [43].

Biofilms are complex microbial communities that are aggregated on either biotic or abiotic surfaces. These clustered communities of microbes are coated in a self-generated matrix that is typically comprised of polysaccharides, proteins and DNA [44]. Microbial strains utilize this polymer matrix as a protective barrier against the antimicrobial agents [45]. Among the plant secondary metabolites that have shown a devastating effect against microbial assemblies are beta-sitosterol glucoside [46], thymol [47] and eugenol [48].

Efflux pumps are cytoplasmic proteins responsible of transmitting toxic compounds and xenobiotics from inside the cell to the surrounding environment. Such proteins exist in Gram positive bacterial cells, Gram negative bacterial cells and similarly in the eukaryotic cells [49]. An accumulating body of evidence demonstrated the role of efflux pumps in the microbial resistance to the antimicrobial drugs [50,51]. Intriguingly, a number of secondary metabolites showed their ability to suppress the function of these transporters. Examples of efflux pumps inhibitors derived from plants include reserpine, chalcone, carnosol and carnosic acid [52].

In addition to the previously discussed mechanisms, phytochemicals exert their antimicrobial action through other mechanisms such as the destruction of the microbial cell wall, caspase activation and ROS generation [53].

1.2.2 Dietary phytochemicals as a chemopreventive agents

Cancer is one of the most serious diseases that characterized by a rapid and uncontrolled division of the normal cells in the human body [54]. The common types of cancer management include surgery, radiotherapy and chemotherapy [55]. In fact, these kinds of cancer therapies suffer from several major drawbacks such as the non-selectivity to the cancer cells and the development of resistance to these treatments [56]. Currently, the trending strategy is to focus on prevention rather than treatment. It has been suggested that physical activity and the consumption of plant-based foods play a major role in reducing the risk of cancer incidence [57]. A number of dietary phytochemicals, including curcumin, epigallocatechin gallate (EGCG) and resveratrol have emerged as a promising chemopreventive agents [58]. Dietary phytochemicals may exhibit their anticancer activity through the induction of cell cycle arrest and the inhibition of oncogene expression [59].

Curcumin is a yellow colored polyphenol, which being derived from the rhizome of *Curcuma longa* and from other species that belong to the same genus [60]. The interest in studying the anti-cancer properties of curcumin is attributed to the selective role of curcumin towards the tumor cells as well as to its non-toxicity to the normal cells [61]. Evidence indicates that curcumin exhibited therapeutic effects on many different cancer types including lung [62], ovarian [63] and colon [64] cancers. Curcumin exerts it s anticancer effect through the suppression of transcription factors and the upregulation of p53 expression [65].

EGCG is a bioactive polyphenol found in green tea and possesses many health benefits [66]. A number of studies have demonstrated the inhibitory effects of EGCG on various tumor cells [67 69]. The mechanisms of action underlying the anticancer effect of EGCG involve suppression of the NF_KB activation and the induction of cell cycle arrest [70]. Moreover, EGCG has shown to exhibit antioxidant, antidiabetic and antiinflammatory activities [71].

Resveratrol is a major phytoalexin produced by grapes as a defense response against the various environmental stimuli [72]. Resveratrol found in plants in *cis* and *trans* configurations [73]. Recently, resveratrol has evoked considerable interest due to its beneficial effects on a number of chronic diseases such as diabetes, cardiovascular diseases and cancer [74]. Resveratrol has shown to exhibit an inhibitory effects on colon [75], breast [76] and gastric [77] cancer cells. It mediates its antitumor effects through the induction of cell cycle arrest and the activation of Forkhead proteins [78].

1.2.3 Phytochemicals in pest management

In the last decades, synthetic pesticides played a major role in controlling pests that threat the survival of the agricultural systems [79]. Nevertheless, majority of chemical pesticides are toxic to living organisms and disturb the natural balance of the ecosystem [80]. In addition, synthetic pesticides have been highly linked to many different cancers such as brain, pancreatic, breast, kidney and prostate cancers [81]. Therefore, all of these drawbacks combined have necessitated the search of other novel effective alternatives.

Plants exude a plethora of allelopathic chemicals as a defense mechanism against other organisms in the surrounding environment [82]. The use of plant natural products in crop pest management attracted attention in recent years. Plant-derived pest control agents are ecofriendly, more biodegradable than their synthetic counterparts and pose less risk to the human health [83]. The mechanisms of action of botanical pesticides include suppressing acetylecholinestrase activity, perturbing sodium ion channels of nerves and blocking octopamine receptors [84].

There are several examples of pesticides developed from plant derived natural compounds. Callicarpenal and intermedeol are natural terpenoids derived from the leaves of American beautyberry (*Callicarpa americana*) and Japanese beautyberry (*Callicarpa japonica*). These two natural compounds have shown to exhibit significant insect repellent activities [85]. Rotenone is another example of pesticide of plant origin. Rotenone is a natural hydrophobic compound found mainly in the roots and stems of *Lonchocarpus* and *Derris* species [86]. It s mode of action involves inhibition of cellular respiration [84].

1.3 Antioxidant defense system in plants

Plant exposure to stressful conditions lead to excessive production of reactive oxygen species, which are highly reactive molecules that can cause irreversible damages to macromolecules such as lipids, DNA and proteins [87]. The accumulation of such toxic radicals in plant cells lead to the phenomenon of the so-called oxidative stress. Oxidative stress occurs when the level of oxidants exceed the level of antioxidants, causing a perturbation in redox signaling and a drastic impairment at the molecular level [88]. However, despite their damage, reactive oxygen species perform, at low concentration, important functions for aerobic organisms. The term redox biology describes how is a slight elevation in ROS levels lead to the activation of signaling pathways to start the cellular processes [89].

Plants deploy an intricate antioxidant defense machinery to cope with the overproduction of ROS under unfavorable environmental conditions. Antioxidants perform their bio-protective role through donating electrons and reducing reactive oxygen species to less toxic compounds [90]. Despite the attempts to classify plant antioxidant system according to their molecular weight, mechanism of action and hydrophobicity, their classification according to their catalytic activity is the most common approach among these various classifications [91]. Enzymatic defenses include superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase. The non-enzymatic antioxidants are represented by ascorbic acid, alpha-tocopherol and glutathione [92]. The following is a short illustration of the major enzymatic and non-enzymatic antioxidants that are involved in the process of ROS nullification in plants.

1.3.1 Enzymatic antioxidants

1.3.1.1 Superoxide dismutase (SOD)

Superoxide dismutase (SOD) is one of the major antioxidant enzymes that catalyzes the dismutation of superoxide radical to molecular oxygen and hydrogen peroxide [93]. According to the metal cofactor that attached to their catalytic site, SODs have been classified into four categories: FeSOD, MnSOD, CuZnSOD and NiSOD, which operate in the various subcellular compartments. The prokaryotic cells contain all of the four classes of SODs. However, in the eukaryotic cells, FeSOD can be detected in the chloroplasts, MnSOD can be detected in the mitochondria and in the peroxisomes and CuZnSOD can be found in the cytosol, in the chloroplast and in the extracellular space [94]. It has been reported that plant exposure to environmental stresses such as high temperature [95], high salinity [96] and metal toxicity [97] is accompanied with an increase in the SOD activity in the plant cells. SOD has been postulated to be important in plant tolerance to the various forms of stresses as well as in hindering the potential onset of cellular oxidative damage [98].

1.3.1.2 Catalase (CAT)

Catalase (CAT) is a dismutase enzyme that catalyzes the breakdown of two molecules of hydrogen peroxide into oxygen and water [99]. CAT is a tetrameric heme-containing enzyme that possesses a rapid turnover rate. In other words, one CAT molecule has the capability to change approximately 6 million molecules of hydrogen peroxide into oxygen and water in one minute [100]. In addition, although studies have indicated the presence of CAT in other cellular compartments, it s evident that peroxisome is the major site of CAT, where it detoxifies hydrogen peroxide and mitigates the damage of oxidative stress [101]. In transgenic cassava, overexpression

of catalase genes enhanced cassava resistance to oxidative stress that triggered by *Tetranychus cinnabarinus* [102].

1.3.1.3 Glutathione reductase (GR)

Glutathione reductase (GR) is a member of NADPH-dependent oxidoreductase family and exists in prokaryotic cells as well as in eukaryotic cells. This enzyme works by catalyzing the reduction of GSSG to GSH, where the latter is considered as an important antioxidant molecule that involves in ROS detoxification and in plant tolerance against oxidative stress [103]. A number of studies have indicated an increase in GR activity in parallel with plant exposure to cadmium-induced stress [104 107]. Moreover, UV radiation augmented the production of GR in *Coleus forskohlii* [108] and in *Arachis hypogaea* [109].

1.3.1.4 Glutathione peroxidase (GPx)

Plant glutathione peroxidase belongs to thioredoxin-dependent peroxidase family [110]. The biochemical role of this selenium-dependent enzyme, is to reduce hydrogen peroxide and lipid hydroperoxides to water and the corresponding alcohols, respectively, utilizing thioredoxin as an electron donor [111]. In fact, the activity of glutathione peroxidase can be linked with glutathione transferase (GST) isoenzymes, where both have shown a pivotal role in eliminating lipid hydroperoxides and other free radicals in plants under different environmental circumstances [110]. Haluskova *et al.* [112], reported that the activity of glutathione peroxidase has increased in barley root tips when it was exposed to different abiotic stresses along with an increase in the activity of other antioxidant enzymes. Moreover, a recent study showed that fluoride stress caused an increment of glutathione peroxidase activity in olive plants [113].

1.3.2 Non-enzymatic antioxidant molecules

1.3.2.1 Ascorbic acid (Vitamin C)

Ascorbic acid, also known as vitamin C, is one of the powerful antioxidant molecules that plays an important role in plant tolerance against oxidative stress induced by aerobic cellular metabolism and photosynthesis [114]. Ascorbic acid is biosynthesized in plant mitochondria via the oxidation of L-galactono-1,4-lactone (L-GalL), and then it transported to the other cell compartments [115]. There are many supporting evidence for the role played by ascorbic acid in plant acclimation under harsh environmental conditions [116,117]. In humans, vitamin C is essential for many enzyme-catalyzed reactions, collagen production, free radicals scavenging, neurotransmitters synthesis and tyrosine metabolism. Unfortunately, vitamin C can t be synthesized by the human body, since humans lack the enzyme needed for the last step in vitamin C synthesis. Therefore, vitamin C should be obtained from exogenous sources to compensate it s deficiency in human bodies. [118].

1.3.2.2 ستocopherol (Vitamin E)

Tocopherols are solely found in the plastid and in the thylakoid membranes, and can be synthesized only by plants, algae and some cyanobacteria [119]. Tocopherols, also known as vitamin E, are lipophilic potent antioxidant molecules. These molecules protect the lipids and other membrane constituents from the damage induced by oxidative stress. The amount of ستocopherol increases remarkably during plant growth and during plant response to the external stimuli [90]. For example, vitamin E level has increased during *Arabidopsis thaliana* exposure to photoinhibition and photooxidative stresses [120].

1.4 Plant-derived drugs

Despite the emergence of recent techniques in drug design such as molecular modelling, plants are still considered as one of the indispensable sources of drug discovery and development [121]. Plants are used in therapy either as crude extract or provide the chemicals (secondary metabolites) which act as precursor for the synthesis, or the pharmacophore for drug discovery or the pharmacological tools to understand the pharmacological and molecular mechanism of action [122]. The following is a short illustration of some plant-based drugs and their pharmacological activities.

Artemisinin was isolated from the Chinese herb *Artemisia annua* and was utilized to combat *Plasmodium falciparum* malaria [123]. Artemisinin was firstly discovered by the Chinese chemist, Tu Youyou, who recently received the 2015 Noble Prize in Physiology or Medicine for her discovery and scientific contribution [124]. To date, there has been little agreement on artemisinin s mechanism of action. The most accepted theory leans toward the cleavage of the endoperoxide bridges by the intraprasitic heme or iron. This results in the formation of free radicals that will eventually deteriorate the function of the macromolecules (e.g., proteins) in the parasite s cells and subsequently to parasite death [125]. Moreover, artemisinin and its derivatives have shown to exhibit anticancer, antiinflammatory, antifungal and antiviral activities [126].

Bicyclol is another typical example of drugs that were derived from medicinal plants. Bicyclol is a novel synthetic drug which has been used to treat hepatitis and gained acceptance in several countries around the world [127]. The story of bicyclol discovery started when a group of Chinese scientists began studying *Fructus Schizandrae*, a Chinese herb that exhibited hepatoprotective effects. After isolating a

number of chemical compounds, schizandrin C was found to be the most effective compound against liver damage. Subsequently, schizandrin C was subjected to total chemical synthesis, however, the attempts to achieve this were unsuccessful. Fortunately, schizandrin C analogues were synthesized and evaluated for potential hepatoprotective effects [128]. Bicyclol, which derived from one of the analogues (DDB), showed remarkable hepatoprotective effects, good bioavailability and pharmacodynamics [129]. A number of studies demonstrated the hepatoprotective effects of bicyclol on liver injury induced by alcohol [130], dimethylnitrosamine [131] and concanavalin A [132] in experimental rats. Bicyclol mediates its hepatoprotective effects via different mechanisms such as scavenging free radicals, impeding fibrogenesis and sustaining the glutathione redox status in the hepatic mitochondria [133].

The genus *Taxus* has attracted attention, mainly because of the presence of diterpene alkaloids [134]. Among these diterpene alkaloids is paclitaxel **(**Taxol®). Paclitaxel is a cancer chemotherapy medication derived from the bark of *Taxus brevifolia (*Pacific yew tree) [135]. It was firstly identified by Monroe Wall and Mansukh Wani in 1967. After four years, they successfully determined its chemical structure [136]. Many studies referred to taxol as an effective anticancer agent that has been capable of inhibiting the growth of cancerous tumors in breast [137], ovarian [138] and lung [139]. The mechanisms of action underlying the anticancer effect of taxol involve targeting tubulin and promoting cell cycle arrest [140]. Furthermore, it has been reported that taxol targets the mitochondria and suppresses the function of the anti-apoptotic protein Bcl-2 [141].

Chapter 2: Literature Review

2.1 *Acridocarpus orientalis*

Acridocarpus orientalis (Figure 1) is a valuable medicinal herb found mostly in Africa, Mediterranean, Asia and in some regions of the Arabian Peninsula. This plant has been utilized in the traditional medicine for various therapeutic purposes such as relieving headache pain and treating paralysis [142]. There are also other *Acridocarpus* species that are widely employed in the traditional medicine around the world. In Yemen, *Acridocarpus socotranus* is utilized to mitigate headache and muscle pain [6]. Moreover, *Acridocarpus chloropterus* has shown to exhibit antiplasmodial, antitrypanosomal and antileishmanial activities [143].

Figure 1: *Acridocarpus orientalis*

2.1.1 Phytochemistry

Investigations of the chemical compounds of *Acridocarpus orientalis* resulted in the isolation of two flavonoids: morin **(1)** and morin-3-*O*-سD-glucopyranoside **(2)** [142]. The chemical structure of the isolated compounds are illustrated in Figure 2.

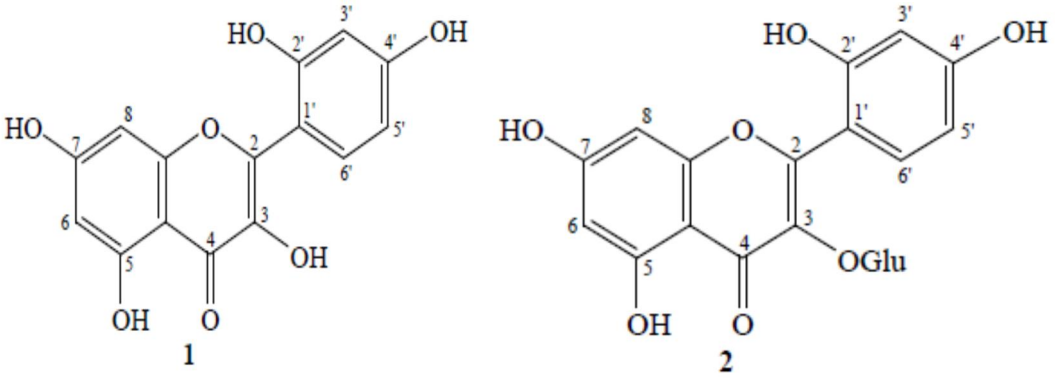


Figure 2: Chemical structure of two flavonoids from *Acridocarpus orientalis* [142]

2.1.2 Pharmacology

2.1.2.1 Anticancer activity

Hussain *et al.* [142], studied the cytotoxic effects of two flavonoids isolated from *Acridocarpus orientalis* on three cancer cell lines: colorectal adenocarcinoma (HT29), colorectal adenocarcinoma (HCT116) and human hepatoma derived cell line (HepG2) using MTT colorimetric assay. Results revealed that at low concentration (0.1 to 50 ppm) both flavonoids failed to show cytotoxic effects on the cancer cells. However, at a concentration of 100 ppm, both isolated compounds decreased the cell viability of the cancer cells.

2.1.2.2 Lipoxygenase inhibitory activity

Ksiksi and Hamza [6], sought to investigate the LOX inhibitory activity of the ethanolic extract of *Acridocarpus orientalis* that grows in Alain and Oman. Results revealed that *Acridocarpus orientalis*-Alain extract exhibited a potent capability in suppressing LOX activity (IC_{50} = 50.58 µg/mL) compared to *Acridocarpus orientalis*-Oman extract (IC_{50} = 58.61 µg/mL). However, both extracts showed a lower LOX inhibitory activity than the positive standard NDGA (IC_{50} = 4.87 µg/mL).

2.1.2.3 Histone deacetylase inhibitory activity

Histone deacetylase inhibitory activity of the ethanolic extract of *Acridocarpus orientalis* that grows in Alain and Oman was examined. Results revealed that *Acridocarpus orientalis*-Alain extract exhibited a potent capability (IC_{50} = 93.28 µg/mL) in inhibiting histone deacetylase activity compared to *Acridocarpus orientalis*-Oman extract (IC_{50} = 102.5 µg/mL) [6].

2.2 *Leptadenia pyrotechnica*

Asclepiadaceae family is characterized by its content of various medicinal plants that have been used for different therapeutic purposes [144]. Examples of medicinal plants that belong to Asclepiadaceae family include *Tylophora indica*, *Calotropis gigantia* and *Hemidesmus indicus* [145]. *Leptadenia pyrotechnica* (Figure 3) is a plant species that belongs to Asclepiadaceae family and found in tropical Africa, Asia, Mediterranean region and in the Western Gulf countries [146]. *Leptadenia pyrotechnica* has been used in the traditional medicine to treat several diseases including productive cough, abortion, diabetes and fever [147].

Figure 3: *Leptadenia pyrotechnica*

2.2.1 Phytochemistry

Chemical constituents of *Leptadenia pyrotechnica* include vanillic acid, epicatechin, phytol, squalene**,** taraxerol, fernenol and سamyrin [148]. Structures of phytol and سamyrin are depicted in Figure 4.

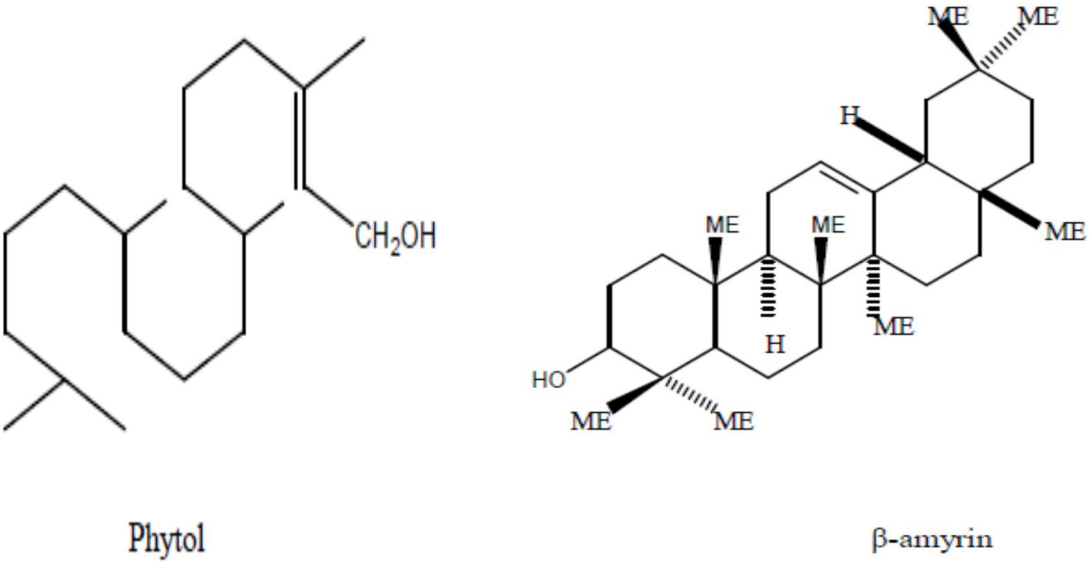


Figure 4: Structures of some chemical constituents of *Leptadenia pyrotechnica* [148]

2.2.2 Pharmacology

2.2.2.1 Lipoxygenase inhibitory activity

Khasawneh *et al.* [149], reported the anti-lipoxygenase activity of *Leptadenia pyrotechnica.* Ethyl acetate fraction of the ethanolic extract showed the highest anti-lipoxygenase activity (IC_{50} = 1.41 ـهـg/mL). Moreover, the anti-lipoxygenase activity of the ethyl acetate fraction was higher than the positive standard NDGA (IC_{50} = 4.82 ـهـg/mL).

2.2.2.2 Hepatoprotective activity

The hepatoprotective activity of the methanolic extract of *Leptadenia pyrotechnica* was evaluated against paracetamol-induced injury in experimental rats. Results revealed that the treatment with *Leptadenia pyrotechnica* extract has led to significant decrease in the raised levels of SGOT, SGPT, ALP and Total bilirubin [150].

2.2.2.3 Cytotoxic activity

The cytotoxic activity of the ethanolic extract of *Leptadenia pyrotechnica* was evaluated against human breast cancer cell line. Results showed that the ethyl acetate fraction of the ethanolic extract exhibited the highest cytotoxic activity (IC_{50} = 43.16 µg/mL) among the other fractions and dose-dependently reduced the cancer cell viability [149].

2.3 *Calotropis procera*

Asclepiadaceae family encompasses approximately 175-180 genera and 2200 species found mainly in the tropical and subtropical areas [151]. *Calotropis procera* (Figure 5) is a medicinal plant distributed in Asia, Africa and South America [152]. Traditionally, *Calotropis procera* has been used for the treatment of different ailments such as ulcers, tumors and piles [153]. *Calotropis procera* produces latex which can be obtained with abundant quantities from its leaves and barks. Interestingly, the latex of *Calotropis procera* contains chitinases, proteinases and antioxidant enzymes [154]. Moreover, several scientific investigations reported the pharmacological activities such as antiinflammatory and anticancer activities associated with the latex of *Calotropis procera* [155].

Figure 5: *Calotropis procera*

2.3.1 Phytochemistry

Investigations of the chemical constituents of *Calotropis procera* resulted in the isolation and identification of several chemical compounds from its different parts.

Latex: Chundattu *et al.* [156], isolated sterols from the latex of *Calotropis procera* namely سsitosterol, stigmasterol, and multiflorenol. Moreover, caoutchouc, calotropin, calotoxin, calactin, uscharin, voruscharin, uzarigenin, syriogenin and proceroside were also isolated from the latex of *Calotropis procera* [157].

Leaves: phytochemical investigations of the leaves of *Calotropis procera* revealed the presence of سamyrin, سamyrin acetate, urosolic acid, cardenolides and calotropagenin [157].

Flowers: different chemical compounds were isolated from the flowers of *Calotropis procera* such as queretin-3-ratinoside, sterol, lupeol, proceroside, proceragenin, syriogenin, gigantin, giganteol and isogiganteol. Other examples of phytochemicals isolated from *Calotropis procera* flowers include uscharidin, 3-epimoretenol and سlactuceryl isovalerate [157].

Roots: examples of terpenoids isolated from the roots of *Calotropis procera* include phytyl iso-octyl ether, procerasesterterpenoyl triglucoside, and dihydrophytoyl tetraglucoside [158]. Moreover, calotropursenyl acetate, akundarol isovalerate, mundarol isovalerate and quercetin-3-rutinoside were also found in the root bark of *Calotropis procera* [157].

2.3.2 Pharmacology

2.3.2.1 Hepatoprotective activity

The hepatoprotective activity of the ethanolic extract of *Calotropis procera* flowers was investigated using paracetamol as a hepatotoxic compound. The changes in the biochemical markers levels such as SGPT, SGOT, ALP, bilirubin, cholesterol, HDL and tissue GSH were examined in rats. Paracetamol elevated the SGPT, SGOT, ALP, bilirubin and cholesterol levels and decreased the levels of HDL and GSH, inducing a hepatic damage in rats. The administration of the ethanolic extract (70%) of *Calotropis procera* flowers resulted in a significant hepatoprotective effects. Results indicated that *Calotropis procera* flower extract significantly decreased the biochemical markers levels and also significantly increased the reduced levels of HDL and GSH [159].

2.3.2.2 Antimicrobial activity

The aqueous and the ethanolic extracts of the leaves and the latex of *Calotropis procera* were screened for *in vitro* activity against pathogenic microorganisms, namely *Eschericia coli, Salmonella typhi, Bacillius subtilis, Candida albicans* and *Aspergillus niger*. The antimicrobial activity of *Calotropis procera* leaves and latex were assayed using agar well diffusion method. The ethanolic extract showed superiority in inhibiting the growth of the pathogenic microorganisms compared to the aqueous extract. The latex extract had a minimum inhibitory concentration (MIC) ranged from 3-7.5 mg/ml and 5-7 mg/ml for the bacteria and the fungi, respectively. Moreover, the MIC for the leaf extract ranged from 5-10.5 mg/ml and 11-15 mg/ml for the bacteria and the fungi, respectively [160].

2.3.2.3 Anti-diabetic activity

The anti-diabetic activity of *Calotropis procera* latex was examined in rats. The latex (100 mg/kg and 400 mg/kg) reduced the levels of blood glucose and elevated the hepatic glycogen levels in a concentration-dependent manner. Moreover, the orally administrated latex hindered the loss of body weight in the alloxanized rats and remarkably reduced the daily water consumption [161].

2.3.2.4 Wound healing activity

The wound healing activity of *Calotropis procera* latex was investigated. Following a 7 days of treatment, *Calotropis procera* latex exhibited a remarkable wound healing activity in guinea pigs compared to the controls. Results revealed that *Calotropis procera* latex raised the levels of collagen, DNA and proteins in the wound area [162].

2.3.2.5 Antidiarrheal activity

The latex of *Calotropis procera* was examined against castor oil-induced diarrhea in rats. Results revealed that the dry latex of *Calotropis procera* (500 mg/kg) exhibited a remarkable anti-diarrheal activity compared to the control groups. The latex of *Calotropis procera* exerted its anti-diarrheal activity by decreasing the intestinal transit and preventing the intestinal fluid accumulation (enteropooling) [163].

2.4 *Tecomella undulata*

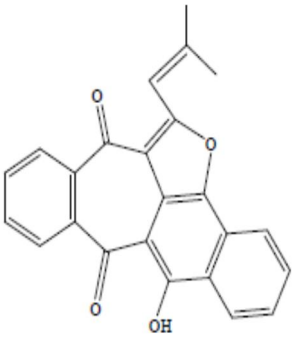
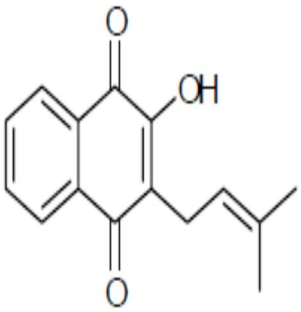
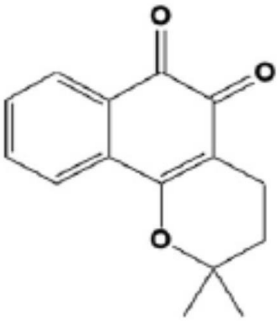
Bignoniaceae family is a widely distributed family that contains different medicinal plants that possess diverse pharmacological actions [164]. Bignoniaceae family contains 82 genera and 827 species [165]. It has been reported that many Bignoniaceae species possess anti-inflammatory, antidiabetic, antimicrobial, antiplasmodial and antioxidant activities [166]. Among the species that belong to Bignoniaceae family is *Tecomella undulata*. *Tecomella undulata* (Figure 6) is a medicinal plant mainly found in Arabia, southern Pakistan and in India [167]. Traditionally, *Tecomella undulata* has been used to treat liver and abdominal problems [168].

Figure 6: *Tecomella undulata*

2.4.1 Phytochemistry

Tecomella undulata represents a vast store house of potentially useful chemical compounds. Table 2 shows some chemical constituents of *Tecomella undulata*.

Table 2: Examples of chemical constituents of *Tecomella undulata*

Compound Name	Chemical Structure	Biological activity	References
Radermachol		Antiinflammatory	[169]
Lapachol		Antitumor activity	[170]
سlapachone		Anticancer activity	[171]

2.4.2 Pharmacology

2.4.2.1 Hepatoprotective activity

The hepatoprotective activity of *Tecomella undulata* bark extracts against paracetamol-induced hepatic injury was examined in rats. Methanolic fraction of the ethanolic extract exhibited a notable hepatoprotective activity. The methanolic fraction decreased the elevated levels of AST, ALT, ALP, total bilirubin and the levels of serum total protein [172].

2.4.2.2 Antihyperglycemic activity

An *in vivo* study evaluated the antihyperglycemic activity of *Tecomella undulata* leaves extract against streptozotocin-nicotinamide-induced diabetes in mice. The extract attenuated the blood glucose levels and raised the liver glycogen levels compared to the control groups [173].

2.4.2.3 Antiproliferative activity

A study examined the inhibitory effect of the bark extract of *Tecomella undulata* on cancer cell proliferation. Results showed that the bark of *Tecomella undulata* induced a dose-dependent inhibition (IC_{50} = 30 μg/mL) on the chronic myeloid leukemia cell proliferation [174].

2.4.2.4 Antiobesity activity

An *in vivo* study assessed the antiobesity activity of *Tecomella undulata* bark extract in mice. The bark extract showed a notable decline in adipogenesis and lipogenesis [175].

2.5 *Euphorbia larica*

Euphorbiaceae family is one of the diverse families that contain over 300 genera and 8,000 species [176]. *Euphorbia* is considered as one of the largest genera and comprises about 2,000 species [177]. In the traditional medicine, *Euphorbia* species were used to treat skin problems, wounds, migraines and intestinal parasites [178]. *Euphorbia larica* (Figure 7) is a perennial medicinal plant characterized by its erect leafless stems [179]. *Euphorbia larica* has been rarely investigated. Therefore, the analysis of the phytochemicals and the biological activities of *Euphorbia larica* was among the objectives of the current study.

Figure 7: *Euphorbia larica*

2.6 *Cyperus conglomeratus*

Cyperaceae family is a large family that contains about 5,000 species and 100 genera [180]. The genus *Cyperus* comprises approximately 600 species found in different regions around the world [181]. This genus is characterized by its content of many medicinal plants that have been utilized for various therapeutic purposes [182]. *Cyperus rotundus* is a well-known medicinal plant of the genus *Cyperus*. It has been reported that *Cyperus rotundus* possesses cytotoxic [183], antibacterial [184] and antidiarrheal activities [185]. *Cyperus conglomeratus* (Figure 8) is a medicinal plant that has been used in the folk medicine for different therapeutic purposes [181].

Figure 8: *Cyperus conglomeratus*

2.7 Aims and Objectives

The medicinal plants studied in this work were: *Acridocarpus orientalis, Leptadenia pyrotechnica, Calotropis procera, Tecomella undulata, Euphorbia larica* and *Cyperus conglomeratus*. The overall aim of this study was to contribute to the field of medicinal natural product research. Specific objectives of this work were:

1) Qualitative and quantitative determination of phytochemicals in the crude extracts of the selected medicinal plants.
2) Quantification of macronutrients, micronutrients and toxic elements using inductively coupled plasma-optical emission spectrometry (ICP-OES).
3) Investigation of the *in vitro* antioxidant activity of the crude extracts of the selected medicinal plants using DPPH, ABTS and FRAP assays.

Chapter 3: Materials and Methods

3.1 Materials

Ferric chloride solution, sodium hydroxide (NaOH) solution, chloroform, sulphuric acid, benzene, ammonia solution, hydrochloric acid (HCl), Dragendorff's reagent were the chemicals that used for the preliminary phytochemical screening. Gallic acid, Folin-Ciocalteu reagent, sodium carbonate, quercetin, sodium nitrate, aluminum chloride were the chemicals that used for the quantification of the phenolic and flavonoids compounds. Nitric acid (HNO_3), hydrogen peroxide (H_2O_2) and hydrochloric acid (HCl) were the chemicals that used for the digestion of the plant samples for the elemental analysis. 2,2-diphenyl-1-picrylhydrazyl (DPPH), dibutylhydroxytoluene (BHT), methanol, 2,2-azinobis(3-ethylbenzothiazoline-6-sulphonate) (ABTS), potassium persulfate, ascorbic acid, sodium acetate trihydrate ($C_2H_3NaO_2 \cdot 3H_2O$), glacial acetic acid ($C_2H_4O_2$), 4, 6-tripyridyl-s-triazine and ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) were the chemicals that used for the *in vitro* antioxidant assessment. Some of the chemicals were obtained from Sigma Chemical Corporation and some others were purchased from local commercial suppliers.

The plant materials were botanically identified at the Department of Biology, UAE University by Professor Taoufik ksiksi. More information relating to plants analyzed in this study are summarized in Table 3.

Table 3: Information relating to plants analyzed in this study

Plant Name	Collection Month and Year	Collection Place	Part Studied
Acridocarpus orientalis	October 2016	Hafeet Mountain-Alain	Leaves
Leptadenia pyrotechnica	September 2016	UAEU Campus	Stems
Calotropis procera	October 2016	UAEU Campus	Leaves
Tecomella undulata	April 2016	Diba Al-Fujairah	Leaves
Euphorbia larica	November 2016	Hafeet Mountain-Alain	Stems
Cyperus conglomeratus	December 2016	Alsalamat-Alain	Stems

3.2 Methods

3.2.1 Preparation of the crude extracts

The crude extracts were prepared as previously described [6]. The plant materials were washed, dried using oven at 40 °C and were ground into fine powder using electrical blender. About 10 g of each plant powder was suspended in 200 mL of 70% ethanol and the mixture was kept in the shaker for 72 h at 4 °C. The mixture was filtered using Whatman N 1 filter paper. After filtration, the filtrate was evaporated to dryness using rotary evaporator at 40 °C. The crude extracts were collected, weighed, dissolved in 50% ethanol and stored at 20 °C for subsequent analysis.

3.2.2 Phytochemical screening

3.2.2.1 Qualitative phytochemical screening

3.2.2.1.1 Test for phenols

A few drops of 5% ferric chloride solution were added to the plant extracts. The change of the solution color to dark green color signifies the presence of phenols [186].

3.2.2.1.2 Test for flavonoids

A few drops of dilute sodium hydroxide (NaOH) solution were added to 1 mL of the plant extracts in a test tube. To indicate the presence of flavonoids, the solution was observed for the development of a yellow color, which disappears after the addition of dilute acid [187].

3.2.2.1.3 Test for terpenoids

About 2 mL of chloroform was added to 5 mL of the plant extracts. To this mixture, 3 mL of sulphuric acid was added. The presence of reddish-brown color was taken as a positive test for the presence of terpenoids [188].

3.2.2.1.4 Test for anthraquinones

The plant extracts were mixed vigorously with 10 mL of benzene. This was followed by a proper filtration and the addition of 5 mL of 10% ammonia solution. The presence of pink, violet or red color in the lower ammonia layer signifies the presence of anthraquinones [189].

3.2.2.1.5 Test for saponins

About 5 mL of distilled water was added to 0.2 mL of the plant extracts. The mixture was shaken strongly for 5 min. The formation of foams was taken as an indication of the presence of saponins [190].

3.2.2.1.6 Test for alkaloids

About 5 mL of 1% aqueous hydrochloric acid (HCl) was added to 2 mL of the ethanolic extracts. To 1 mL of this mixture, a few drops of Dragendorff's reagent was added. The formation of orange-red precipitate indicated the presence of alkaloids [191].

3.2.2.2 Quantitative phytochemical screening

3.2.2.2.1 Determination of total phenolic content

The total phenolics were analyzed spectrophotometrically using Folin Ciocalteu colorimetric method. Five different concentrations (ranging from 0.1 to 5 mg/mL) of the standard gallic acid were prepared and used in generating the standard curve. A 100 µL of each concentration of the standard was allowed to react with 500 µL of water and 100 µL of Folin-Ciocalteu reagent for 6 min. This was followed by the addition of 1 mL of 7% sodium carbonate and 500 µL of distilled water. This procedure was similarly applied on the different plant extracts. The absorbance of the plant extracts and the standard was measured at 760 nm after 90 min using UV spectrophotometer. The total phenolic content of the plant extracts were expressed in in milligrams of gallic acid equivalent per gram of dry extract (mg GAE/g DE). All the experiments were conducted in nine replicates [192].

3.2.2.2.2 Determination of total flavonoid content

The total flavonoid content was analyzed spectrophotometrically using aluminum chloride colorimetric method. Five different concentrations (ranging from 0.1 to 5 mg/mL) of the standard quercetin were prepared and used in generating the standard curve. A 100 µL of each concentration of the standard was allowed to react with 500 µL of water and 100 µL of 5% sodium nitrate for 6 min. This was followed by the addition of 150 µL of 10% aluminum chloride solution and the mixture was allowed to stand for 5 min. Then, 200 µL of 1M sodium hydroxide solution was added. This procedure was similarly applied on the different plant extracts. The absorbance of the plant extracts and the standard was measured at 510 nm by using UV spectrophotometer. The total flavonoid content of the plant extracts were expressed in milligrams of quercetin equivalent per gram of dry extract (mg QE/g DE). All the experiments were conducted in nine replicates [192].

3.2.3 Elemental analysis

3.2.3.1 Plant sample digestion

Plant samples were subjected to acid digestion according to the EPA guidelines [193], with slight modifications. About 0.5 g of the plant samples were weighed and placed in a beaker. Five mL of HNO_3 was added to the plant samples and the beaker was placed in a hot plate. After 30 min, five mL of HNO_3 was added again and the mixture was allowed to evaporate until the volume is approximately 10 mL. After the solution development of bright yellow color, 2 mL of HCl was added. The beaker was removed from hotplate and 1 mL of H_2O_2 was added. The digested samples were filtered into 100 mL volumetric flask and filled to the mark with water.

3.2.3.2 Instrumentation

Varian inductively coupled plasma-optical emission spectrometry (ICP-OES) model 715-ES simultaneous axially viewed plasma with full PC control of instrument settings and compatible accessories was used for the elemental analysis of the digested plant samples. The operating conditions for the ICP-OES instrument were: power: 1.3 KW; plasma gas flow: 15 L/min; auxiliary gas flow: 1.5 L/min; nebulizer flow: 0.75 L/min; nebulizer type: seaspray; pump rate: 15 rpm; sample uptake delay: 30 sec; replicate read time (S): 10 sec; rinse time: 10 sec; instrument stabilization delay: 15 sec. The following wavelengths were used: Ca: 317.933; Mg: 279.800; K: 766.491; Na: 588.995; Fe: 288.995; Mn: 257.491; Zn: 206.200; Cu: 324.754; Cr: 267.716; Co: 228.615; Al: 396.152; Cd: 226.502; Pb: 220.353. All analyses were performed in triplicate. The mineral concentrations were determined from a standard curve and calculated on a dry weight basis (mg/kg).

3.2.4 *In vitro* antioxidant assays

3.2.4.1 DPPH radical scavenging assay

A DPPH radical scavenging assay was adopted to assess the free radical scavenging activity of the plant extracts, as previously described by Sahu *et al.* [194], with minor modifications. Different concentrations of the positive standard (BHT) and the plant extracts were prepared. The negative control was prepared by adding 100 µL of ethanol and 900 µL of DPPH solution. A 900 µL of a 0.1 mM solution of DPPH in 50% methanol was added to 100 µL of different concentrations of the plant extracts and the positive standard. The mixtures were covered and allowed to stand for 30 min at room temperature. The absorbance was measured at 517 nm against a blank using UV spectrophotometer. The % of inhibition was calculated using the following equation:

$$\text{Inhibition } \% = [(Ac-As)/Ac] \times 100$$

Ac = absorbance of the control; As = absorbance of the test sample. The IC_{50} (concentration providing 50% inhibition) of extracts and standards was determined by linear regression analysis of dose-response curve of % of inhibition against concentrations. All the experiments were conducted in nine replicates.

3.2.4.2 ABTS radical scavenging assay

The method described by Adedapo *et al.* [195], was used for the ABTS radical scavenging assay with slight modifications. The stock solution of 7 mM ABTS solution and 2.4 mM potassium persulfate solution was prepared. The ABTS working solution was prepared by mixing the two stock solutions in equal quantities. The mixture was stored in the dark at room temperature for 12 h. Further, the solution was

diluted with ethanol to give an absorbance of 0.706 ± 0.001 units at 734 nm using UV spectrophotometer. Fresh ABTS solution was prepared for each experiment. Different concentrations of the positive standard (ascorbic acid) and the plant extracts were prepared. The negative control was prepared by adding 100 µL of ethanol and 900 µL of ABTS solution. A 900 µL of the diluted ABTS solution was added to 100 µL of different concentrations of the plant extracts and the positive standard. The mixtures were allowed to stand for 7 min at room temperature. The absorbance was measured at 734 nm against a blank using UV spectrophotometer. The % of inhibition was calculated using the following equation:

$$\text{Inhibition } \% = [(Ac\text{-}As)/Ac] \times 100$$

Ac = absorbance of the control; As = absorbance of the test sample. The IC_{50} (concentration providing 50% inhibition) of extracts and standards was determined by linear regression analysis of dose-response curve of % of inhibition against concentrations. All the experiments were conducted in nine replicates.

3.2.4.3 Ferric reducing antioxidant power assay

A ferric reducing antioxidant power assay was used to measure reducing power, as described previously [196]. The stock solution of 300 mM acetate buffer (3.1 g $C_2H_3NaO_2 \cdot 3H_2O$ and 16 mL $C_2H_4O_2$), pH 3.6, 10 mM TPTZ (2, 4, 6-tripyridyl-s-triazine) solution in 40 mM HCl, and 20 mM $FeCl_3 \cdot 6H_2O$ solution was prepared. The preparation of the FRAP working solution was by mixing 25 mL acetate buffer, 2.5 mL TPTZ, and 2.5 mL $FeCl_3 \cdot 6H_2O$. The FRAP solution was allowed to stand at 37°C. Fresh FRAP solution was prepared for each experiment. Different concentrations of the positive standard (ascorbic acid) and the plant extracts were prepared. The negative control was prepared by adding 150 µL of ethanol and 2850 µL of FRAP solution. A

2850 µL of FRAP solution was added to 150 µL of different concentrations of the plant extracts and the positive standard. The mixtures were allowed to stand for 30 min at room temperature in dark. The absorbance was measured at 593 nm against a blank using UV spectrophotometer. All the experiments were conducted in nine replicates.

3.2.5 Statistical analysis

Data were expressed as means ± SD. The statistical analysis was carried out using Excel by using two sample t-test. *P* values <0.05 were taken as significant.

Chapter 4: Results and Discussion

4.1 Phytochemical screening

4.1.1 Qualitative phytochemical screening

Preliminary phytochemical screening of the ethanolic extracts of six medicinal plants collected from the natural flora of the UAE was performed. Different chemical tests were used to detect the presence/absence of some plant secondary metabolites namely phenols, flavonoids, terpenoids, anthraquinones, saponins and alkaloids. The results are summarized in Table 4.

Table 4: Qualitative phytochemical screening of selected UAE medicinal plants

Phytochemicals	AO	LP	CP	TU	EL	CC
Phenols	+	+	+	+	+	+
Flavonoids	+	+	+	+	+	+
Terpenoids	+	+	+	+	+	+
Anthraquinones	+	-	-	+	-	-
Saponins	-	-	-	+	-	-
Alkaloids	-	-	-	+	-	-

Key: AO = *Acridocarpus orientalis*; LP = *Leptadenia pyrotechnica*; CP = *Calotropis procera*; TU = *Tecomella undulata*; EL = *Euphorbia larica*; CC = *Cyperus conglomeratus*. (+) = Present; (-) = Absent.

In the current study, phenols and flavonoids were found in all of the investigated plant extracts (Table 4). Plant phenolics possess a broad spectrum of physiological activities such as antiinflammatory, antimicrobial and antithrombotic activities [197]. Flavonoids are one of the common classes of polyphenolic compounds and are distributed ubiquitously in plants [198]. A number of studies demonstrated the biological activities such as the antibacterial activity [199], tumor cell growth inhibitory activity [200] and the antiinflammatory activity [201] associated with the flavonoid compounds.

In the light of the published literature, similar outcomes were found by Al-Abri *et al.* [202], where phenols and flavonoids were detected in *Acridocarpus orientalis* that grown in Oman natural flora. Moreover, previous studies in Nigeria and India have reported the presence of phenols and flavonoids in other species of *Leptadenia*, namely *Leptadenia hastata* [203] and *Leptadenia reticulata* [204]. A number of published studies revealed the presence of phenols and flavonoids in *Calotropis procera* that grown in different region around the world [160,205]. Interestingly, a bioactive flavonoids namely rutin and tiliroside were isolated from the leaves and the flowers of *Tecomella undulata* using HPLC-ESI-MS/MS [206], which is a further confirmation of the results in the current study. To the best of our knowledge, this is the first study that reported the chemical composition of *Euphorbia larica* and *Cyperus conglomeratus.* However, the chemical content of other plants that belong to the same genus was studied. Phenols and flavonoids were found in *Cyperus rotundus* [207], *Euphorbia hirta* [208] and *Euphorbia prostrata* [209].

Terpenoids were detected in all of our crude extracts (Table 4). Terpenoids contain numerous valuable substances that have been utilized in pharmaceutical and medical products [210]. Several monoterpenes and diterpenes have shown a pivotal role in combating malaria, cancer and inflammation [33]. Our results are supported by the findings of Ravi *et al.* [174], who found triterpenoids in *Tecomella undulata* grown in India. In other studies, terpenoids were detected in other species that belong to *Euphorbia* [211] and *Calotropis* [212] genus.

Anthraquinones were only detected in *Tecomella undulata* and *Acridocarpus orientalis* extracts (Table 4). Anthraquinones are secondary metabolites found in many higher plants, insects, and filamentous fungi [213]. A number of studies showed that anthraquinones and their derivatives have anticancer, antiinflammatory, and antioxidant activities [214]. Our results are in agreement with other findings, where anthraquinones were also detected in *Tecomella undulata* grown in India [215]. However, anthraquinones were not detected in *Acridocarpus orientalis* that grown in Oman [202].

Tecomella undulata extract is the only extract that showed a positive results for saponins as measured by froth test (Table 4). Several biological activities are attributed to saponins such as antiinflammatory, antimicrobial and anticancer activities [216]. Saponins were also found in other plant species that belong to the same family of *Tecomella undulata* (Bignoniaceae) namely, *Oroxylum indicum* [217] and *Tecoma stans* [218].

Alkaloids were observed only in *Tecomella undulata* extract (Table 4). Alkaloids are well-known by their physiological activities such as anticancer, antibacterial, and antiparasitic activities [219]. Laghari *et al.* [168], isolated recently eleven alkaloids from *Tecomella undulata* flowers using GC-MS technique.

The accumulation of phytochemicals in plants is affected by several factors such as environmental circumstances, plant age and the harvest time [220]. Ghasemzadeh *et al.* [221], reported that the quantity of secondary metabolites in *Clinacanthus nutans* were significantly different with respect to the age of the plant. Surprisingly, there are some practices that expose medicinal and crop plants to mild stresses in order to enhance their chemical composition and hence their health promoting quality [222].

4.1.2 Quantitative phytochemical screening

4.1.2.1 Total phenolic content

Phytophenols are one of the major secondary metabolites that are generated in the shikimic acid of plants and pentose phosphate via phenylpropanoid metabolization [223]. Phenolic compounds play an important role in plant defense and in plant tolerance to the various forms of environmental stresses [224]. Phenolic compounds are involved in a number of physiological activities in humans such as cell cycle regulation, platelet functions and caspase dependent pathways [225]. In this study, the total phenolic content of the plant extracts were determined using Folin-Ciocalteu method by generating a standard curve with gallic acid.

The total phenolic content of the studied medicinal plants ranged from 61 to 506.42 mg GAE/g DE. *Acridocarpus orientalis* showed the highest phenolic content (506.42 mg GAE/g DE), followed by *Tecomella undulata* (222.55 mg GAE/g DE), *Calotropis procera* (158 mg GAE/g DE), *Euphorbia larica* (137 mg GAE/g DE) and *Leptadenia pyrotechnica* (90 mg GAE/g DE), whereas *Cyperus conglomeratus* showed the lowest phenolic content (61 mg GAE/g DE) (Figure 9). The results of the current work are generally different from other reports. It was previously reported that total phenolic content for *Tecomella undulata* grown in India was 12.7 mg GAE/g DE [226], which is lower than that obtained in this study. In another study conducted by Basma *et al.* [227], the total phenolic content reported in *Euphorbia hirta* was 65.70 mg GAE/g DE. Moreover, the phenolic content of *Cyperus conglomeratus* reported in the current study was lower than the phenolic content reported by Essaidi *et al.*[228], for *Cyperus rotundus*.

Although phenolics are ubiquitous in plant kingdom, there is still a quantitative variation in phenolic compounds between plants [229]. Numerous factors can influence the levels of phenolic compounds in plants such as genetic and environmental factors [230]. Papoulias *et al.*[231], reported that genetic material is one of the most important factors that influenced phenolic content in white asparagus spears. Moreover, other studies showed the effects of temperature [232] and UV radiation [233] on the phenolic content of different plant species.

Folin-Ciocalteu method is one the common methods that has been used for the quantification of phenolic compounds in plant samples. However, Folin Ciocalteu reagent can react with other constituents that possess hydroxyl groups such as ascorbic acid and reducing sugars, which will result in overestimation of phenolic compounds present in the sample [234]. Interestingly, different methods have been suggested to promote the efficacy of Folin-Ciocalteu method. One approach suggested that plant extracts should be treated with oxidative agents such as hydrogen peroxide to eliminate reducing compounds from the plant samples [235]. Another way to enhance the specificity of Folin-Ciocalteu method include the partial purification of plant extracts using solid phase extraction (SPE) [236]. Moreover, the calculation of accurate total phenolic content through the subtraction of the reducing activity of reducing compounds have also been proposed [237].

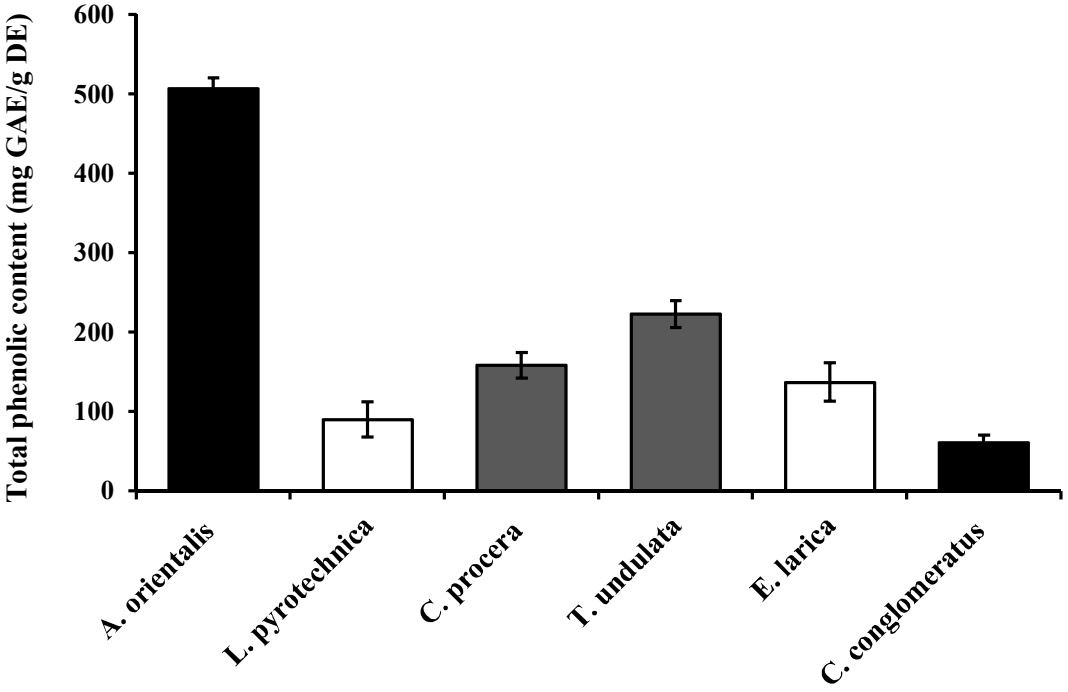


Figure 9: Total phenolic content in 70% ethanolic extracts of six UAE medicinal plants. Vertical bars represent mean ± SD, n=9. GAE: gallic acid equivalents; DE: dried extract.

4.1.2.2 Total flavonoid content

Flavonoids are natural compounds produced by plants and play a vital role in plant adaptation to the various forms of stresses [238]. Flavonoid compounds are characterized by their antioxidant properties and they possess a potent capability to donate hydrogen and electrons [239]. In this study, the total flavonoid content of the plant extracts were determined using aluminum chloride colorimetric method by generating a standard curve with quercetin.

The results indicated that the total flavonoid content of the plant extracts in the range of 9.54-454.37 (mg QE/g DE). The highest total flavonoid content was revealed in *Acridocarpus orientalis*, while *Cyperus conglomeratus* had the least total flavonoid content (Figure 10). In general, the total flavonoid contents in the majority of the analyzed medicinal plants were higher than those given in the existing literature. Mishra *et al.* [240], quantified total flavonoid content to be 34.85 mg QE/g DW in *Leptadenia pyrotechnica* grown in India. In another study, the total flavonoid content of *Byrsonima japurensis* that belongs to Malpighiaceae family was reported as 2.38 mg QE/g DE [241]. Moreover, earlier study reported the total flavonoid content in *Calotropis procera* as 3.72 mg QE/g DW [242]. The discrepancies in the results obtained in this study with those found in literature may be due to the differences in extraction conditions such as extraction time, extraction temperature and solvent concentration [243]. A study found that the total flavonoid content in *Ficus Carica* varied when that plant material extracted at different extraction temperature and with different solvent concentrations [244].

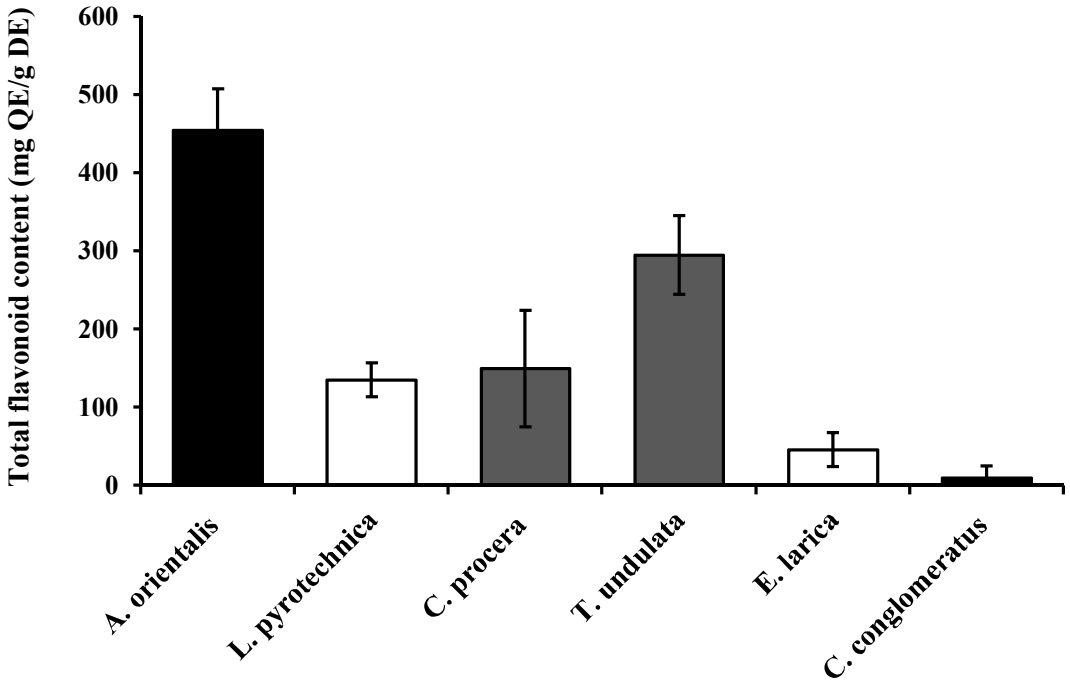


Figure 10: Total flavonoid content in 70% ethanolic extracts of six UAE medicinal plants. Vertical bars represent mean ± SD, n=9. QE: quercetin equivalents; DE: dried extract.

4.2 Elemental profiles of selected UAE medicinal plants

Numerous studies have pointed to the biological activities and the health benefits that are associated with medicinal plants such as the antioxidant and anticancer activities [245 247]. The therapeutic properties of medicinal plants were usually attributed to the presence of bioactive organic compounds such as phenolic compounds, vitamins and flavonoids. Surprisingly, many of the curative effects of herbal plants are also due to their content of various minerals (macro and trace elements) [248]. However, despite these minerals could contribute to the nutritional value of medicinal plants, they may result in undesirable effects if they cross the permissible limits. The long-term ingestion of medicinal herbs that contain high mineral concentration may trigger their accumulation in the human bodies, which eventually will result in severe adverse effects [249]. Therefore, close monitoring of mineral concentration in medicinal plants is essential to ensure their quality and efficiency [250].

In this study, we aimed to assess the nutritional value, edibility and safety of selected UAE medicinal plants through the quantification of macronutrients, micronutrients and toxic elements using ICP-OES. The macro-elements that were quantified in this study were calcium (Ca), magnesium (Mg), potassium (K) and sodium (Na). The trace and toxic elements examined in this study were iron (Fe), manganese (Mn), zinc (Zn), copper (Cu), chromium (Cr), cobalt (Co), aluminum (Al), cadmium (Cd) and lead (Pb). The results of the mean concentrations of the elements in the studied medicinal plants are presented in Table 5.

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Table 5: Elemental concentration of medicinal plants from UAE natural flora (mean ± SD ppm, n=3)

Species name	Ca	Mg	K	Na	Fe	Mn	Zn	Cu	Cr	Co	Al	Cd	Pd
A. orientalis	25, 827 ± 2302. 59	9789.48 ± 801.96	8637 ± 1271.98	4555.24 ± 550.87	67.37 ± 14.76	321.92 ± 32.86	28.05 ± 4.52	7.85 ± 0.86	13.68 ± 1.62	2.70 ± 0.40	16 ± 4.92	0.71 ± 0.31	*BDL
L. pyrotechnica	15,307 ± 1151.73	5211.1 ± 37.30	10,792 ± 48.8	536 ± 33.53	54.50 ± 18.90	45.98 ± 0.53	28.00 ± 3.14	13.92 ± 0.28	15.41 ± 1.50	1.61 ± 1.53	19.16 ± 1.45	*BDL	5.77 ± 1.9
C. procera	37,596 ± 1268.89	13,472 ± 94.58	15,562 ± 1335.11	6837.46 ± 68.02	56.87 ± 6.31	468.3 ± 11.63	46.22 ± 0.98	18.55 ± 2.32	18.86 ± 1.17	5.00 ± 0.70	18.36 ± 1.70	0.50 ± 0.08	*BDL
T. undulata	17,223 ± 3163.51	6867 ± 1199.3	4964 ± 1034.35	782.49 ± 149.11	98.36 ± 7.08	13.82 ± 2.15	18.05 ± 4.55	6.66 ± 1.09	13.52 ± 1.01	*BDL	66.63 ± 11.20	0.55 ± 0.50	4.71 ± 2.5
E. larica	14,570 ± 97.34	4610.09 ± 179.84	13,113 ± 500.40	1435.08 ± 38.04	88.26 ± 9.41	136.17 ± 6.27	11.64 ± 2.14	11.12 ± 1.35	17.50 ± 2.77	2.08 ± 0.91	27.09 ± 3.07	*BDL	*BDL
C. conglomeratus	3175 ± 788.15	567.49 ± 136.03	4452.16 ± 1168.78	205.31 ± 53.77	80.18 ± 14.25	11.24 ± 2.78	11.04 ± 0.84	4.37 ± 0.08	6.11 ± 3.31	*BDL	41.65 ± 5.20	0.72 ± 0.12	7.05 ± 4.1

*DBL= Below Detectable Limit

4.2.1 Macro-elements

Macro-elements are those chemical elements that are needed in a large amounts to perform different functions for the living organisms [251].

4.2.1.1 Calcium (Ca)

Calcium is the most abundant mineral in the human body and is considered essential for the health of teeth and bones. Calcium plays a vital role in the intracellular signaling, neurotransmission, hormone production and in the regulation of muscle contraction [252]. It has been proposed that calcium intake up to 1500 mg/day may not result in undesirable effects [253].

The concentration of calcium in the analyzed plant species in the decreasing order was: *Calotropis procera* > *Acridocarpus orientalis* > *Tecomella undulata* > *Leptadenia pyrotechnica* > *Euphorbia larica* > *Cyperus conglomeratus* (Table 5). The concentration of calcium found in this study for *Calotropis procera* was higher than the value reported by Verma [254], who showed 3694 mg/kg of Ca in the same plant species. Moreover, the calcium concentration of the stems of *Leptadenia pyrotechnica* was lower than the concentration reported by Gwarzo *et al.* [255], for the stems of *Leptadenia lancefolia*. Such variation in Ca bioavailability may be due to the presence of some chelating agents such as oxalate and phytic acid [256]. For example, the interaction between the phytic acid phosphate that bears a negative charge with the divalent cation species such as Mn^{2+} and Ca^{2+} lead to the inhibition of mineral absorption in plants which as a result will minimize their nutritional value [257]. A previous study showed that the calcium bioavailability in dehusked rice was low due to its high content of phytic acid [258].

4.2.1.2 Magnesium (Mg)

Magnesium is a chemical element required for DNA and protein synthesis, cell division and energy metabolism. Magnesium acts as cofactor in numerous enzymatic reactions in the human body [259]. The deficiency of magnesium has been related with many diseases such as high blood pressure, diabetes, stroke and Alzheimer s disease [260]. It has been proposed that magnesium intake up to 400 mg/day may not result in undesirable effects [253].

The concentration of magnesium in the studied plant species decreased in the following order: *Calotropis procera* > *Acridocarpus orientalis* > *Tecomella undulata* > *Leptadenia pyrotechnica* > *Euphorbia larica* > *Cyperus conglomeratus* (Table 5). The magnesium concentration determined in the current study varied with those found in the published literature. For example, the concentration of magnesium in *Calotropis procera* was higher than the concentration reported by Moustafa *et al.* [261],who found 1040 ppm of magnesium in *Calotropis procera* that grown in Egypt. In addition, the magnesium concentration in *Tecomella undulata* was higher than the concentration reported in four different species belong to Bignoniaceae family namely *Tecoma gaudichaudi, Tecoma capensis*, *Tecoma stans* and *Tabebuia rosea* [262]. In general, several factors affect the elemental content in plants such as air pollution, physiochemical properties of the soil, atmospheric conditions and the geographic origin of the plant species [263]. One study quantified the concentration of five metals in *Moringa oleifera* that was collected from different geographical sites. Results revealed that the concentration of the different metals in *Moringa oleifera* varied according to the location in which it grew [264].

4.2.1.3 Potassium (K)

Potassium is considered as one of the most essential minerals that offers numerous benefits for plants, animals and humans [265]. Potassium plays a crucial role in regulating elevated blood pressure as well as in maintaining bone health [266]. It has been proposed that potassium intake up to 3700 mg/day may not result in apparent adverse effects [253].

The highest concentration of potassium was found in *Calotropis procera* (15,562 ppm), followed by *Euphorbia larica* (13,113 ppm), *Leptadenia pyrotechnica* (10,792 ppm), *Acridocarpus orientalis* (8637 ppm), *Tecomella undulata* (4964 ppm) and *Cyperus conglomeratus* (4452.16 ppm) (Table 5). In a study, Parvez *et al.* [267], found the amount of potassium in *Euphorbia granulata* as 12,800 ppm. Moreover, the concentration of potassium found in the present work for *Calotropis procera* was lower than the concentration reported for *Calotropis gigantea* [268]. Soil moisture is one of the most important factors that influences potassium uptake by plants [269]. Low soil water content can lead to low rate of mineral transport from the soil matrix to the plant root system. Moreover, water deficit stress can lead to stomatal closure, which will decrease the rate of transpiration and hence a low translocation of minerals from the root to the shoot [270]. All of these factors combined can adversely affect plant growth and development. Different studies have shown the effect of water deficit stress on potassium bioavailability by different plants. In earlier studies, reduced levels of potassium have been observed in maize [271] and olive trees [272] under drought stress.

4.2.1.4 Sodium (Na)

Although sodium is well-known of causing high blood pressure, it is required for many functions in the living organisms. The biological role of sodium include maintaining the cellular homeostasis within the body and controlling electrolyte balance [273].

The highest concentration of sodium in the studied plant species was found in *Calotropis procera* (6837.46 ppm), followed by *Acridocarpus orientalis* (4555.24 ppm), *Euphorbia larica* (1435.08 ppm), *Tecomella undulata* (782.49 ppm), *Leptadenia pyrotechnica* (536 ppm) and *Cyperus conglomeratus* (205.31 ppm) (Table 5). Stef *et al.*[274], quantified the concentration of sodium in 33 Romanian medicinal plants. Our results were comparable to their findings, in which they found the sodium concentration in the range of 210 to 6420 ppm.

4.2.2 Micro and toxic elements

Microelements are chemical elements required in trace amounts and play a significant role in metabolism and in protein synthesis. However, these elements become toxic upon exceeding the allowable limits [275].

4.2.2.1 Iron (Fe)

Iron involves in many different cellular functions in the living organisms and is a vital constituent of hemoglobin [276]. Iron involves in DNA synthesis, cell proliferation and biomolecule synthesis [277]. Iron is a main constituent of many enzymes such as oxidases, cytochromes and aconitases [278]. According to FAO/WHO, the allowable level for iron in edible plants is 20 ppm [263].

In this study, all the medicinal plants exceeded the accepted limits. The iron concentration in the studied medicinal plants followed the hierarchy of *Leptadenia pyrotechnica* < *Calotropis procera* < *Acridocarpus orientalis* < *Cyperus conglomeratus* < *Euphorbia larica* < *Tecomella undulata* (Table 5). The concentrations of iron in this study was different from the concentrations found in other studies. The mean concentration of iron in *Euphorbia dracunculoides* L. was 3.043 ppm [279]. Moreover, the iron concentration in *Cyperus conglomeratus* found in the present study was lower than the concentration reported by Ozcan *et al.* [280], for *Cyperus esculentus*. It has been reported that iron bioavailability in plants is enhanced by the presence of ascorbic acid and citric acid, while on the other hand tannins may hinder it s absorption [281]. The intake of the analyzed plants mentioned above may trigger the accumulation of iron. Immoderate accumulation of iron may lead to ROS production and subsequent biomolecules damage [282].

4.2.2.2 Manganese (Mn)

Manganese is an important microelement necessary for normal growth and cellular homeostasis. Manganese plays a major role in blood glucose regulation, maintenance of bone health and macromolecules metabolism [283]. Manganese acts as a cofactor for many antioxidant enzymes such as superoxide dismutase [284]. The recommend FAO/WHO level of manganese in edible plants is 2 mg/kg [263].

In this study, the concentration of manganese exceeded the permissible limits in all the medicinal plants. The concentration of manganese ranged between 11.24 ppm and 468.3 ppm (Table 5). The highest concentration of manganese was recorded in *Calotropis procera*, while the lowest concentration was recorded in *Cyperus conglomeratus*. Jagtap and Satpute [285], reported a value for manganese concentration of 56.15 ppm in *Euphorbia fusiformis* from India. Other studies have also reported the concentrations of manganese in *Calotropis procera* (1590 ppm) [261] and in *Tecomella undulata* (1.288 ppm) [286]. The main factors that govern the bioavailability of manganese in plants is the soil pH and redox potential [287]. Although there are different oxidation states of manganese (Mn^{1+}, Mn^{2+}, Mn^{3+}, Mn^{4+}, Mn^{6+}, and Mn^{7+}), Mn^{2+} is the only phytoavailable form [288]. Moreover, at high pH less manganese is available to plants [289], while at low pH more manganese is absorbed by plants [290]. It s noteworthy to mention that the long-term ingestion of plants that contain high concentration of manganese can result in different types of disorders. Chronic exposure to manganese has been related with oxidative stress, neuronal loss, cognitive decline and disruption of motor behavior [291].

4.2.2.3 Zinc (Zn)

Zinc is an important trace element necessary for cell replication and for DNA and protein synthesis [292]. Zinc is an essential constituent of a wide variety of proteins such as enzymes, transcription factors, receptors and cytokines [293]. Zinc deficiency has been related with many diseases such as diabetes, cancer, pneumonia, malaria and tuberculosis [294]. The allowable level of zinc set by FAO/WHO in edible plants is 27.4 ppm [263].

Out of the six analyzed medicinal plants, three plants showed zinc above the permissible limit. These species are *Acridocarpus orientalis* (28.05 ppm), *Leptadenia pyrotechnica* (28.00 ppm) and *Calotropis procera* (46.22 ppm). These values are relatively different from other studies. For instance, a study has reported 5.15 ppm concentration of zinc in *Calotropis procera* grown in Pakistan [295]. In another study conducted by Gwarzo *et al.* [255], the concentration of zinc reported in *Leptadenia lancefolia* was 129 ppm. Several factors affect the bioavailability of zinc in plants. These factors include the concentration of zinc in the soil, soil pH, soil organic matter, redox states, rhizosphere microorganism s activity, soil water content and the levels of some microelements and macroelements such as phosphorus [296]. Zinc is poorly available for plants at high soil pH, low organic matter and low soil water content [297]. Wang *et al.* [298], found that the addition of manure compost which is considered as a rich source of organic matter increased the bioavailability of zinc in wheat straw and grain.

4.2.2.4 Copper (Cu)

Copper is an essential trace element that acts as cofactor for many enzymes such as cytochrome C oxidase and superoxide dismutase [299]. Copper deficiency can cause harmful effects in the cardiovascular system, immune system and bones [300]. The recommended level for copper set by FAO/WHO in edible plants is 3 ppm [263].

In the current work, all the plants showed copper above the allowable level. The concentration of copper varied between 4.37 ppm and 18.55 ppm (Table 5). The highest concentration of copper was recorded in *Calotropis procera*, while the lowest concentration was recorded in *Cyperus conglomeratus*. In a study conducted by Naeem *et al.* [301], the concentration of copper in *Calotropis procera* was 0.320 ppm. Another study has reported 1.30 ppm of copper in *Cyperus esculentus* [302]. Despite the important functions of copper, it possesses risk to human health at high levels. The accumulation of this essential toxin in the human body can lead to cellular oxidative stress [303]. Moreover, an overload of this metal can cause abdominal pain, diarrhea and nausea [304].

4.2.2.5 Chromium (Cr)

Chromium is one of the common trace elements found in the Earth s crust [305]. Chromium is required for lipid and sugar metabolism [306]. Chromium plays a major role in increasing insulin activity [307] The recommended level for chromium set by FAO/WHO in edible plants is 0.02 ppm [263].

The concentration of chromium in all the analyzed medicinal plants exceeded the permissible limit. The concentration of chromium ranged between 6.11 ppm and 18.86 ppm (Table 5). The highest concentration of chromium was recorded in *Calotropis procera* while the lowest concentration was recorded in *Cyperus conglomeratus*. In a

study reported by Devi *et al.* [308], the concentration of chromium in *Calotropis gigantea* was 2.9 ppm. In another published report, the concentration of chromium in *Cyperus odoratus* was mentioned as 22.9 ppm [309]. It s noteworthy to mention that Cr^{6+} is the most phytoavailable form, which is unstable form under normal soil conditions. The Cr^{6+} bioavailability is highly affected by soil characteristics such as soil texture and soil pH [263]. Moreover, other forms such as Cr^{3+} and many complex Cr anions such as chromate ion (CrO_4^{2-}) can also be readily available to plants [310].

4.2.2.6 Cobalt (Co)

Cobalt is a vital component of vitamin B12 and plays a major role in amino acid formation [311]. Currently, there is no regulatory limit for cobalt concentration in edible plants.

In this study, the highest concentration of cobalt was found in *Calotropis procera* (Table 5). The findings of this study are consistent with the literature. A study has reported 2.54 ppm of cobalt in the leaves of *Calotropis procera* [254]. In another study conducted by Habibu *et al.* [312], the concentration of cobalt in *Leptadenia hastata* was reported to be 6 ppm.

4.2.2.7 Aluminum (Al)

Aluminum is a toxic non-essential metal that exists ubiquitously in the environment [313]. A recent meta-analysis has shown that the prolonged exposure to aluminum increased the risk of Alzheimer s disease incidence [314]. In addition, aluminum is a phytotoxic element that leads to ROS generation in plant cells as well as it causes growth retardation in plant roots [315]. The recommend WHO level of aluminum in edible plants is 15 mg/kg [316].

The concentration of aluminum in all six medicinal plants exceeded the permissible limit. The concentration of aluminum ranged between 16 ppm and 66.63 ppm (Table 5). The highest concentration of aluminum was recorded in the leaves of *Tecomella undulata*, while the lowest concentration was recorded in the leaves of *Acridocarpus orientalis*. In fact, aluminum concentration in medicinal plants has been rarely investigated. Delavar *et al.* [317], examined the concentration of toxic metals in Iranian medicinal plants and they found a higher concentrations of aluminum than the concentrations reported in this study. Moreover, aluminum concentrations in Ghanaian medicinal plants were comparable to the concentrations obtained in this study [264]. Soil pH is one of the most important factors that influences aluminum uptake by plants. The low pH of ultisols renders aluminum in soluble form and facilitates its uptake by plant root system [318]. Soil acidification can result from several natural and anthropogenic factors such as acid rain and the use of fertilizers [319]. Dong *et al.* [320], examined the influence of soil pH on aluminum absorption by soybean plant and they showed an inverse relationship between soil pH and aluminum absorption. Their study demonstrated that as the soil pH decreases, the aluminum uptake by soybean plant increases.

4.2.2.8 Cadmium (Cd)

Cadmium is a highly toxic element that causes severe damage to the organ systems in the human body [321]. Numerous studies have shown a positive relationship between exposure to cadmium and the development of some cancers [322]. The recommend WHO level of cadmium in edible plants is 0.3 ppm [323].

In the current study, the cadmium concentration in 4 plants exceeded the allowable level. These include *Cyperus conglomeratus* (0.72 ppm), *Acridocarpus orientalis* (0.71 ppm), *Tecomella undulata* (0.55 ppm) and *Calotropis procera* (0.50 ppm). The cadmium concentrations of *Calotropis procera* that grown in India [324] and Pakistan [295] were found to be higher than the concentration reported in this study. Moreover, cadmium concentration of *Tecomella undulata* was higher than the value reported by Nahida *et al.* [325], for the same plant species. A number of studies have demonstrated that soil pH plays a major role in cadmium uptake by plants [326,327]. Furthermore, it has been reported that some plants tend to sequester toxic metals as a defense mechanism against herbivores [328,329].

4.2.2.9 Lead (Pb)

Lead is a non-essential toxic element that is usually released to the environment as a result of the anthropogenic activities such as mining and fossil fuel combustion [330]. Bones are considered as the main site of lead accumulation in the human body. Lead causes severe dysfunctions in the central nervous, hepatic and cardiovascular system [331]. The highest lead concentration in this study was found in *Cyperus conglomeratus* (7.05 ppm). The lead concentration in all the studied medicinal plants falls within the permissible limit (10 ppm) [323].

4.3 *In vitro* antioxidant assessment of selected UAE medicinal plants

Excessive production of free radicals can lead to oxidative damages. In humans, oxidative damage has been associated with many diseases such as cancer, atherosclerosis, diabetics and myocardial infarction [332]. Antioxidants are well-known by their pivotal role in protecting cells against oxidative damage [333]. Human bodies are equipped with a strong antioxidant defense system, which can protect cells from the harmful effects of free radicals [334]. Nonetheless, some external factors such as smoking and radiation can increase the levels of free radicals in living cells and weaken the ability of the antioxidant system to quench and neutralize them [335]. Therefore, the consumption of exogenous antioxidants is highly recommended to mitigate the damages of oxidative stress [336].

Synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tertbutylhydroquinone (TBHQ) have been widely used in food industry [337]. In fact, synthetic antioxidants have been associated with some health problems such as carcinogenesis and stomach problems [338]. Currently, intensive research activities are being carried out by many biological researchers on plant-derived antioxidants. Medicinal plants and foods such as fruits and spices are rich sources of naturally occurring antioxidants [339]. There are different assay methods used for the estimation the antioxidant activities of plant extracts such as DPPH, reducing power and metal chelating assays [340]. In this study, the antioxidant activities of six UAE medicinal plants were examined using DPPH, ABTS and FRAP assays.

4.3.1 *In vitro* antioxidant activity of *Acridocarpus orientalis*

Overall, our findings showed that DPPH free radical scavenging activity of *Acridocarpus orientalis* increases in a dose dependent manner at a concentration of 20 µg/mL to 100 µg/mL (Figure 11A). The concentration required to scavenge 50% of radical of the plant extract and BHT were 34 µg/mL and 28 µg/mL, respectively. In the ABTS radical scavenging assay, a dose-response relationship was also observed. The antioxidant activity increased as the concentration of the plant extract increased (Figure 11B). The IC_{50} of the plant extract and ascorbic acid were 45 µg/mL and 30 µg/mL, respectively. In the ferric reducing antioxidant power assay, the optical density value at 593 nm increased as the plant extract concentration increased between 0 (control) and 100 µg/mL (Figure 11C).

Different researchers examined the antioxidant activities of different plants that belong to Malpighiaceae family. Premathilaka and Silva [341], assessed the antioxidant activity of the fruits of *Bunchosia armeniaca*. The DPPH radical scavenging ability of *Bunchosia armeniaca* fruits (IC_{50} = 981 µg/mL) was higher than the value reported in this study for *Acridocarpus orientalis*. The DPPH radical scavenging activity of *Acridocarpus orientalis* ethanolic extract was relatively lower than the activity reported for *Byrsonima duckeana* (IC_{50} =14.88 µg/mL) [342]. In another study conducted by Vargas *et al.* [343], the concentration required to scavenge 50% of ABTS radical of the ethanolic extract of *Byrsonima japurensis* was 12.3 µg/mL. Moreover, their findings was similar to our results, where *Byrsonima japurensis* has shown to have an ABTS radical scavenging activity less than the positive standard (ascorbic acid).

Earlier in this study, the highest total phenolic content was observed in *Acridocarpus orientalis* (Figure 9). The antioxidant activity of *Acridocarpus orientalis* may attributed to the presence of phenolic compounds. Numerous studies have shown a positive correlation between the total phenolic content and the antioxidant activity of different plant extracts. For instance, Augusto *et al.* [344], found a liner correlation between the total phenolic content and the antioxidant activities of murtilla fruits extracts. In fact, the antioxidant activities of phenolic compounds might be based on various mechanisms. Phenolic compounds possess hydroxyl groups in their aromatic rings that are highly capable of donating hydrogen to reactive oxygen species and hence hampering the occurrence of cellular oxidative damage in the living organisms [345]. In addition, phenolic compounds act as chelators of redox active metal ions that are involved in the production of free radicals [346]. Some metals can undergo Fenton and Fenton-like reactions, which include the reduction of hydrogen peroxide (H_2O_2) by reduced metals to form hydroxyl radical ($OH^{\cdot}$). The generation of oxy radicals such as $OH^{\cdot}$ can result in oxidative cell damage and subsequent cell death [347]. Interestingly, the functional groups of phenolic compounds such as hydroxyl and carboxyl groups are capable of binding metals (e.g., iron and copper), thus hindering their interaction with hydrogen peroxide (H_2O_2) [348]. Another potential mechanism by which phenolic compounds act as antioxidants relates to their inhibition of the activity of enzymes involved in the production of free radicals such as cyclooxygenase (COX) and lipoxygenase (LOX) [349]. Moreover, phenolic compounds may contribute to the antioxidant activities through their synergistic interaction with the antioxidant molecules such as ascorbic acid and alpha-tocopherol [15].

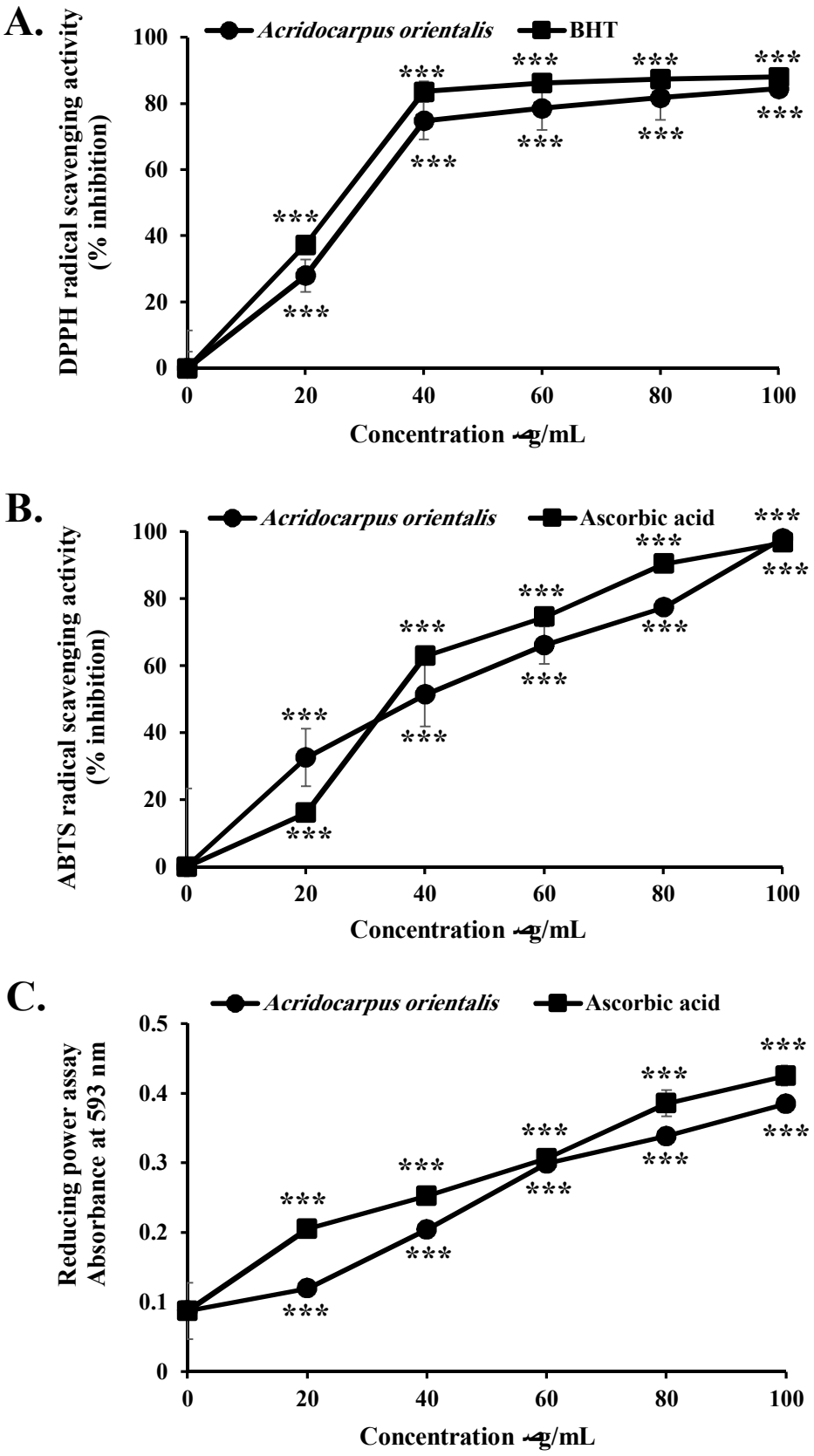

Figure 11: Antioxidant activities of *Acridocarpus orientalis* as determined by various *in vitro* antioxidant assays namely DPPH (A), ABTS (B) and FRAP (C) assays. Data are mean ± SD, n=9. ***P < 0.001, versus non-treated controls by the t-test.

4.3.2 *In vitro* antioxidant assessment of *Tecomella undulata*

DPPH method is one of the simple and sensitive methods that has been extensively used to evaluate the hydrogen donating abilities of the antioxidant compounds [350]. 2,2-diphenyl-1-picrylhydrazyl (DPPH) is a stable free radical with a dark violet color [351]. The antioxidant compound donates an electron or hydrogen to the DPPH radical and convert it to a stable diamagnetic molecule. This stoichiometric reaction is accompanied with a color change of the DPPH radical from violet to yellow. The antioxidant potential through DPPH radical scavenging is evaluated by the reduction in absorbance at 517 nm. A notable reduction in the absorbance of the reaction mixture implies a significant antioxidant ability [352]. Overall, the DPPH free radical scavenging activity of *Tecomella undulata* increases in a dose dependent manner at a concentration of 50 µg/mL to 250 µg/mL (Figure 12A). The IC_{50} value of DPPH free radical scavenging capacity of *Tecomella undulata* extract and the positive control BHT were 137 µg/mL and 29 µg/mL, respectively. A previous study evaluated the antioxidant activity of *Tecomella undulata* grown in India and recorded the IC_{50} value of DPPH free radical scavenging ability as 277.82 µg/mL [226].

ABTS method is one of the common methods that has been widely used to test the antioxidant activities of plant extracts [353]. The oxidation of ABTS by oxidizing agents such as potassium persulfate and manganese dioxide leads to an electron loss from the ABTS nitrogen atom and subsequent generation of ABTS radical cation [354]. The blue-green chromophore ($ABTS^{+}$) receives an electron or hydrogen from antioxidants, resulting in solution decolorization [351].

In this study, the ABTS radical scavenging activity of *Tecomella undulata* increased as the concentration of the plant extract increased (Figure 12B). The concentration required to scavenge 50% of radical of the plant extract and ascorbic acid were 141 µg/mL and 45 µg/mL, respectively. A study conducted by Bhardwaj *et al.* [355], the IC_{50} of *Tecomella undulata* of ABTS radical scavenging assay was 425 µg/mL.

The FRAP assay is one of the simple and rapid antioxidant assays that do not require specialized apparatus [356]. In the FRAP assay, the presence of antioxidants in test samples causes the reduction of Fe^{3+} to Fe^{2+} at low pH [357]. The reducing power of *Tecomella undulata* ethanolic extract and ascorbic acid increased steadily with increasing concentration of plant sample (Figure 12C).

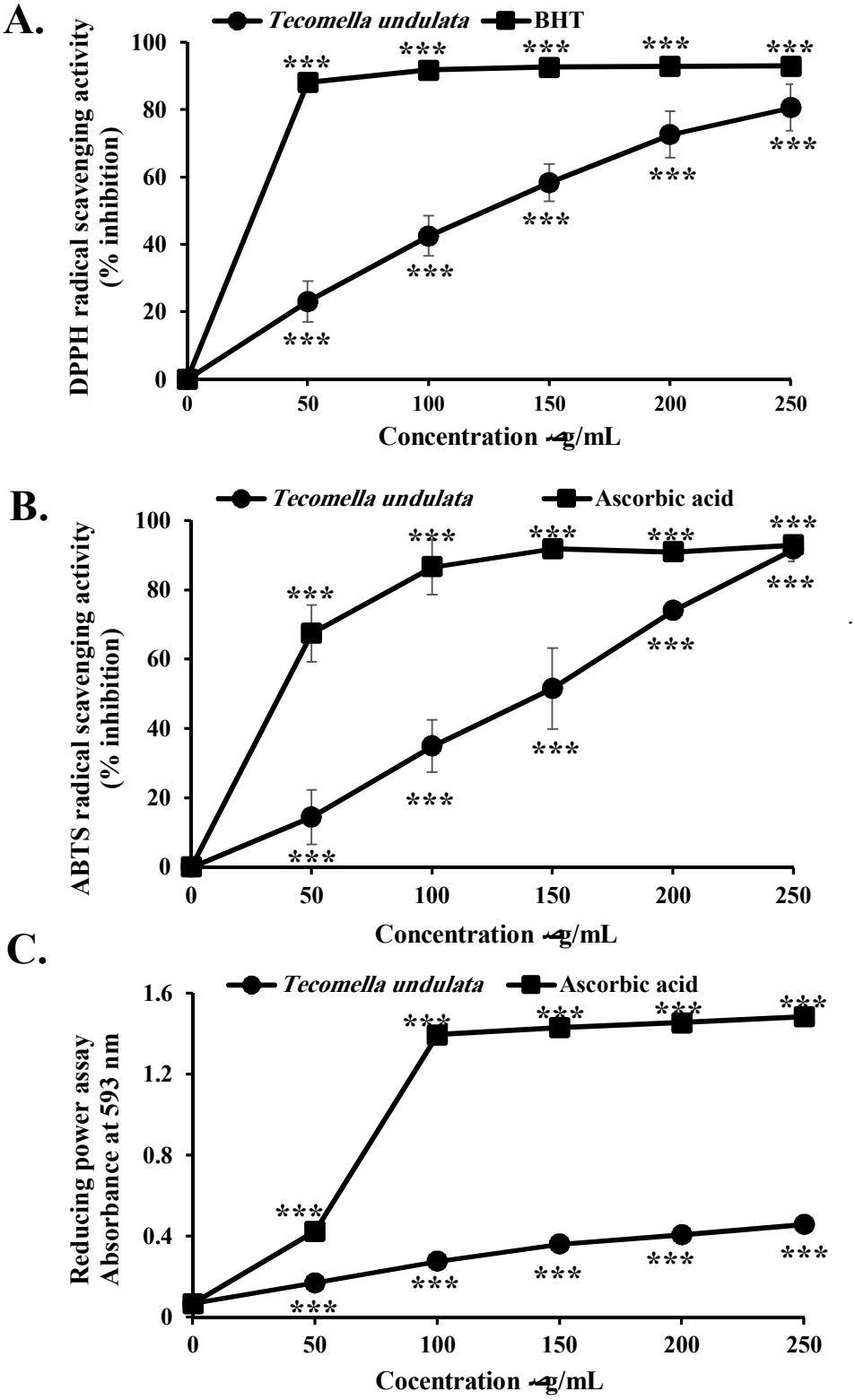

Figure 12: Antioxidant activities of *Tecomella undulata* as determined by various *in vitro* antioxidant assays namely DPPH (A), ABTS (B) and FRAP (C) assays. Data are mean ± SD, n=9. ***P < 0.001, versus non-treated controls by the t-test.

4.3.3 *In vitro* antioxidant assessment of *Calotropis procera*

Calotropis procera ethanolic extract significantly decreased the DPPH radical from concentrations of 50 250 µg/mL, in a concentration response manner (Figure 13A). The calculated IC_{50} of *Calotropis procera* ethanolic extract was 147 µg/mL. BHT also significantly reduced the DPPH radical (IC50 = 29 µg/mL). This extract also significantly reduced the ABTS radical at concentrations of 50 250 µg/mL, as did ascorbic acid (Figure 13B). The calculated IC_{50} of ABST radical scavenging activity of *Calotropis procera* extract was 57 µg/mL. In the ferric reducing antioxidant power assay, the optical density value at 593 nm increased as the plant extract concentration increased between 0 (control) and 250 µg/mL (Figure 13C).

Calotropis procera is well-known for its ample medicinal properties. Several studies examined the antioxidant activities of *Calotropis procera in vitro* and *in vivo*. Sayed *et al.* [358], examined the antioxidant activities of *Calotropis procera* latex on Catfish (*Clarias gariepinus*) subjected to 4-nonylphenol. The latex of *Calotropis procera* decreased the elevated levels of superoxidase dismutase, catalase, acetylcholinesterase, glutathione-s-transferase and cortisol. In another study, Kumar and Padhy [359], studied the antioxidant activities of the aqueous suspension of the dried latex of *Calotropis procera* in diabetic rats. The administration of the aqueous suspension to the diabetic rats has led to a reduction in the elevated levels of TBARS and an increase in the reduced levels of GSH.

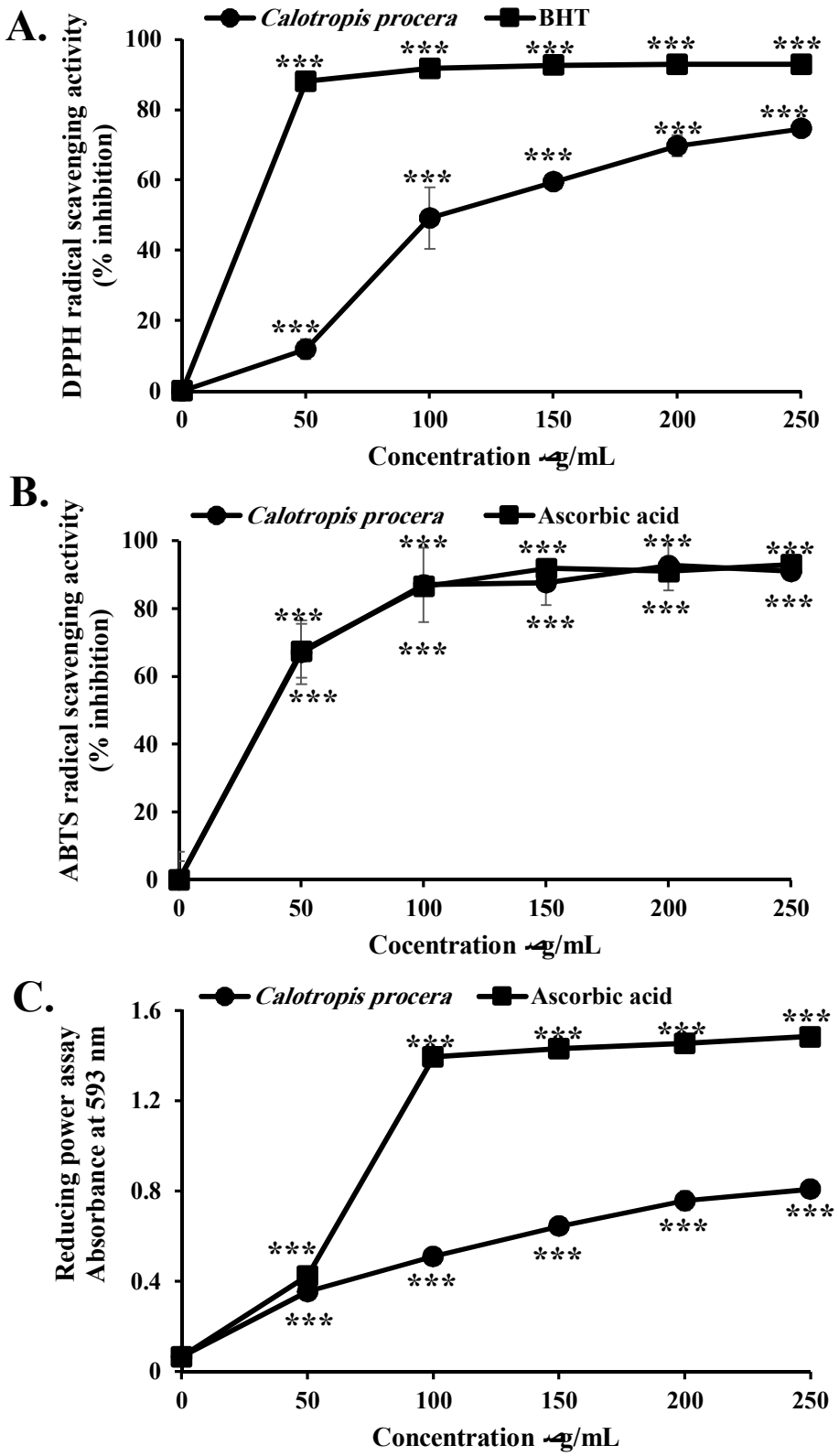

Figure 13: Antioxidant activities of *Calotropis procera* as determined by various *in vitro* antioxidant assays namely DPPH (A), ABTS (B) and FRAP (C) assays. Data are mean ± SD, n=9. ***P < 0.001, versus non-treated controls by the t-test.

4.3.4 *In vitro* antioxidant assessment of *Leptadenia pyrotechnica*

As shown in Figure14A and Figure14B, the *Leptadenia pyrotechnica* extract exhibited potent radical scavenging ability in a concenrtation-dependent manner, pointing to its antioxidant activity. The antioxidant ability of *Leptadenia pyrotechnica* extract to scavenge purple colored DPPH and blue-green colored $ABTS^{+}$ radicals was compared to that of BHT and ascorbic acid, respectively. The DPPH radical scavenging activity provided an IC_{50} value of 250 µg/mL (lower than that of BHT). The IC_{50} value for the $ABTS^{+}$ radical was 149 µg/mL, which was also lower than that of ascorbic acid. The reducing power of the *Leptadenia pyrotechnica* extract and ascorbic acid (as indicated by the absorbance at 595 nm) increased with increasing concentration of the samples (Figure 14C).

The DPPH radical scavenging activity of *Leptadenia pyrotechnica* ethanolic extract was comparable to that reported for *Leptadenia reticulate* (IC_{50} = 267.13 µg/mL) [360]. In another published study, the concentration required to scavenge 50% of ABTS radical of *Leptadenia hastata* was 62.24 µg/mL [361]. The antioxidant activity of plants is highly affected by several factors such as environmental conditions, geographical location, UV radiation, drought stress and temperature stress [362].

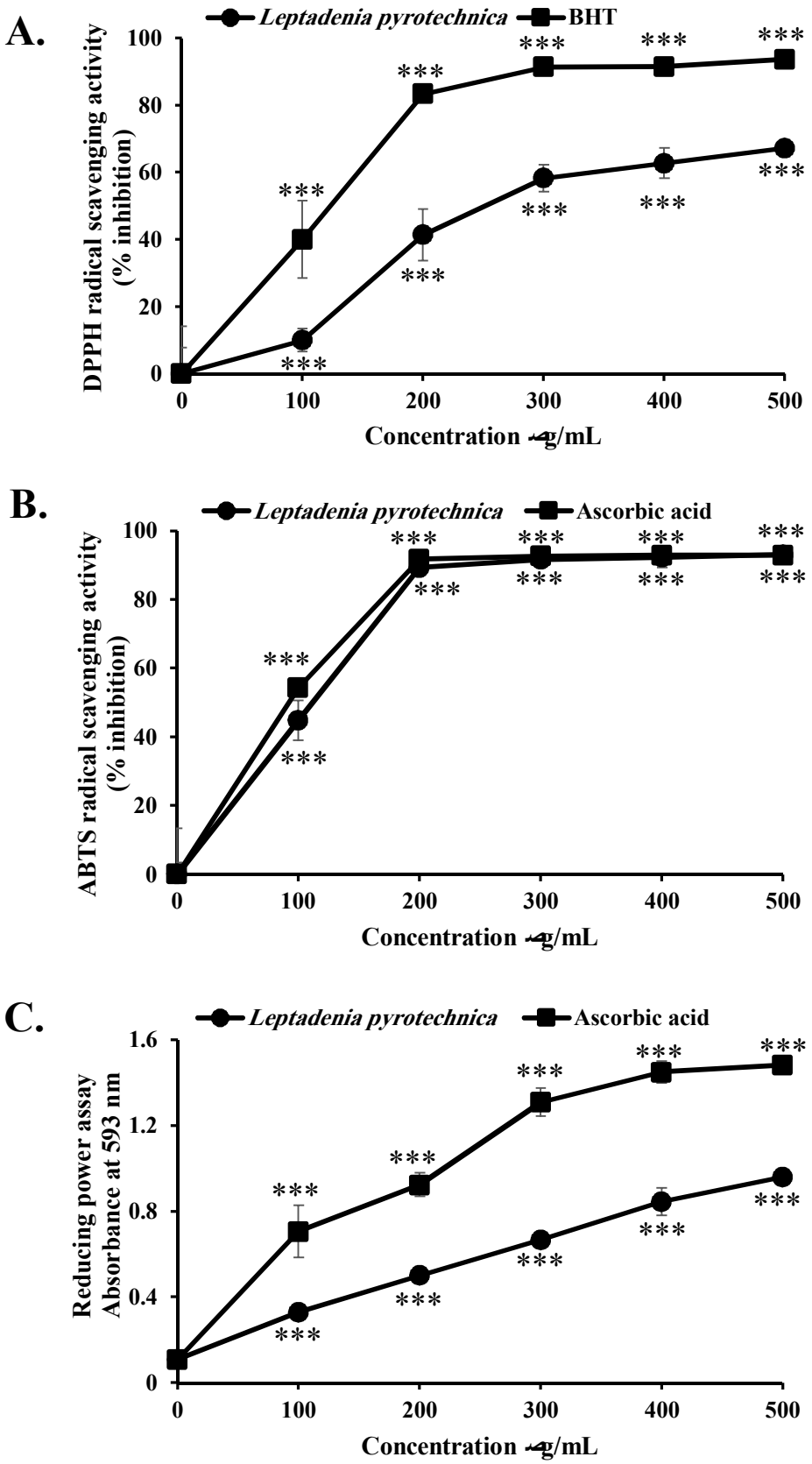

Figure 14: Antioxidant activities of *Leptadenia pyrotechnica* as determined by various *in vitro* antioxidant assays namely DPPH (A), ABTS (B) and FRAP (C) assays. Data are mean ± SD, n=9. ***P < 0.001, versus non-treated controls by the t-test.

4.3.5 *In vitro* antioxidant assessment of *Euphorbia larica*

The DPPH scavenging activity of *Euphorbia larica* increased with increasing concentration (Figure 15A). The scavenging activity of BHT was higher than *Euphorbia larica* at all concentration. The IC_{50} value of *Euphorbia larica* of the DPPH assay was 256 µg/mL. The IC_{50} value for the $ABTS^{+}$ radical of *Euphorbia larica* was 305 µg/mL ,which was also lower than that of ascorbic acid (Figure 15B). The dose response curve for the reducing power of the *Euphorbia larica* extract (as indicated by the absorbance at 595 nm) is shown in Figure 15C. Increased absorbance indicates increased reducing power. The reducing power of *Euphorbia larica* extract was lower than that of ascorbic acid. Different researches examined the antioxidant activity of other species that belong to *Euphorbia* genus [227,363].

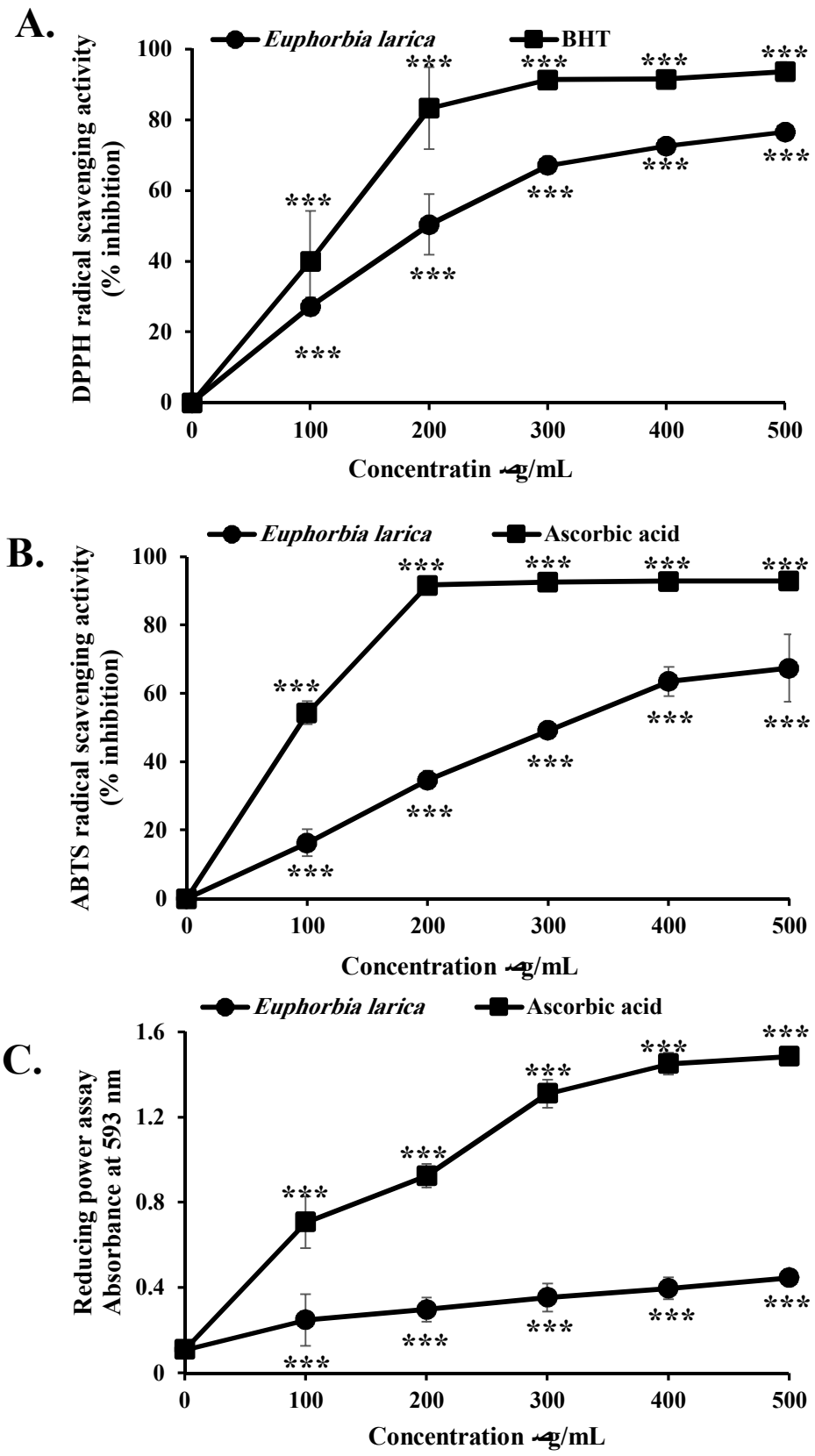

Figure 15: Antioxidant activities of *Euphorbia larica* as determined by various *in vitro* antioxidant assays namely DPPH (A), ABTS (B) and FRAP (C) assays. Data are mean ± SD, n=9. ***P < 0.001, versus non-treated controls by the t-test.

4.3.6 *In vitro* antioxidant assessment of *Cyperus conglomeratus*

The DPPH radical scavenging activity of *Cyperus conglomeratus* showed a concentration-dependent response (Figure 16A) and the IC50 value of the plant ethanolic extract with DPPH was 304 µg/mL. BHT, which was used as positive control in the DPPH assay, had an IC50 value of 161 µg/mL. The scavenging effects of *Cyperus conglomeratus* extract and ascorbic acid on ABTS radical are presented in Figure 16B. The ABTS radical formation was inhibited by the plant extract with an IC50 value of 212 µg/mL and 125 µg/mL for ascorbic acid. Reducing power of *Cyperus conglomeratus* extract was characterized by increased absorbance. The reducing power of the plant ethanolic extract increased with the increase in concentration as shown in Figure 16C. The reducing power of *Cyperus conglomeratus* were compared to those of ascorbic acid.

To the best of our knowledge, this is the first study that examined the antioxidant activities of *Cyperus conglomeratus*. However, the antioxidant activities of other species that belong to the same genus were studied. *Cyperus rotundus* is a well-known medicinal plant that have shown to exhibit antiinflammatory, anticancer and antibacterial activities [364]. A study conducted by Mannarreddy *et al.*[183], found that the concentration required to scavenge 50% of DPPH radical of the methanolic extract of *Cyperus rotundus* was 28.35 µg/mL. In another study, Kakarla *et al.*[365], examined the antioxidant activities of some chemical constituents isolated from *Cyperus rotundus*. According to their results, the concentrations required to scavenge 50% of ABTS radical of kaempferol, gallic acid and quercetin was 0.45 µg/mL, 0.56 µg/mL and 0.067 µg/mL, respectively.

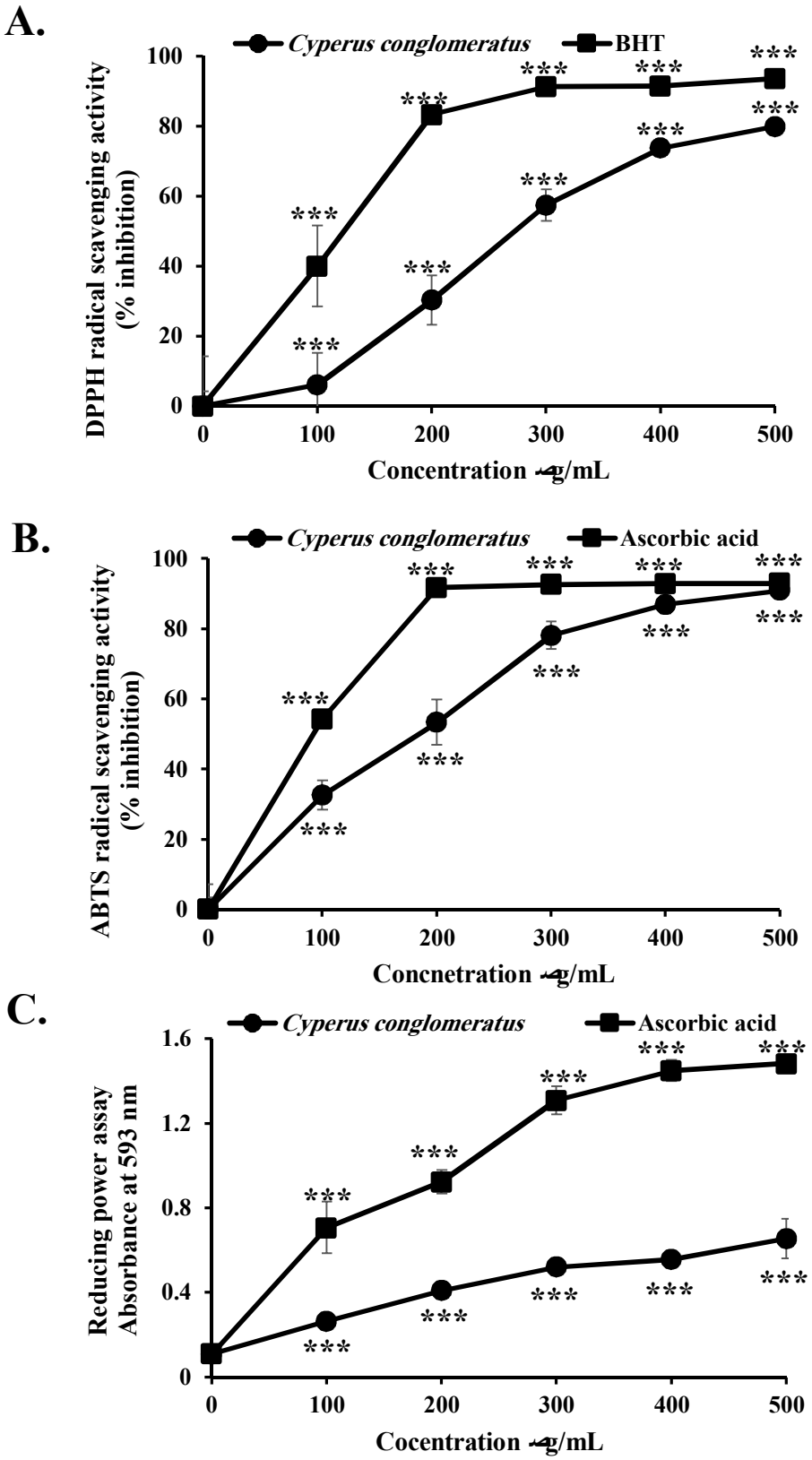

Figure 16: Antioxidant activities of *Cyperus conglomeratus* as determined by various *in vitro* antioxidant assays namely DPPH (A), ABTS (B) and FRAP (C) assays. Data are mean ± SD, n=9. ***P < 0.001, versus non-treated controls by the t-test.

Chapter 5: Conclusion

The research on medicinal plants and their bioactive constituents is an active research area. The UAE natural flora contains different medicinal plants that have been utilized for various therapeutic purposes. The objectives of the current study include: i) qualitative and quantitative determination of phytochemicals in the crude extracts of six UAE medicinal plants ii) quantification of macronutrients, micronutrients and toxic elements using inductively coupled plasma-optical emission spectrometry (ICP-OES) iii) investigation of the *in vitro* antioxidant activity of the crude extracts of six UAE medicinal plants using DPPH, ABTS and FRAP assays.

The preliminary phytochemical screening revealed the presence of different bioactive compounds in the studied crude extracts. In particular, phenols, flavonoids and terpenoids were found in all of the analyzed plants. The further quantitative phytochemical screening revealed that our crude extracts are rich with phenols and flavonoids. The highest phenols and flavonoids content was observed in *Acridocarpus orientalis* extract. Further studies are recommend to confirm the presence of the studied phytochemicals and their derivatives using analytical techniques.

The concentrations of the macro-elements varied within the studied medicinal plants. Calcium was found to be the highest among the macro-elements while sodium was found to be the lowest. Majority of the analyzed plants exceeded the permissible limits set for iron, manganese, copper, chromium, aluminum and cadmium. The regular consumption of such medicinal plants that contain high concentrations of aforementioned metals can lead to severe adverse effects. Therefore, close monitoring of such medicinal plants is recommended to ensure their safety and efficacy. The present study suggests that the different plant extracts are potential sources of natural

antioxidants. *In vivo* safety of these plant extracts requires to be thoroughly investigated in experimental animal before to its potential application as an antioxidant ingredient.

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