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Antioxidant and α-amylase Inhibition Activities of Six Plants Used in the Management of Diabetes in Morocco

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Abstract: Diabetes mellitus is one of the major health problems in the world. Conventional antidiabetic drugs are effective; however, they also with unavoidable side effects. On the other hand, plants may be an alternative source of antidiabetic agents. In the present study, six plants (*Cynara scolymus*, *Ceratonia siliqua*, *Centaurium erythraea*, *Marrubium vulgare*, *Salvia officinalis*, and *Ziziphus lotus* reputed for their antidiabetic effect in Moroccan traditional medicine were chosen. The work was focused on the determination of the antioxidant activities by several methods, including as well as their α-amylase inhibitory capacity. It was noted that *S. officinalis* extract contained the highest phenolic contents and the strongest ABTS and nitric oxide scavenging activities. *C. erythraea* has the highest total flavonoid content and the best total antioxidant activity. *M. vulgare* showed the best α-amylase inhibitory activity and the best chelating power abreast with *C. scolymus*, which presented very weak antioxidant activities unless good α-amylase inhibition. Principal component analysis (PCA) showed a very good correlation between total phenolic content and 2,2-diphenyl-1-picrylhydrazyl (DPPH) along with 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) free radicals scavenging activities. *M. vulgare* displayed the best α-amylase inhibition capacity.

Keywords: *Cynara scolymus*; *Ceratonia siliqua*; *Centaurium erythraea*; *Marrubium vulgare*; *Salvia officinalis*; *Ziziphus lotus.*

Abbreviations: A_0 - absorbance of the control; A_1 - absorbance of the sample; AAE – Ascorbic acid equivalent; ABTS - 2,2'-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid); AGEs - advanced glycation end products; BC – blank control; BS – Blank sample; C – Control; ; DM – Diabetes mellitus; DPPH - 2,2-Diphenyl-1-picrylhydrazyl; Dw – Dried weight; GAE – Gallic acid equivalent; IC_{50} – half maximal inhibitory concentration or half maximal scavenging concentration; LPS – lipopolysaccharide; NO – Nitric oxide; ONOO – Peroxynitrite; PC – Principal component; PCA - Principal component analysis; PBS - Phosphate buffer saline; QE – Quercetin equivalent; RNS - Reactive nitrogen species; ROS – Reactive oxygen species; S – Sample; SD - Standard deviation; TAC – Total antioxidant capacity; TFC – Total flavonoid content; TPC – Total phenol content; USA – United States of America; VSMC – Vascular smooth muscle cells.

1. Introduction

Oxidative stress plays an important role in the initiation and progression of several diseases, such as cancer, cardiovascular disorders, diabetes, and neurological diseases, and it underlies the major complications in diabetes mellitus (DM) [1]. Many studies have shown that diabetic patients undergo chronic oxidative stress due to reactive oxygen species (ROS) produced mainly through the glycation reaction, which occurs in various tissues, leading to oxidative stress, which possibly causes various forms of tissue damage in patients with diabetes [2,3]. Hence, new strategies with classic and new antioxidants should be implemented in treating diabetes [4].

α-Amylase is an enzyme that is secreted by the pancreas and salivary glands that can hydrolyze starches and oligosaccharides into simple sugars. Inhibition of this enzyme can retard carbohydrate digestion, thus causing a decrease in the absorption of glucose and consequently reducing postprandial blood glucose levels [5]. Therefore, inhibiting this enzyme activity in digestive organs is considered a therapeutic approach for managing diabetes [6].

Salvia officinalis L., sage, belongs to the Lamiaceae family. The aerial parts of this shrub have a long history of use in cookery and traditional medicine. Leaves from this plant are one of the most frequently used for the traditional treatment by diabetic patients in Morocco [7,8], hypertension [9], cardiovascular disease [10], digestive system, cosmetology [9], and intestinal pain as spasmolytic [11].

Marrubium vulgare L. (Lamiaceae family), commonly known as horehound, is a native aromatic plant to the Mediterranean Sea region, which can be found in many temperate regions of Europe, North Africa, and Asia [12]. In Morocco, this medicinal plant is one of the most commonly used to treat diabetes [7,8,13-15], hypertension, cardiovascular diseases, bronchopulmonary infections, insomnia, asthenia, cough, and pain [16-18].

Centaurium erythraea Rafn, a common centaury (Gentianaceae family), is growing in almost all Europe, North Africa, and Southwest Asia. It is recommended for treating gastrointestinal disorders and to reduce hypercholesterolemia and hypertension in ethnomedicinal practice [19]. The use of *C. erythraea* in traditional medicine has been described in the pharmacopeia of 23 different countries [20]. This species has been reported to be used for treating diabetes in ethnobotanical surveys in Morocco [21] and other uses [22].

Cynara scolymus L. (artichoke) (Asteraceae family); is a native species of the Mediterranean basin; represents an important ingredient of the Mediterranean diet. This plant is widely used to treat several ailments, such as diabetes, abdominal and gastric pain, and respiratory and cardiovascular problems in Morocco [19, 23-27].

Ceratonia siliqua L. (Fabaceae family), or carob trees, is a leguminous evergreen tree that grows throughout the Mediterranean region, mainly in Spain, Italy, Portugal, and Morocco. It is well known for its medicinal features and has a long history of use in the human diet (over 4,000 years) [28]. The carob tree's fruit has been widely used classically in folk medicine in treating gastrointestinal disorders and diabetes [29], and many other ailments [29-34]. Recently, it has been reported in a review article that the tree is studied as having multiple pharmacological activities, especially in the digestive tract, including antioxidant, antidiabetic, antidiarrheal, antibacterial, anti-ulcer, and anti-inflammatory actions [35].

Ziziphus lotus L. (Lam) (jujube) (Rhamnaceae) is a widespread traditional medicinal plant. In Africa, *Z. lotus* is widely distributed in Mediterranean regions like Algeria, Morocco, Tunisia, and Libya [36]. It is known in Morocco as "Sedra" and spread in many habitats in arid

and semi-arid regions, and is being used in nutrition, health, and cosmetics [37]. This plant is known for several medicinal applications as antidiabetic [7,13,22], sedative, bronchitis, heart disease, circulatory and urinary affections, digestive system, gastrointestinal disorders and antidiarrhea, dementia, hair care, against rheumatism and cold by local populations [30,38-43].

In the markets of the medina of Fez there are many merchants dedicated to selling medicinal plants. Some species, such as sage, horehound, common centaury, artichoke, carob tree, and jujube, are sold to treat inflammation or diabetes. The present work aims to evaluate the antioxidant activities using several antioxidants protocols along with the α-amylase inhibitory activities of those species purchased by herbalists in the street fairs in the region of Fez, Morocco.

2. Materials and Methods

2.1. Plant material

Plants material *C. scolymus* head flowers, *C. siliqua* fruits, the aerial part of *C. erythraea*, and leaves from *M. vulgare*., *S. officinalis*, and *Z. lotus* have been purchased from herbalists in the region of Fez, Morocco. These plant parts were ground and then subjected to extraction.

2.2. Plant solvent extraction

Extraction of phenols was performed by sonication on an ice bath for 6 min using a VC300 Vibracell sonicator (Sonics and Materials, USA) with a 20 kHz frequency. One gram of dried powder in 10 mL of a hydro-alcoholic solution (70%) was used. After sonication, the samples were centrifuged for 5 min at 2,000 *g* at 20 °C, and the supernatant was removed and kept at −20 °C for successive analyses.

2.3. Total phenolic content (TPC)

The total phenolic content was determined using the Folin-Ciocalteu reagent according to the method described by Singleton and Rossi [44], with some modifications to adapt it to 96 well microplates. Plant hydro-alcoholic extracts (25 µL) were mixed with 125 µL of Folin-Ciecalteu reagent (0.2 N) and 100 µL of 7.5% Na_2CO_3. The absorbance was measured at 760 nm after 2 h of incubation at room temperature. The total polyphenol content was expressed as mg per g of gallic acid equivalents (GAE) using a calibration curve. Tests were carried out in triplicate.

2.4. Total flavonoid content (TFC)

The amounts of flavones and flavonols in extracts were determined according to the method previously described [45] with minor modifications. An amount of 100 µL of $AlCl_3$ (20%) was added to 100 µL of extract, and after 1h incubation at room temperature, the absorbance was measured at 420 nm. Total flavones and the flavonols content were calculated as quercetin equivalents (QE) (mg per g) using a calibration curve. Tests were carried out in triplicate.

2.5. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) radicals scavenging activities

The DPPH free radical scavenging activity was performed as previously described [46]. A hydro-alcoholic stock solution (50 µL) of each sample at different concentrations was placed in a cuvette, and 2 mL of 60 µM ethanolic solution of DPPH (2,2-diphenyl-1- picrylhydrazyl) was added. Absorbance measurements were made at 517 nm (Shimadzu 160-UV spectrophotometer, Tokyo, Japan) after 60 min of reaction at room temperature. The percentage of scavenging ability was determined according to the following formula: $[(A_0 - A_1)/A_0 \times 100]$, in which A_0 is the absorbance of the control and A_1 is the absorbance of the sample. Percentage inhibition was plotted against sample concentration, and IC_{50} was determined (sample concentration able to scavenge 50% of DPPH free radical). Tests were carried out in triplicate.

2.6. 2,2'-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation scavenging activities

The ABTS radical cation decolorization assay was carried out using the method reported by Ling *et al*. [47] with slight modifications. ABTS radical cation ($ABTS^{\cdot+}$) was produced by reacting 7 mM stock solution of ABTS with 2.45 mM potassium persulfate (final concentration) and allowing the mixture to stand in the dark at room temperature for 12–16 h before use. The $ABTS^{\cdot+}$ solution was diluted with ethanol to an absorbance of 0.7 ± 0.02 at 734 nm. An ethanolic solution (10 µL) of the samples at various concentrations was mixed with 990 µl diluted $ABTS^{\cdot+}$ solution. After the reaction at room temperature for 6 min, the absorbance at 734 nm was measured. Lower absorbance of the reaction mixture indicates higher $ABTS^{\cdot+}$ scavenging activity. The capability to scavenge the $ABTS^{\cdot+}$ was calculated using the formula given below:

$ABTS^{\cdot+}$ scavenging activity (%) = [1 - (S - BS)/(C - BC)] x 100, where S, BS, C, and BC are the absorbances of the sample, the blank sample, the control, and the blank control, respectively. The values of IC_{50} were determined as reported above.

2.7. Total antioxidant capacity (TAC)

The total antioxidant capacity of the plant extracts was evaluated by the phosphomolybdenum method according to the procedure described by Prieto *et al*. [48]. The assay is based on the reduction of Mo(VI) to Mo(V) by the extract and subsequent formation of green phosphate/Mo(V) complex at acid pH. A volume of 0.1 mL of extract was added to 1.5 mL of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate). The absorbance of the reaction mixture was measured at 695 nm using a spectrophotometer against blank after cooling to room temperature. A volume of 0.1 mL of aqueous ethanol (70%) was used in place of the plant extract was used as the blank. The antioxidant activity is expressed as the number of mg Ascorbic Acid equivalent (AAE).

2.8. Nitric oxide scavenging activity

The nitric oxide (NO) scavenging activity of samples was measured according to the method already described [49]. In this method, 50 µL of a serially diluted sample of plant extract was added to 50 µL of 10 mM sodium nitroprusside in phosphate buffer saline (PBS) into a 96-well plate, and the plate was incubated at room temperature for 90 min. Finally, an equal volume of Griess reagent was added to each well, and the absorbance was read at 546 nm.

Several concentrations of samples were made, and the percentage inhibition was calculated from the formula: [1 - (A_{sample} - $A_{sample\ blank}$)/($A_{control}$ - $A_{control\ blank}$)] x 100, where ((A_{sample} - $A_{sample\ blank}$) is the difference in the absorbance of a sample, with or without 10 mM sodium nitroprusside, and ($A_{control}$ - $A_{control\ blank}$) is the difference in the absorbance of the PBS control, with or without 10 mM sodium nitroprusside. Percentage inhibition was plotted against sample concentration, and IC_{50} was determined (concentration of sample able to scavenge 50% of NO free radical).

2.9. Ferrous ions chelating power

The degree of chelating of ferrous ions was evaluated according to that already described [45]. Briefly, samples were incubated with 0.05 mL of $FeCl_2 \cdot 4H_2O$ (2 mM). The addition of 0.2 mL of 5 mM ferrozine initiated the reaction, and after 10 min, the absorbance at 562 nm was measured. An untreated sample served as the control. The percentage of chelating ability was determined according to the following formula: [($A_0 - A_1$)/A_0 x 100], in which A_0 is the absorbance of the control and A_1 is the absorbance of the sample. The values of IC_{50} were determined as reported above.

2.10. α-Amylase inhibitory activity

α -Amylase inhibition assay was carried out in a microtitre plate according to Aazza *et al*. [50] based on the starch-iodine test. The total assay mixture composed of 40 µL 0.02 M sodium phosphate buffer (pH 6.9 containing 6 mM sodium chloride), 0.02 units of enzyme solution, and plant extract were incubated at 37°C for 10 min. Then soluble starch (1%, w/v) was added to each reaction well and incubated at 37°C for 15 min. Hydrochloric acid 1 M (20 µL) was added to stop the enzymatic reaction, followed by the addition of 100 µL of iodine reagent (5 mM I_2 and 5 mM KI). The color change was noted, and the absorbance was read at 620 nm on a microplate reader. The control reaction representing 100% enzyme activity contained no extract sample.

A dark-blue color indicates starch's presence, yellow indicates starch's absence, and brown indicates partially degraded starch in the reaction mixture. In the presence of inhibitors from the extracts, the starch added to the enzyme assay mixture is not degraded and gives a dark blue color complex, whereas no color complex is developed in the absence of the inhibitor, indicating that starch is completely hydrolyzed by α -amylase. The inhibition percentage of the enzyme was calculated using the following formula:

$$\left[1 - \frac{[(A^{-}_{control}) - (A^{+}_{control}) - (A_{sample})}{(A^{-}_{control}) - (A^{+}_{control})}\right] x100$$

Where $A^{+}_{control}$ is the absorbance of 100% enzyme activity (ethanol 70% with enzyme), $A^{-}_{control}$ is the absorbance of 0% enzyme activity (ethanol 70% without enzyme), and A_{sample} represents the absorbance of the sample.

2.11. Statistical analysis

A one-way analysis of variance (ANOVA) followed by the Tukey posthoc test was used to analyze statistical significance ($p < 0.05$) using GraphPad Prism software (Trial version

8.3.1, GraphPad Software, La Jolla, California USA). The Spearman correlation coefficient was applied to evaluate the correlation between the different responses. The analysis was carried out at least in triplicate. Significance and confidence levels were estimated at $p < 0.05$. Principal component analysis (PCA) was performed using PAST software 4.02 to identify relationships between the variables.

3. Results and Discussion

3.1. Total phenolic and total flavonoid contents

Oxidative stress, mediated by hyperglycemia-induced generation of free radicals, contributes to the development and progression of diabetes and related complications like glycoxidation; thus, ameliorating oxidative stress through treatment with antioxidants might be an effective strategy to reduce diabetic disorders [4]. The phenolic compounds may be considered useful as antiglycoxidative agents [51]. In this study, total phenolic and flavonoid contents (TPC and TFC, respectively) were determined to evaluate the amount of the main antioxidant components in each plant extract. The results are depicted in Figure 1. Total phenolic content depends on plant species and showed a wide variation ranging from 0.45 ± 0.05 mg GAE/g to 39.84 ± 2.17 mg GAE/g of dry weight. Among the six plants, *S. officinalis* presented the highest concentration of TPC, followed by *M. vulgare* and *C. erythraea* (21.40 ± 0.83) mg/g, whereas *C. scolymus* flower head extract presented a considerably smaller concentration of phenols. The differences among the six plants were significant ($p < 0.05$) unless for *M. vulgare* and *C. erythraea*, which presented 22.59 ± 1.20 and 21.40 ± 0.83 mg GAE/g dw, respectively, without significant difference.

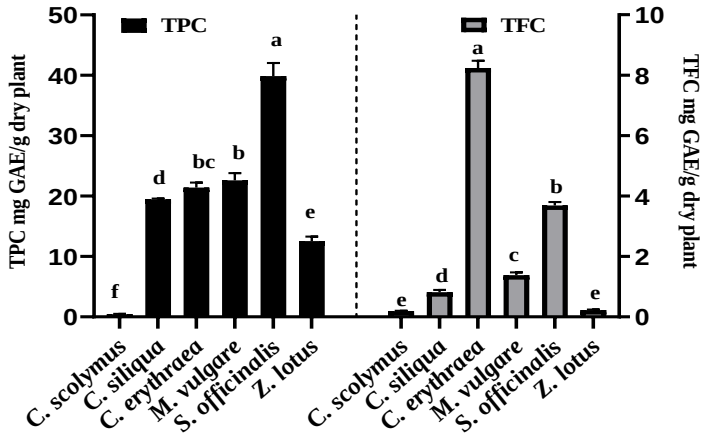


Figure 1. Total phenolic (TPC) and total flavonoid contents (TFC) of the extracts. Data are presented as mean ± SD (standard deviation) for $n = 3$. Values with the same letter are not significantly different ($p > 0.05$) by Tukey's multiple range test.

The total flavonoid content of the six plants is shown in Figure 1. The content differences among plants were statistically significant ($p < 0.05$) and ranged between 0.19 and 8.24 mg QE/g (dw). TFC in *C. erythraea* was found to be much higher than in the other five plants.

The phenolic composition of medicinal plants is quite different in the literature, depending on the variety, geographical origin, weather conditions, harvesting and storage, and extraction methodologies [52].

C. scolymus flower head extract presented a considerably smaller concentration of phenols than the studied species and other reported works for flower head methanolic extracts [53]. For *Marrubium vulgare*, the results obtained in the present work were inferior to those reported by other authors, which ranged between 40.7 and 160 mg GAE/g [54,55]. Lower TPC and TFC from *C. erythraea* concentration ranging from 1.23 ± 0.02 - 12.46 ± 0.15 mg GAE/g dw and 1.18 ± 0.07 to 3.35 ± 0.03 mg GAE/g dw, respectively, were reported [56]. *S. officinalis* extracted with ethanol, reported by Roby *et al*. [57], presented lower TPC amounts than those found in the present work, while similar contents ranging from 35.39 to 72.73 mg/g dry plant have been reported by Zheng and Wang [53] for *M. officinalis*.

TFC in *C. erythraea* extract was found to be much higher than the other five plants and greater than the values reported by some authors [56,58]. *S. officinalis* and *M. officinalis* extracts also demonstrated high content of total flavonoid content compared to the finding of other authors [59-61], respectively. *M. vulgare* TFC content was, for times, much lower amount than the values (6.02 ± 0.01) reported by Amri *et al*. [62].

3.2. ABTS and DPPH radicals scavenging activities

In normal physiology, free radicals play a co-regulatory second messenger function necessary for attaining the biological effect of insulin nevertheless, an imbalance between radical-generating and radical scavenging systems may originate reactions between these radicals and biomolecules, such as proteins, producing different types of modifications, which have an impact in a combinatorial fashion on the insulin signaling cascade, contributing to insulin resistance [63].

Hyperglycemia can directly cause increased ROS production, and glucose can undergo autoxidation and generate new ROS, such as hydroxyl free radicals. In addition, there is also enhanced glucose metabolism through the polyol (sorbitol) pathway, which also results in enhanced production of superoxide radical anions. Moreover, glucose can react with proteins in a nonenzymatic manner leading to the formation of advanced glycation end products (AGEs) [4,64]. Therefore, new strategies based on free radical scavenging should be implemented in the treatment of diabetes.

The free radical scavenging activities of the studied plants were evaluated using ABTS and DPPH methods, and the results are shown in Figure 2. The results are expressed as the IC_{50} values (the amount of antioxidants necessary to decrease the initial DPPH or ABTS concentration by 50%). All plants showed dose-dependent antioxidant activity.

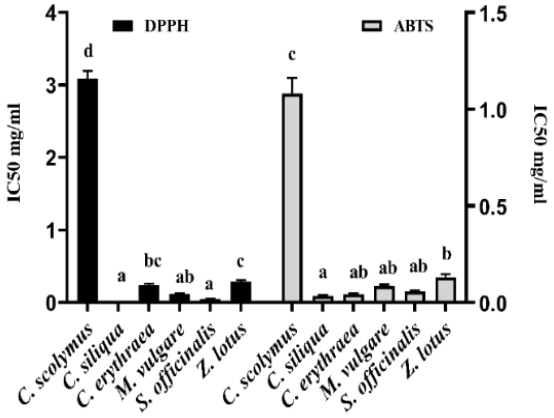


Figure 2. DPPH and ABTS free radicals scavenging activities of the extracts. Data are presented as mean ± SD (standard deviation) for $n = 3$. Values with the same letter are not significantly different ($p > 0.05$) by Tukey's multiple range test.

The best activity of *C. siliqua* extract in contrast to *C. scolymus*, which demonstrated the lowest activity, can be explained in this case by its low contents of phenolic compounds and flavonoids as compared to the *C. siliqua*, although this extract did not present the highest phenol and flavonoid content (Figure 1). Thus, *C. siliqua* extract could be beneficial for the prevention and treatment of type 2 diabetes. *C. erythraea*, *S. officinalis*, and *M. vulgare* had similar capacities for scavenging ABTS free radicals, despite the dissimilar amounts of phenols and flavonoids in the extracts. These results point out that beyond the phenol amounts, their structures and other components contribute to the capacity for scavenging free radicals. For example, the main categories of phenolic compounds found in carob fruit are phenolic acids, gallotannins, and a large number of condensed tannins [65], the last ones known for their strong antioxidant activity [66], although the glycosylated flavonoid quercitrin can also be an important role over the antioxidant activity [67] According to Amri *et al*. [62], *M. vulgare* possesses high antioxidant activity which can be attributed to its richness in phenylethanoids and flavonoids. The highest amounts of flavonoids in *C. erythraea* extract can also explain the good antioxidant activity. According to the review made by El Menyiy *et al*. [68], twenty-two flavonoids glycosides, comprising derivatives of acylated quercetin, kaempferol, and isorhamnetin were isolated from an aqueous extract of this species, which can be able to scavenge the DPPH and ABTS free radicals [69].

3.3. Total antioxidant capacity (TAC)

This assay is based on the reduction of phosphomolybdate ion in the presence of an antioxidant resulting in the formation of a green phosphate/MoV complex measured spectrophotometrically [48]. As aforementioned, the amounts of phenols and, particularly, their structures may positively influence the total antioxidant capacity. In the present case, it is clear that flavonoids in relatively high concentrations in the aqueous extract of *C. erythraea* had an important role in the reduction of the phosphate/MoVI complex. According to Prieto *et al*. [48], carotenoids and flavonoids might contribute to the total antioxidant capacity beyond vitamin E.

According to the results obtained from phosphomolybdenium assay, depicted in Figure 3, it is evident that *C. erythraea* exhibited the highest activity (31.33±1.15 mg AAE/g dried plant), followed by *C. siliqua (*25.53±1.09 mg AAE/g dried plant) and *S. officinalis* (24.50±0.81 mg AAE/g dried plant). *C. scolymus* showed the weakest total antioxidant activity (2.95±0.17 mg AAE/g dried plant).

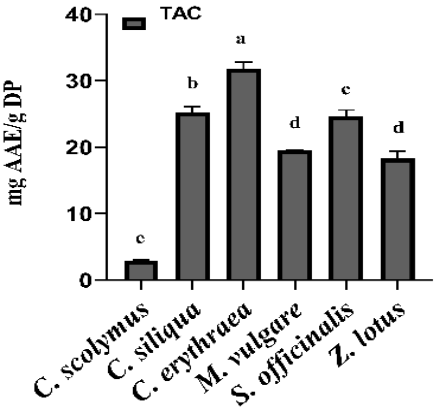


Figure 3. Total antioxidant capacity (TAC) of the extracts. Data are presented as mean ± SD (standard deviation) for $n = 3$. Values with the same letter are not significantly different ($p > 0.05$) by Tukey's multiple range test.

3.4. Nitric oxide scavenging activity

Reactive nitrogen species RNS, such as nitric oxide (•NO), are generated in small amounts during normal cellular processes. •NO generated by the action of nitric oxide-synthase on intracellular arginine mediates endothelium-dependent vasorelaxation by its action on guanylate cyclase in vascular smooth muscle cells (VSMC), initiating a cascade that leads to vasorelaxation [4]. However, its reaction with superoxide, which is overproduced in diabetic patients, results in the formation of ONOO•, which in its turn induces lipid peroxidation in lipoproteins and triggers a cascade of harmful events [70]. Furthermore, excessive production of NO• in blood vessels is implicated in circulatory failure that takes place in systemic inflammatory reactions, and it may be cytotoxic for surrounding tissues.

The results of the NO-scavenging capacities of the extracts are shown in Figure 4. The •NO scavenging activity of the extracts increased in a concentration-dependent manner. *S. officinalis* extract showed the highest NO• scavenging ability, which may be explained not only by the highest amounts of TPC in the extracts but also by the presence of phenolic abietane diterpenes (e.g., carnosic acid and its derivatives, carnosol, and rosmanol isomers), generally found in sage extracts, which contribution for the radical scavenging is more remarkable than flavonoids [71]. In addition, the diterpene manool at relatively low concentrations was also able to suppress lipopolysaccharide (LPS)-induced production of NO, nevertheless at higher concentrations (> 4.0 μg/mL), increased NO production in LPS-induced murine macrophages [72].

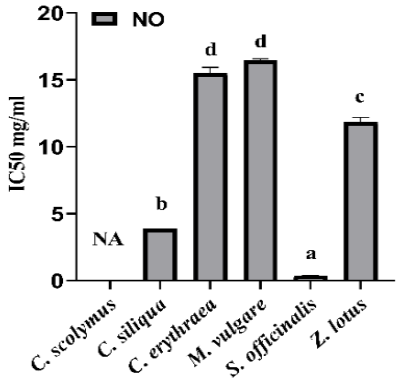


Figure 4. Nitric oxide scavenging activity of the extracts. Data are presented as mean ± SD (standard deviation) for $n = 3$. Values with the same letter are not significantly different ($p > 0.05$) by Tukey's multiple range test. NA: no activity for determining IC_{50} value.

3.5. Ferrous ions chelating power

The ability to chelate transition metals is one of the mechanisms of antioxidative action. The main strategy to avoid ROS generation associated with redox-active metal catalysis involves the chelating of the metal ions, thus preventing the catalysis of hydroperoxide decomposition and Fenton-type reactions [73]. Moreover, iron overload is a risk factor for diabetes. It plays a direct and causal role in diabetes pathogenesis mediated by β-cell failure and insulin resistance. The rates of diabetes were declined since the use of iron chelation therapy, indicating its causal role in the pathogenesis of diabetes [74]. The results of ferrous ions' chelating power are depicted in Figure 5. The best chelating activity observed for *M. vulgare* and *C. scolymus* can be attributed to the presence of phenethyl glycosides [61,75] and cynarin [23], respectively, which by possessing *ortho*-dihydroxyphenyl group can facilitate the chelating bonds with metal ions [76].

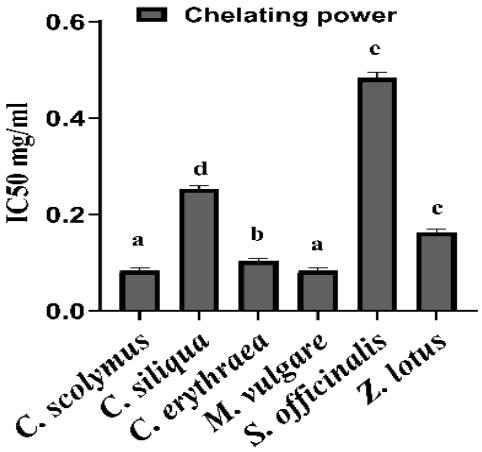


Figure 5. Ferrous ions chelating power of the extracts. Data are presented as mean ± SD (standard deviation) for $n = 3$. Values with the same letter are not significantly different ($p > 0.05$) by Tukey's multiple range test.

3.6. α-Amylase inhibitory activity

Serious complications, such as organ failures and/or destruction of the kidneys, eyes, and various cardiovascular diseases, can be caused by high blood sugar levels in diabetic patients. α-Amylase, an enzyme that is secreted by the pancreas and salivary glands (1,4-α-*D*-glucan-glucanohydrolase), catalyzes the hydrolysis of α-1,4-glucan bonds in starch, maltodextrins, and malto-oligosaccharides into simple sugars [77,78]. Therefore the inhibition of pancreatic α-amylase is one of the therapeutic approaches to reducing the increase of postprandial hyperglycemia by retarding the absorption of glucose through the inhibition of this carbohydrate-hydrolyzing enzyme [64]. Synthetic and natural product inhibitors of carbohydrate-degrading enzymes such as acarbose and voglibose can reduce type 2 diabetes and its complications [78]. The results regarding the α-amylase inhibitory activity of the six studied plants are depicted in Figure 6. The results of the present work reveal that *M. vulgare* displayed the best α-amylase inhibition capacity that may delay carbohydrate digestion and absorption, supporting its traditional use in DM control. The same conclusion has been reported for the Algerian species [79]. The leaf extract of *M. vulgare*, also used in Brazilian and Mexican traditional medicine for its antidiabetic role, showed a significant *in vivo* hypoglycaemic effect by reducing the plasma glucose level by 0.64% in patients with type II non-controlled diabetes mellitus [80], maybe due to the presence of flavonoids and, particularly, phenylethanoid glycosides such as verbascoside derivatives, known as antidiabetic agents [79].

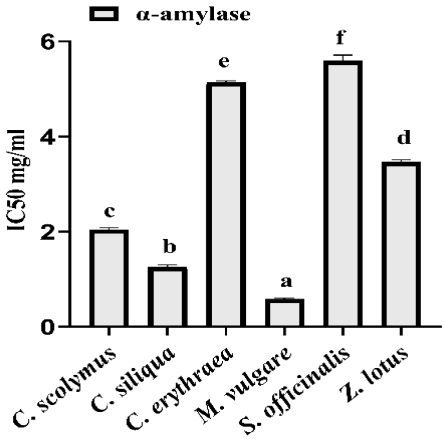
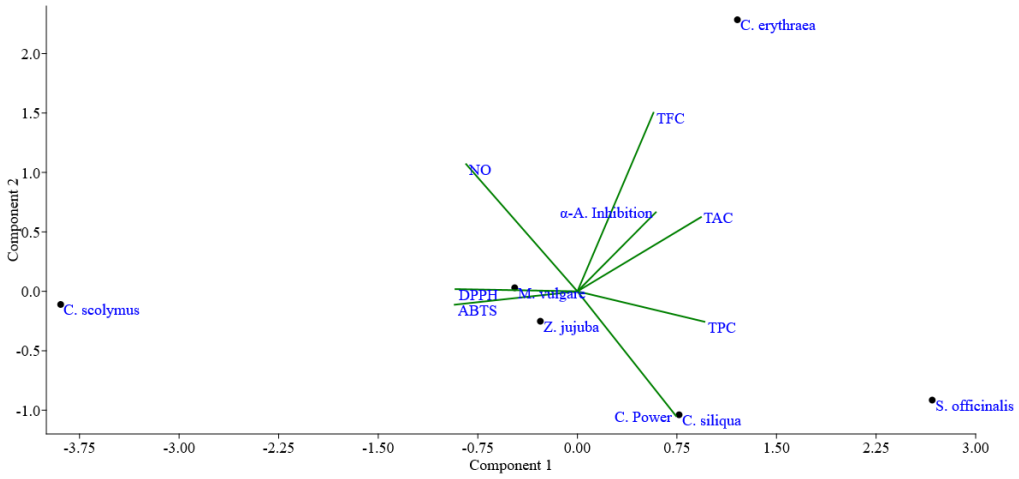


Figure 6. α-Amylase inhibition activity of the extracts. Data are presented as mean ± SD (standard deviation) for $n = 3$. Values with the same letter are not significantly different ($p > 0.05$) by Tukey's multiple range test.

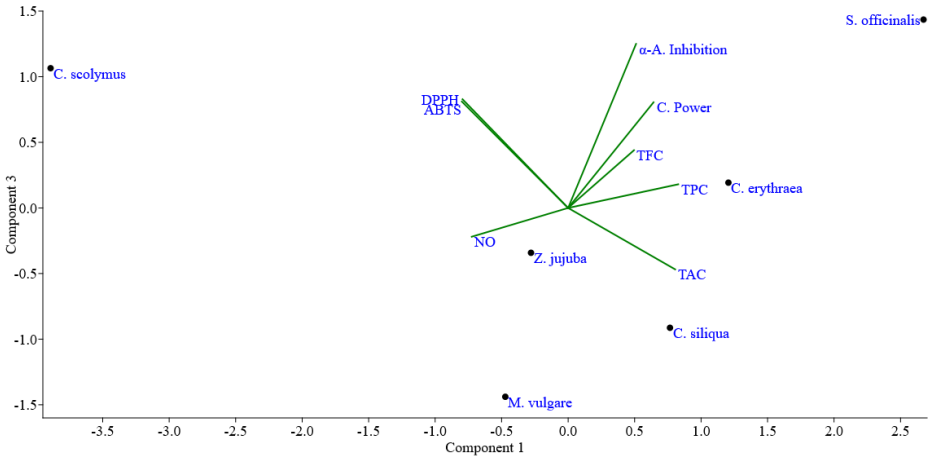
In fact, the sole difference between *M. vulgare* and the remaining plants is the presence of phenylethanoid glycosides in that species. These secondary metabolites have been reported to inhibit the α-glucosidase activity. Some of these compounds can present an activity similar to the anti-type 2 diabetic drugs, acarbose [81]. Therefore, this can explain the best activity found for *M. vulgare*, in spite of other secondary metabolites (terpenoids, fatty acids, flavonoids, and tocopherols) had been described as possessing antidiabetic effects in Moroccan plants [82,83].

3.7. Principal component analysis.

Principal component analysis (PCA) was performed to provide an overview of the similarities and differences between different variables, and to distinguish the samples according to the phenolic and flavonoid contents, antioxidant activities, and α-amylase inhibition activity (Figure 7). Principal component 1 (PC1) explained up to 61.58 % of the total variance, and PC2 explained 18.03% (Figure 7a), while PC3 explained 15.63% (Figure 7b). Thus the two-dimensional graph presenting the first two PCs could explain 79.61 % of the variance in the data, which was high enough to represent all the variables. Furthermore, the PC1 and PC3 plots explained 77.21 % of the total variance. Species were separated along the first principal component (Component 1) by differences observed in total phenolic compounds and antioxidant activities (TAC, ABTS, and DPPH). The species with intermediate activity were grouped (*M. vulgare*, *Z. lotus*, *C. siliqua*), while *S. officinalis* and *C. scolymus* discriminated from the other species in opposite directions, whereas *C. erythraea* discriminated along the PC2 (Component 2), is characterized by the total flavonoid content. The loading plot of the variables showed that the ABTS and DPPH radical-scavenging activities share the same vector direction for PC1 (Factor 1) and are strongly and positively correlated to TPC content, which may indicate the antioxidative compounds responsible for reducing ABTS and DPPH are similar. The chelating power and nitric oxide scavenging activity were negatively correlated and discriminated from the other antioxidant tests. This might be because different compounds that react in these tests. We can also notice a moderate correlation between TPC, TFC, and total antioxidant activity.



a



b

Figure 7. Principal component analysis (PCA) using the phenolic and flavonoid content and the *in vitro* biological properties of the six Moroccan plants. (a) Plot using the first and the second component. (b) Plot using the first and the third components.

3.8. Correlation between antioxidant capacity and inhibition of α-amylase activity and total phenolic content.

Despite the presence of a wide range of the total antioxidant capacities and total phenolic and flavonoid contents among the studied plants, linear positive and moderate relationships (Table 1) were found between the TPC values and the respective antioxidants activities (DPPH, ABTS, TAC, and NO), as well as between the TFC value and ABTS and TAC. A very strong correlation was found between TAC and TFC content, indicating that flavonoids contribute to the total antioxidant activities of these plants. A very strong correlation among the results using the two methods of measuring antioxidant capacity (ABTS-DPPH) and (ABTS-TAC) can be detected. Interestingly, we found a very strong correlation between NO scavenging activities and chelating power in these plant extracts. The chelating power and α-amylase inhibition activity were not correlated either with TPC nor TFC, suggesting that other compounds extracted with hydro-alcoholic solvent were responsible for these activities. In fact, it has been reported that cyclitols (e.g., d-pinitol) in *C. siliqua* and labdane diterpenoids (e.g., marrubiin) in *M. vulgare* are secondary metabolites with inhibitory action on α-amylase or α-glucosidase and, therefore, with a beneficial effect on diabetes disease [84-87]. Figure 6 shows that those two species are the most effective as α-amylase inhibitors. Thereby, this property can be related to those types of compounds which are not phenols.

Table 1. Correlation between parameters

	TPC	TFC	DPPH	ABTS	TAC	NO	Chelating Power	α-amylase inhibition
TPC	1.00	0.82	-0.63	-0.50	0.56	-0.48	0.32	0.30
TFC		1.00	-0.46	-0.62	0.81	-0.35	0.22	0.41
DPPH			1.00	0.82	-0.64	0.70	-0.58	0.09
ABTS				1.00	-0.92	0.59	-0.51	-0.08
TAC					1.00	-0.48	0.37	0.24
NO						1.00	-0.93	-0.46
Chelating Power							1.00	0.57
α-Amylase inhibition								1.00

Red color: statistically significant ($p < 0.05$)

4. Conclusions

Several Moroccan plants are reported to have blood sugar-lowering properties that make them beneficial for managing diabetes. Except for *C. scolymus* head flower, the findings of this study support the fact that these plants commonly used for diabetes treatment in Morocco are promising sources of potential antioxidants. These plants can help to prevent diabetes oxidative stress complications along with their ability to inhibit α-amylase enzyme, which can reduce postprandial blood glucose levels. Such results must be the target of further study for deeply evaluating the possibility of implanting these natural products in diabetes treatment, particularly *M. vulgare* and *C. siliqua*. Although the antioxidant and/or α-amylase inhibitory activities had been attributed to some compounds, sometimes, when isolated, these properties undergo a decrease due to the absence of synergism effects among diverse secondary metabolites. In this case, it would be necessary to establish standardized extracts to prevent fluctuations in the amounts of the active metabolites, which generally occur owing to diverse edaphoclimatic conditions and even genetic heritage factors.

Although these conclusions, it is important to notice some limitations of this kind of study, and three main limitations can be considered: the extraction method, the solvent type used, and the absence of the chemical composition of the plant extracts. The utilization of a hydro-alcoholic solvent and sonication for extracting the metabolites can be considered inadequate because these plants are used in folk medicine as infusions. Moreover, comparing the activities with those previously reported is also hampered by the fact that the authors can use several types of extractions and/or solvents to obtain higher amounts of bioactive compounds. Different solvents lead to the extraction of distinct compounds and/or at different concentrations, which makes it difficult to compare results. In addition, although the chemical profile is given in many previous studies (Table S1; Figures S1-S12), information about the relationship between the activities and the bioactive compounds is scarce, which makes it difficult to strengthen the conclusions. Furthermore, unless one wants to isolate this or that constituent from extracts for any reason, it is becoming increasingly clear that in traditional medicine, more focus should be given to extracts or enriched extracts but standardized as already done for *Ginkgo biloba* extracts.

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Smail Aazza and Maria Graça Miguel designed the study; Smail Aazza performed the experiments, analyzed the data, and wrote the draft manuscript. Soukaïna El-Guendouz performed the experiments and analyzed the data. Smail Aazza and Maria Graça Miguel discussed the results; all authors read, revised, and approved the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Supplementary Data

Table S1. Review of the chemical composition of the six studied plants (this review is not exhaustive, that is, only some compounds are cited). The numbers in curved parentheses are the chemical structures represented in the Figures S1-S12.

Species	Chemical compounds
Cynara scolymus	**Phenolic acids***: caffeic (1), chlorogenic (2), cynarin (3), [23], *p*-coumaric (4), ferulic (5), hydroxybenzoic (6), protocatechuic (7), syringic (8), sinapic (9), rosmarinic (10), trihydroxycinnamic (11), feruloylquinic (12), dimethoxybenzoic acids (13) [88] **Flavonoids**: apigenin 7-*O*-glucuronide (24), luteolin 7-*O*-rutinoside (25), luteolin 7-*O*-glucoside (26), narirutin (27), naringenin 7-*O*-glucoside (28), apigenin 7-*O*-rutinoside (29), apigenin 7-*O*-glucoside (30), luteolin 7-*O*-glucuronide (31) [89], quercetin (32), eriodictyol (33), chrysoeriol (34), myricetin (35) and their glycoside forms [88] **Sesquiterpene lactone**: cynaropicrin (55), grosheimin (56), aguerin B (57), 11,13-dihydroxy-8-desoxygrosheimin (58) [90]
Ceratonia siliqua	**Phenolic acids***: gallic (14), syringic, cinnamic, coumaric and ellagic acids (15) [52], ferulic, gentisic (16), caffeic, 4-hydroxybenzoic, protocatechuic acid, benzoic acids (17), hydroxytyrosol (18) [65] **Flavonoids**: apigenin, kaempferol (36), naringenin (37), quercetin rhamnoside (38), myricetin rhamnoside (39), catechin (40) chrysoeriol, eridictyol, genistein (41), luteolin [65] **Tannins**: epicatechingallate (62), epigallocatechingallate (63), epigallocatechin (64), tannic acid (65), prodelphinidin dimer (66) and trimer (67) [28] **Alkaloids**: theophylline (67) [65] **Cyclitols**: D-pinitol (3-*O*-methyl-d-chiro-inositol) (68) [85]
Centaurium erythraea	**Phenolic acids***: caffeic, *p*-coumaric, ferulic, sinapic acids, *p*-coumaroyl derivative [68] **Flavonoids**: quercetin, kaempferol, isorhamnetin, kaempferol-3-*O*-(*p*-coumaroyl, rhamnosyl)rutinoside-7-*O*-rhamnoside (42), quercetin-3-*O*-(rhamnosyl)rutinoside-7-*O*-rhamnoside (43) [29], isovitexin (44) [91] **Xanthones**: di-hydroxy-dimethoxyxanthone (69) [92], eustomin (70) [91] **Secoiridoids glycosides:** gentiopicroside (71), sweroside (72), swertiamarin (73) [92], centapicrin (74), centauroside (75) [91]
Marrubium vulgare	**Phenolic acids*:** gallic, gentisic, protocatechuic, syringic, *p*-hydroxybenzoic, caffeic, cinnamic, coumaric, sinapic, caffeoylmalic (19), rosmarinic, chlorogenic acids [75,93] **Flavonoids:** naringenin, naringin (45), acacetin (46), apigenin, chrysoeriol, diosmetin (47), ladanein (48), luteolin, galangin (49), quercetin, kampferol and their derivatives [75,93] **Coumarins:** umbelliferone (76), aesculin (77), coumarin (78) **Monoterpene derivatives**: marrubic acid (60), sacranoside A (61) [75] **Sesquiterpene lactone**: vulgarin (59) [75] **Diterpenoids**: marrubiin (79), deacetylvitexilactone (80), marrubenol (81), cyllenin A (82), polyodonine (83), carnosol (84), vulgarol (85), vulgarcoside A (86), deacetylforskolin (87), tetrahydroperegrinin (88), peregrinol (89), peregrinin (90) [75,94] **Phenylethanoid Glycosides**: samioside (101), acteoside or verbascoside (102), marruboside (103), alyssonoside (104), arenarioside (105), leucosceptoside A (106), forsythoside B (107), ballotetroside (108) [62,75]
Salvia officinalis	**Phenolic acids*:** chlorogenic, protocatechuic, caffeic, *trans-p-* coumaric, *o*-coumaric, rosmarinic, gallic, cinnamic [95], vanilic (20), ferulic [96], rosmarinic, carnosic acids (21), salvianolic acid B (22), salvianolic acid A (23) [97] **Flavonoids:** luteolin, apigenin, quercetin [1], cirsimaritin (50), genkwanin (51), rutin, hipidulin (52) [1]. **Diterpenoids**: carnosic acid (91), carnosol, manool (92), rosmadial (93) [97] **Triterpenes**: oleanolic acid (109), ursolic acid (110) [97]
Ziziphus lotus	**Phenolic acids*:** quinic, chlorogenic, *p*-coumaric acids [1] **Flavonoids:** epicatechin, rutin, quercitrin (53), naringin, apigenin-7-*O*-glucoside, luteolin-7-*O*-glucoside, quercetin [98] **Dammarane saponins:** Jujuboside A (111) and B (112), Lotoside I (113) and II (114) [36] **Cyclopeptide alkaloids:** Lotusine A (94), B (95), C (96), D (97), E (98), F (99), G (1001) [36] **Proanthocyanidins** [98] **Tannins** [98]

*Only aglycones were considered.

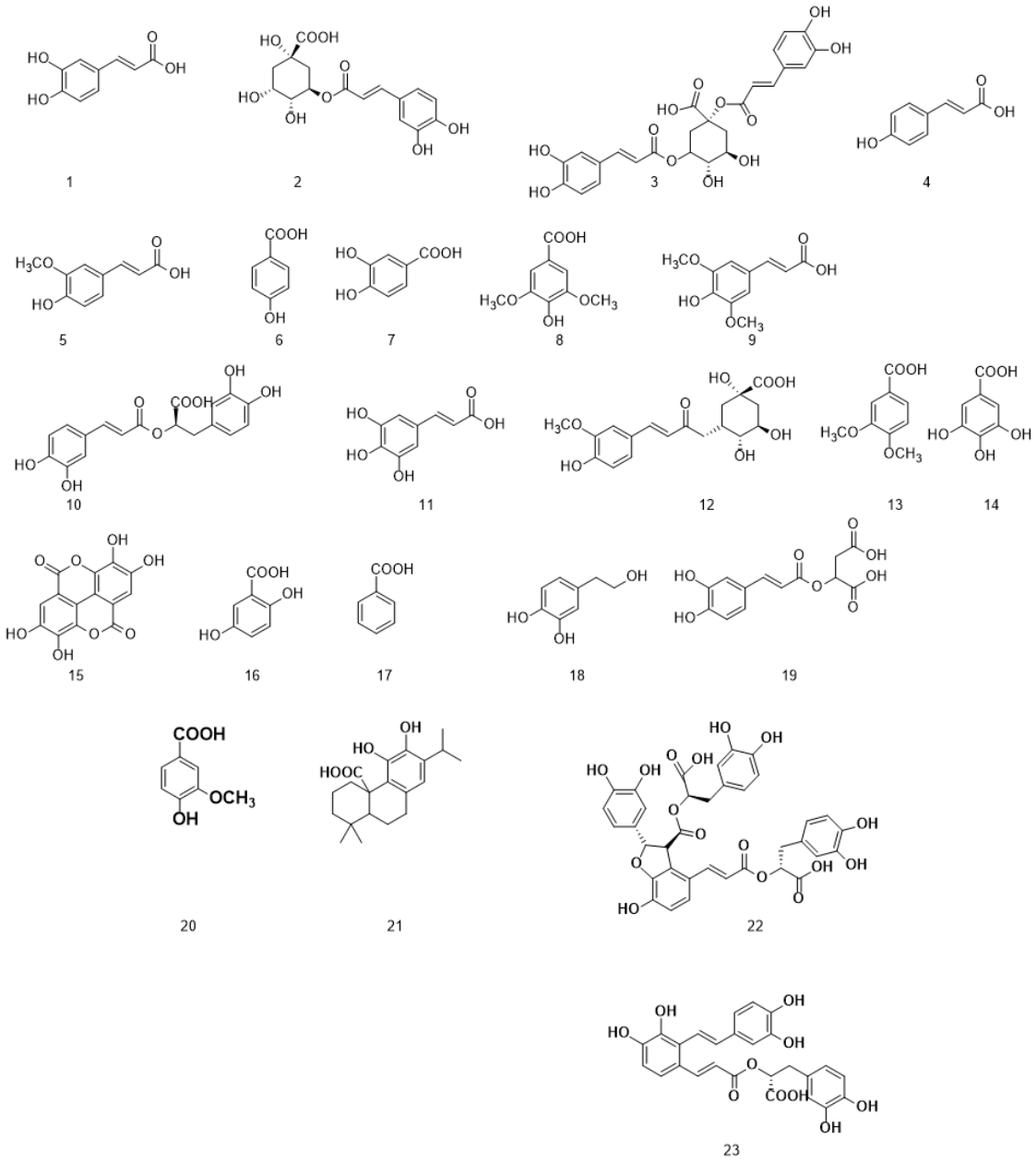
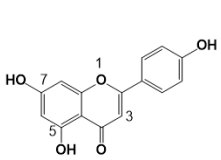


Figure S1. Few examples of aglycones of phenolic acids reported in the six plants.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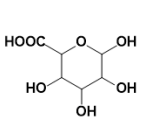
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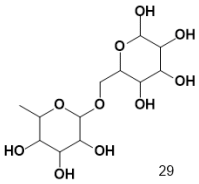
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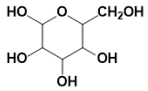
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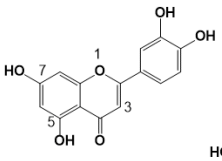
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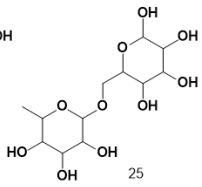
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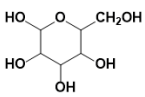
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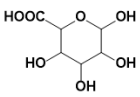
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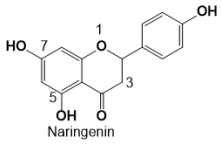
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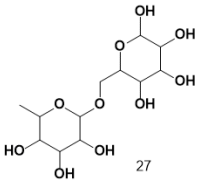
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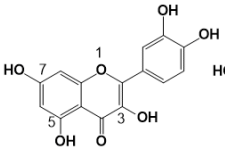
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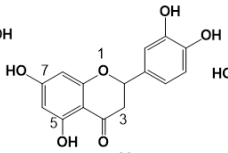
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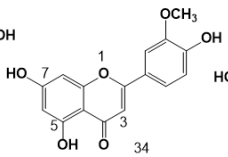
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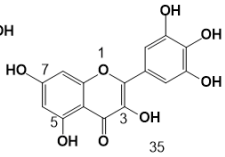
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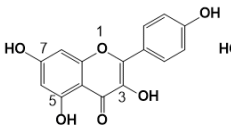
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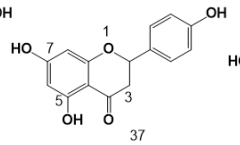
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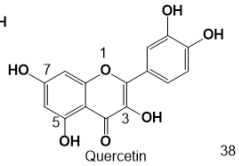
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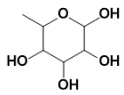
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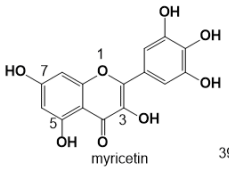
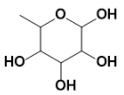

myricetin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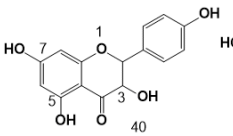
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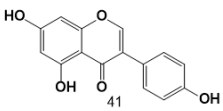
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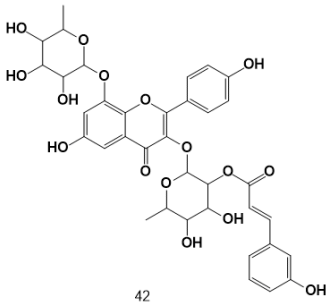
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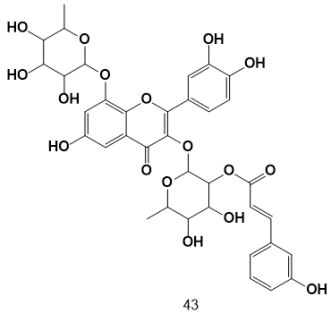
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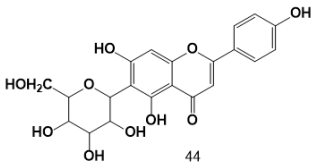
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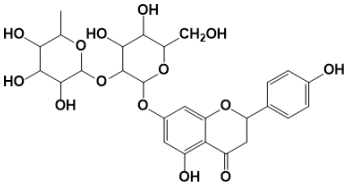
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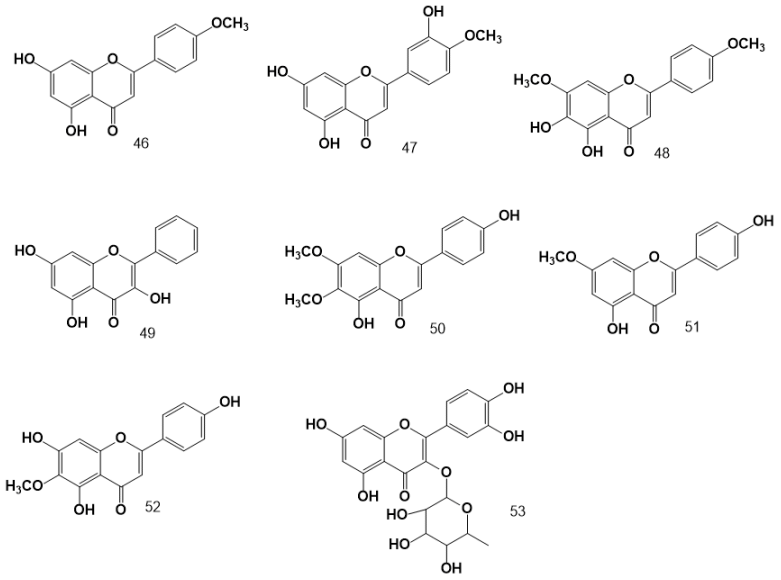


Figure S2. Few examples of flavonoids and their derivatives reported in the six plants.

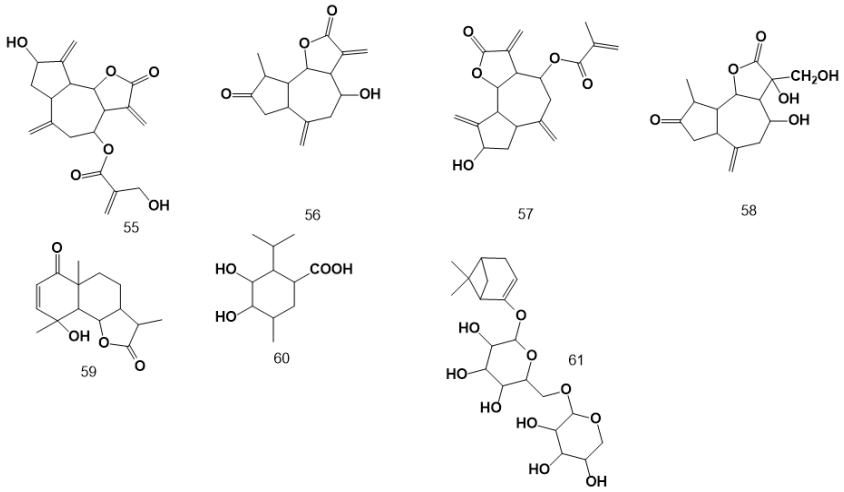
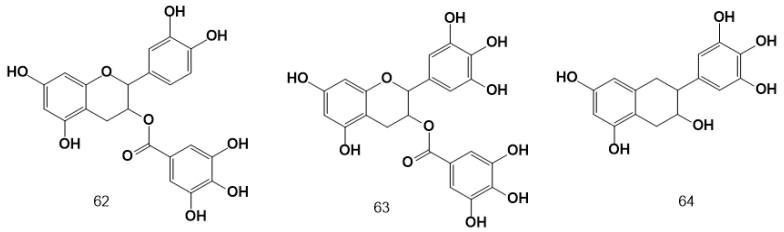


Figure S3. Few examples of some sesquiterpene lactones (55-59) and monoterpene derivatives (60, 61) reported in the plants.



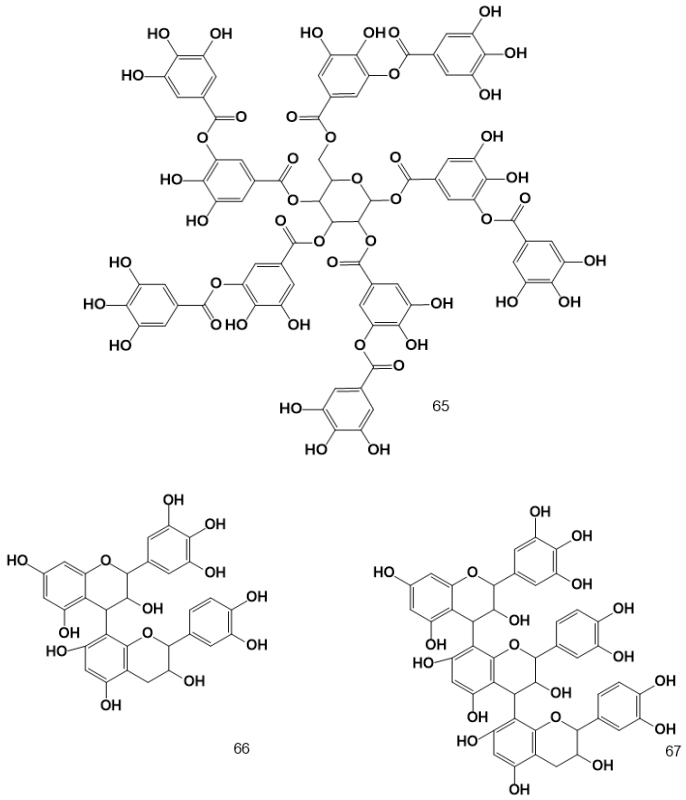


Figure S4. Examples of some tannins reported in the plants.

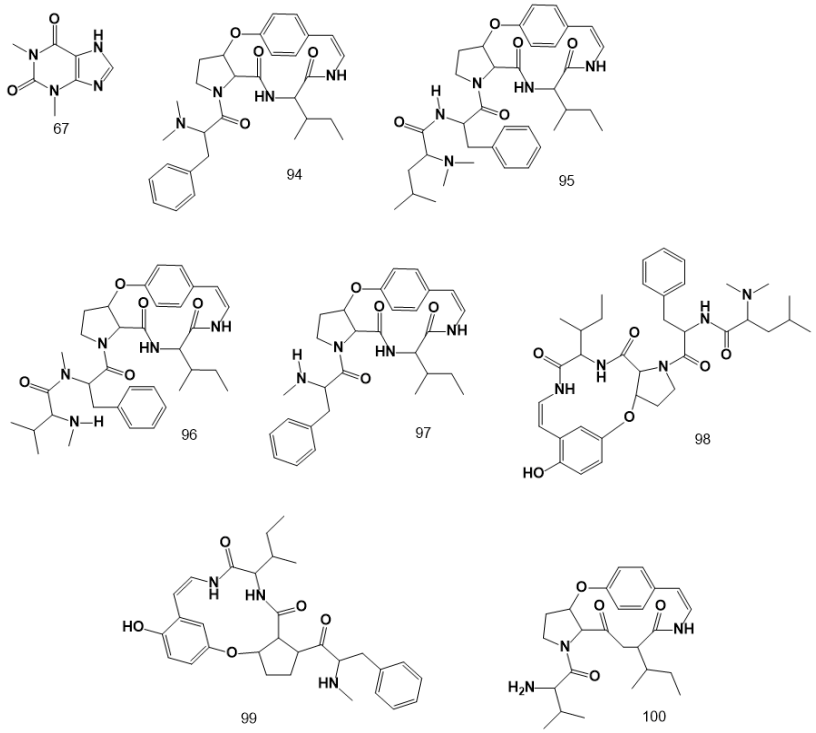


Figure S5. Examples of some alkaloids reported in the plants.

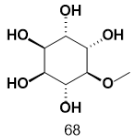


Figure S6. Pinitol present in *C. siliqua*.

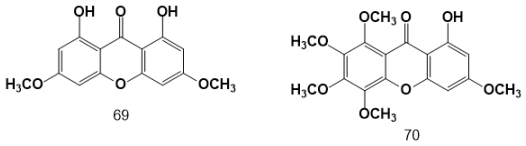


Figure S7. Some xanthones present in *Centaurium erythraea*.

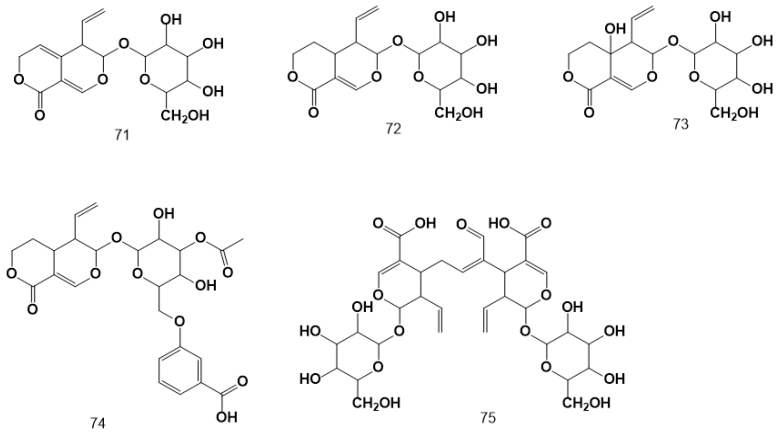


Figure S8. Some secoiridoid glycosides present in some plants.

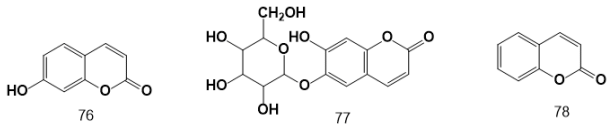


Figure S9. Some coumarins present in some plants.

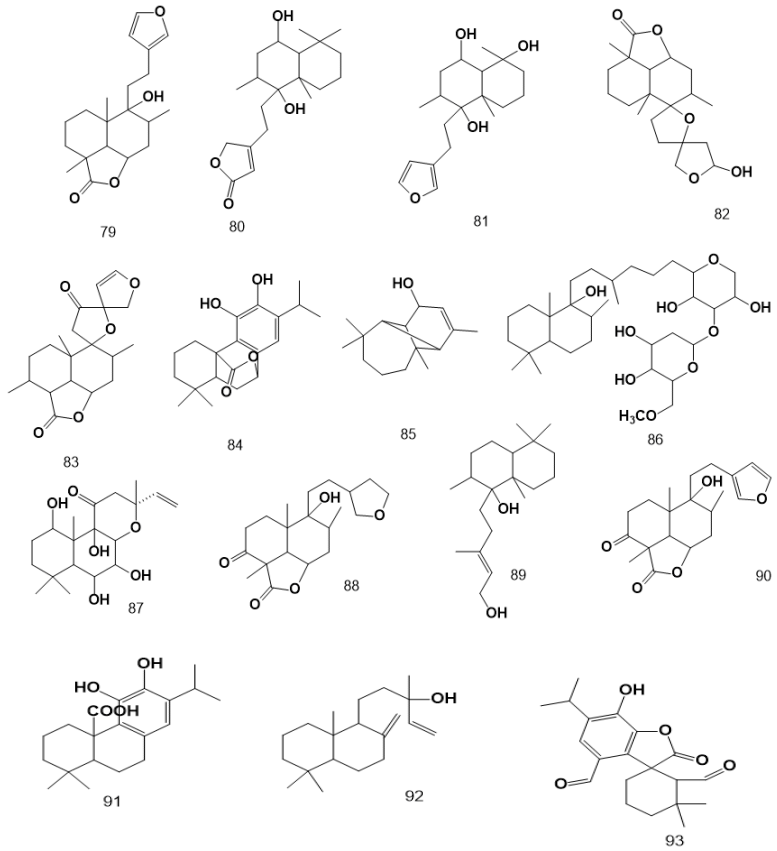


Figure S10. Some diterpenoids present in some plants.

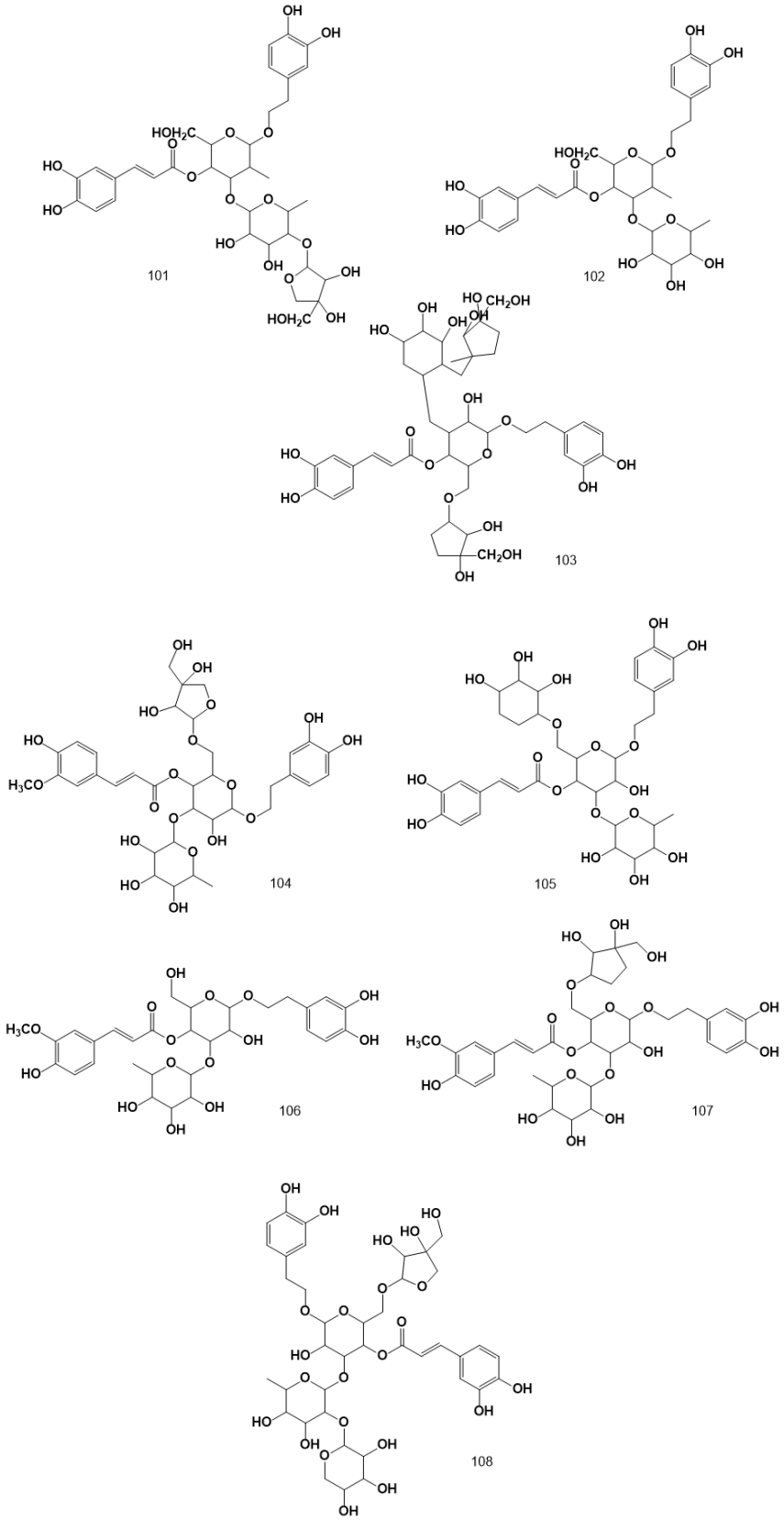


Figure S11. Some phenylethanoid glycosides present in *Marrubium vulgare*.

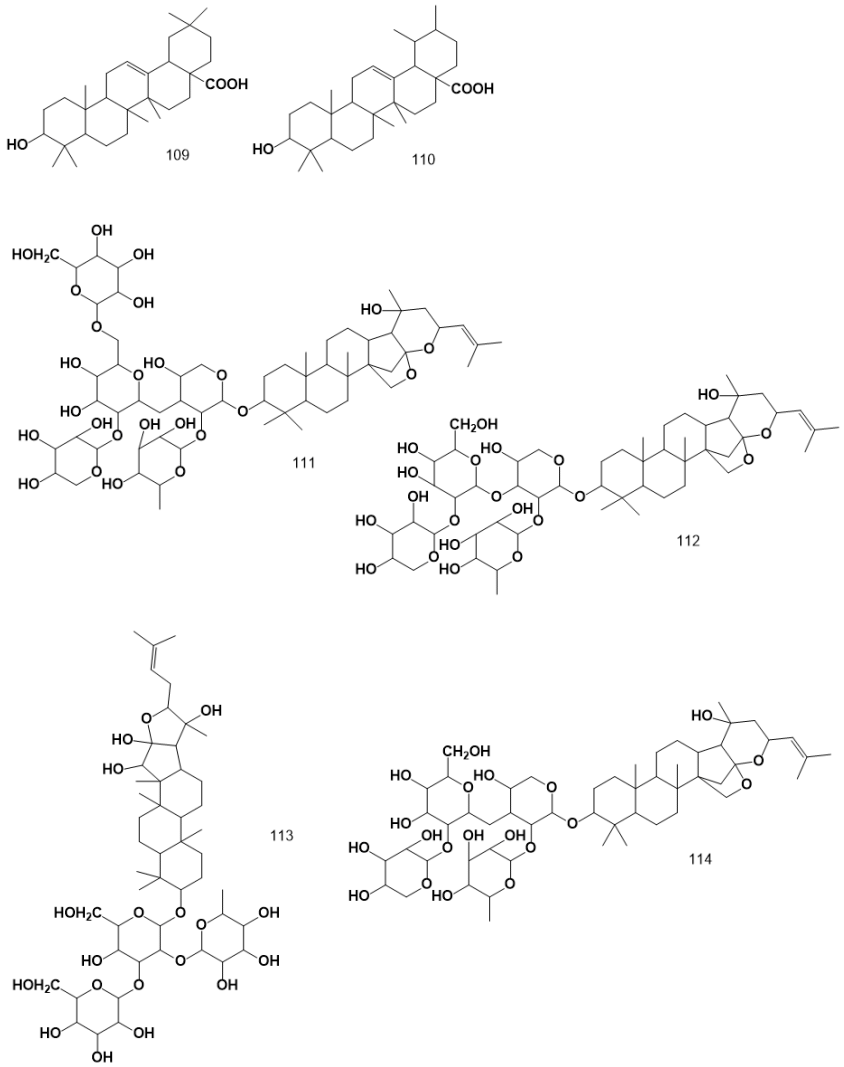


Figure S12. Some examples of triterpenoids (109, 110) and dammarane saponins (111-114) present in *S. officinalis* and *Z. lotus*, respectively