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Chemical Analysis and Biological Potential of Cotton Lavender Ethanolic Extract (*Santolina chamaecyparissus* L., Asteraceae)

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Abstract: Cotton lavender (*Santolina chamaecyparissus* L., Asteraceae) is a widespread medicinal and ornamental plant. This study aimed to evaluate the preliminary and detailed chemical composition as well as the biological activity of ethanolic extract. As part of the preliminary characterization, the content of total phenolics and flavonoids was determined, while the detailed characterization was performed using high-performance liquid chromatography (HPLC). Antioxidant activity was evaluated through four different tests: 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl ($OH^{\bullet}$), and nitroso ($NO^{\bullet}$) radicals, and lipid peroxidation (LP), as well as antihyperglycemic potential through the α-amylase and α-glucosidase inhibition assays. Additionally, in silico molecular modeling was employed to link the chemical composition to the antihyperglycemic potential. Chemical characterization showed that cotton lavender is a valuable source of phenolic compounds, with ferulic and *p*-coumaric acids being the most abundant. Moreover, the antihyperglycemic and antioxidant potential of the ethanolic extract was demonstrated in vitro. The potential mechanism of the antihyperglycemic effect is the inhibition of the enzyme α-glucosidase, which was further investigated in silico using molecular modeling methods. This analysis suggested rutin and quercetin as compounds responsible for anti-α-glucosidase activity. Cotton lavender ethanolic extracts, as a valuable source of phenolic and flavonoid compounds, possess moderate antioxidant effects and notable antihyperglycemic activity. According to in vitro and in silico investigations, it could be a valuable herbal supplement to complement diabetes treatment in medicinal therapy.

Keywords: antihyperglycemic; antioxidant; HPLC; in silico; molecular modeling; phenolic compounds

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1. Introduction

The beneficial effect of aromatic plants and their preparations is reflected in the prevention and therapy of many diseases. Aromatic plants were the first whose pharmacologically active compounds were used in the treatment of various diseases. Although pure pharmacologically active compounds have been isolated or synthesized in the past, and as such dominate conventional medicine, the potential of a large number of well-recognized medicinal plants, including cotton lavender, should not be neglected [1,2]. Data suggest that over the last two decades, a global growing trend of herbal medicinal product application as part of health care has emerged [3]. Moreover, a large part of the world's population uses these products as the first option for self-treatment of minor health problems since their therapeutic effectiveness has been clinically proven, while the long history of application usually confirms the safety [4].

Oxidative stress has been identified as the factor involved in the etiopathology of many diseases such as cancer, empyema, cardiovascular diseases (hypertension, atherosclerosis), and neurodegenerative diseases (Parkinson's, Alzheimer's disease, diabetes, etc.), both as a causative and facilitating agent. Although there are physiological mechanisms preserving the redox state of the organism, they are highly dependent on the external intake of antioxidants, mostly through food [5]. Examples of food rich in antioxidants include fruits, vegetables, grains, spices, seeds, as well as various herbs. Plants are recognized as a valuable source of antioxidants such as polyphenols, tocopherols, flavonoids, and carotenoids, as well as compounds containing nitrogen and organosulfur compounds.

Cotton lavender (*Santolina chamaecyparissus* L.; Asteraceae) is native to the Mediterranean region where it is traditionally used as an antispasmodic, digestive, analgesic, anti-inflammatory, antiseptic, stimulant, and antimicrobial remedy [6,7]. Due to its ethnobotanical uses, as well as ornamental properties, this species has been introduced to other areas as a horticultural and medicinal plant [8]. The cotton lavender is a small, evergreen shrub, tomentose and greyish, that grows up to 50 cm. It blooms from June to August and has distinctly yellow flowers, organized in headlike inflorescences, 6–8 mm wide [9]. It has a strong, pleasant aroma that originates from the volatile compounds of essential oil, such as 1,8 cineole, β-eudesmol, terpinen-4-ol, camphor, cubenol, *p*-cymene, sabinene [10–12]. Cotton lavender has been previously reported as highly abundant in phenolics and flavonoids, which suggests strong antioxidant potential, as well as prominent anti-inflammatory, antioxidant, and antimicrobial activity [13,14].

Bearing in mind the high diversity of reported biological activities, the aim of this research was to perform chemical characterization of the cotton lavender ethanolic extract and to evaluate its antioxidant and antihyperglycemic potential in vitro. Moreover, an in silico molecular simulation model was used to determine chemical compounds from cotton lavender extract responsible for biological potential. Additionally, this article provides a comprehensive review of the chemical composition and biological activity of various cotton lavender extracts.

2. Materials and Methods

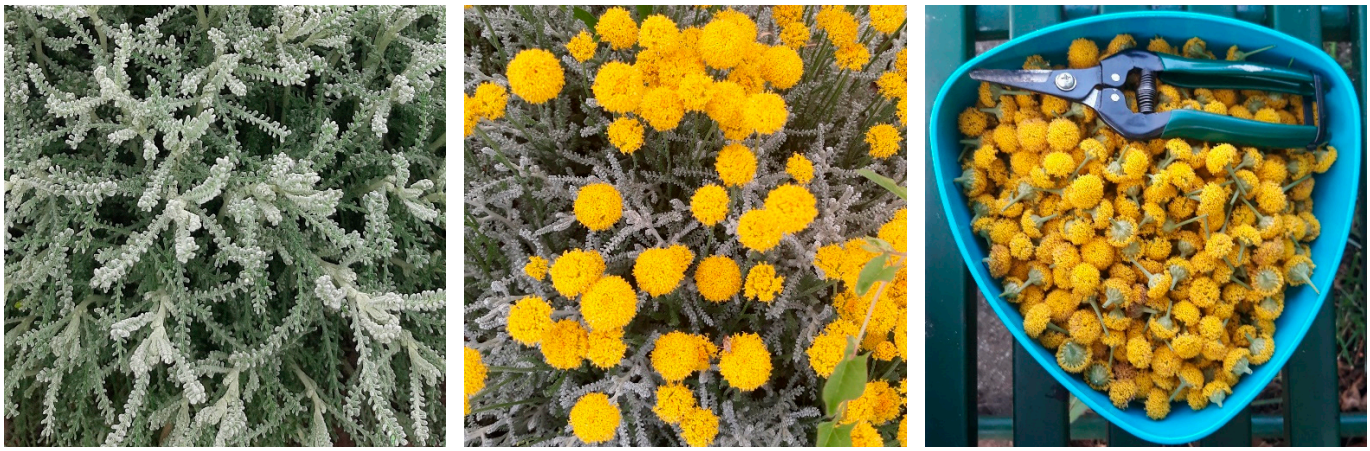
2.1. Chemicals

Chemicals used in the present study included 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical, iron(II)-sulphate heptahydrate, iron(III)-chloride hexahydrate, N-(1-naphthyl)-ethylenediamine dihydrochloride and sulfanilamide purchased from Alfa Aesar (Haverhill, MA, USA). Folin-Ciocalteu (FC) reagent was obtained from Merck (Darmstadt, Germany). Further, 2-thiobarbituric acid, ethanol, ethylenediaminetetraacetic acid disodium salt dihydrate, formic acid, hydrochloric acid, hydrogen peroxide, methanol, potassium dihydrogen phosphate, potassium hydrogen phosphate, sodium carbonate, sodium nitroprusside and trichloroacetic acid were purchased from POCH (Gliwice, Poland). Further, 2,4,6-tris(2-pyridyl)-S-triazine, 2-deoxy-D-ribose, aluminum-chloride, ascorbic acid, butylated hydroxytoluene, caffeic acid, chlorogenic acid, ferulic acid, gallic acid, glutathione (reduced), *p*-coumaric acid, *p*-nitrophenyl-α-D-glucopyranoside, propyl gallate, quercetin, quercetin dihydrate, quercitrin, rosmarinic acid, rutin, Starch azure, *trans*-cinnamic acid, α-amylase, and α-glucosidase were obtained from Sigma Aldrich (St. Louis, MO, USA).

2.2. Plant Material and Extract Preparation

Flowers of cotton lavender collected at full flowering stage were used in the study (Figure 1). The plant material was collected in June 2022 from the botanical garden of the Institute of Field and Vegetable Crops Novi Sad (IFVCNS), Serbia (Department of vegetable and alternative crops Bački Petrovac), dried in the shade until constant weight was achieved, and stored in multilayer paper bags until further analysis. The specimen identity was confirmed by the BUNS Herbarium (Department of biology and ecology) at the Faculty of Science, University of Novi Sad, Serbia (Voucher No 2-1446). Ground plant material was extracted by maceration with 70% (m/m) ethanol over a period of 24 h

(drug:solvent, 1:10; m/m). After the extraction, the solvent was evaporated to dryness, and extraction yield was quantified.



(**a**) (**b**) (**c**)

Figure 1. Cotton lavender plant: (**a**) leaves in vegetative phase; (**b**) flowers in full flowering phase; (**c**) flowers collected for this investigation.

2.3. Chemical Characterization of Cotton Lavender Extract

The total phenolics content was determined spectrophotometrically according to the previously described method based on the complexation of phenolics with the Folin-Ciocalteu reagent. The results were expressed as milligrams of gallic acid equivalents per gram of dry extract (mg GAE/g d.e.), based on the calibration curve obtained for gallic acid under the same experimental conditions [15,16]. Similarly, the total flavonoid content was quantified based on the characteristic of flavonoids to form yellow-coloured complexes with metals, showing the absorbance maximum at 430 nm. The results were expressed as milligrams of quercetin equivalents per gram of dry extract (mg QE/g d.e.), based on the quercetin calibration curve [15,16].

Furthermore, high-performance liquid chromatography (HPLC-DAD) was used to quantify specific representatives of the phenolic and flavonoid class of secondary metabolites [17]. The extract was dissolved in a mixture of mobile phases A and B (1:1, *v*/*v*). A Nucleosil C18 chromatographic column (4.6 mm × 250 mm, 5 µm) was used for the separation of the components of interest. During the run, the column was held at 30 °C, while a 1% aqueous solution of formic acid (*v*/*v*)—(A) and methanol—(B) were used as mobile phases. The gradient elution was applied according to the scheme: 0–10 min, 10% B; 10–20 min, 25% B; 20–35 min, 45% B; 35–40 min, 70% B, 40–43 min, 100% B, and for the final 3 min, 10% B. The total run time was 48 min, whereas 3 µL of the sample solution was injected into the system. Chromatograms were monitored at 280, 330, and 350 nm. The compounds of interest were quantified based on calibration curves obtained for chemical standard compounds analyzed under the same experimental conditions (Supplementary Table S1). The identification of compounds present in the cotton lavender extract was performed by comparing retention times and UV spectra (recorded from 220–400 nm) of unknown chromatographic peaks with those obtained for chemical standard compounds. The content of quantified secondary metabolites was expressed as µg/g of d.e.

2.4. Antioxidant Activity

The ability of the examined extract to neutralize 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl ($OH^{\bullet}$), and nitroso ($NO^{\bullet}$) radicals, as well as to inhibit the process of lipid peroxidation (LP) was evaluated based on the previously reported spectrophotometric methods. The results are expressed as RSC_{50} values (concentrations of extract at which 50% of DPPH,

$OH^{\bullet}$, and $NO^{\bullet}$ radical neutralization and lipid peroxidation inhibition was achieved) [18]. In order to provide a comprehensive assessment of the cotton lavender extract's antioxidant potential, recognized antioxidants (PG (propyl gallate), BHT (butylated hydroxytoluene), QDH (quercetin dihydrate) and AA (ascorbic acid) were analyzed as positive controls under identical experimental conditions.

2.5. Antihyperglycemic Potential

The antihyperglycemic potential of the obtained extracts was evaluated through the α-amylase and α-glucosidase inhibition assays. Both tests were performed according to previously described and modified procedures [18,19]. Acarbose was used as a positive control. The results were expressed as IC_{50} values (concentrations at which 50% of α-amylase and α-glucosidase activity were inhibited).

2.6. In Silico Molecular Modeling

All simulations were performed using the Schrödinger software package and OPLS4 force field [20]. The 3D structure of lysosomal α-glucosidase was retrieved from the Protein Data Bank database (PDB ID: 5NN5). The stated structure was selected for further research due to the presence of an inhibitor (1-deoxynojirimycin) in the active site. Hydrogen atoms were added and protonation types were determined using the Maestro protein preparation workflow. The three-dimensional structures of the investigated compounds identified in the ethanolic extract were constructed using the OPLS4 force field. The geometry optimizations of α-glucosidase protein and the compounds used for molecular docking simulation were performed using the Powell conjugated gradient algorithm method, with a convergence criterion of 0.01 kcal/(mol Å) and a maximum number of 1000 iterations.

The molecular docking simulations were performed with the Glide program [21], in extra precision mode with flexible ligands. Epik state penalties were used for calculating the docking scores. MM-GBSA method with the VSGB 2.0 solvation model and flexible residues up to 4 Å distance from the ligand were used for calculating the ligand binding affinities [22]. The visualization of the results was performed using the PyMol program [23].

2.7. Statistical Processing

The results obtained during the study were processed using Microsoft Excel for Windows (v. 2016) software package. The experimental measurements were performed in triplicate, while the variability of obtained results was described by corresponding standard deviations (the results are presented in the form of arithmetic mean ± standard deviation). The biological potential of the evaluated extract (and positive controls) was reported as concentrations exhibiting 50% of the studied effect (RSC_{50} and IC_{50}) Basically, the effects (free radicals neutralization, inhibition of enzyme activity) of cotton lavender extract recorded at different concentration levels enabled the application of linear regression and efficient extrapolation of concentration values resulting in 50% of the studied effect. The differences between the biological potential of the studied extract and evaluated positive controls were analyzed by application of non-parametric techniques—Mann–Whitney U Test and Kruskal–Wallis test (followed by post-hoc Dunn test)—while the level of significance was set at $p = 0.05$.

3. Results

3.1. Chemical Characterization of Cotton Lavender Ethanolic Extract

The results of the cotton lavender ethanolic extract's preliminary chemical characterization are presented in Table 1.

Table 1. Preliminary chemical characterization of cotton lavender ethanolic extract.

Preliminary Test	Value (Mean ± SD)
Extraction yield (%)	7.08 ± 0.18
Content of total phenolics (mg GAE/g d.e.)	96.04 ± 5.03
Content of total flavonoids (mg QE/g d.e.)	15.82 ± 0.21

GAE—Gallic acid equivalent; QE—quercitrin equivalent; d.e.—dry extract.

Based on the obtained results, the extract can be characterized as rich in both, phenolics and flavonoids. The results of the extract chemical characterization by liquid chromatography instrumental technique (HPLC-DAD, Figure 2) are shown in Table 2 and suggest the highest presence of ferulic acid among the evaluated secondary metabolites. Specifically, the amounts of *trans*-cinnamic and *p*-coumaric acids were eight- and fourfold lower, respectively, when compared to that of ferulic acid. Moreover, the content of quercetin, as well as its glycoside—rutin—in the examined extract was low. The obtained results are consistent with data describing the distribution of secondary metabolites among plant species. Namely, the mentioned flavonoids are found in high amounts only in a small number of plants, which is in contrast to phenolic acids, and especially ferulic acid, which are widely present herbal compounds, also displaying high abundance.

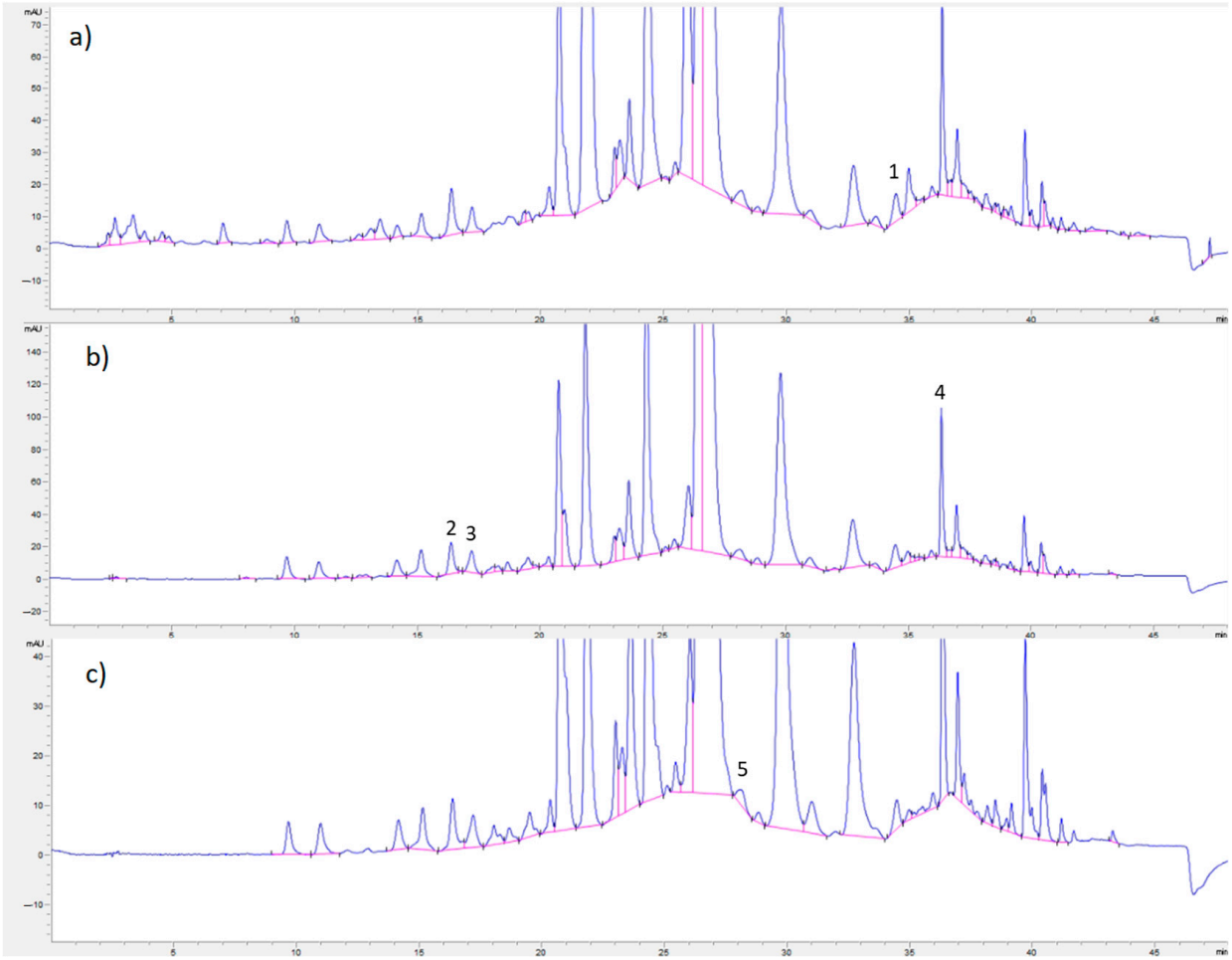
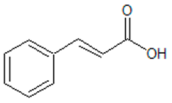
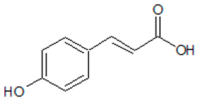
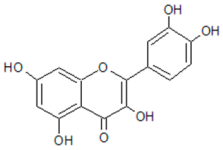
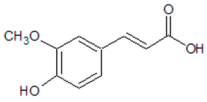
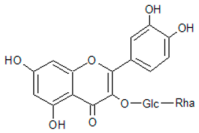


Figure 2. HPLC-DAD chromatogram of cotton lavender extract, with detection at 280 nm (**a**), 330 nm (**b**) and 350 nm (**c**): 1—trans cinnamic acid (t_r = 34.53 min), 2—*p* coumaric acid (t_r = 16.33 min), 3—quercetin (t_r = 17.28 min), 4—ferulic acid (t_r = 36.42 min), 5—rutin (t_r = 28.12 min).

Table 2. Detailed chemical composition of cotton lavender ethanolic extract (expressed as μg/g of d.e.; values reported as mean ± SD).

Phenolic Compounds *	*trans*-Cinnamic Acid	*p*-Coumaric Acid	Quercetin	Ferulic Acid	Rutin
Structural formula					
Content (μg/g d.e.)	141.06 ± 12.58	312.43 ± 24.11	49.71 ± 3.86	1163.64 ± 97.18	95.47 ± 7.46

* Gallic, caffeic, chlorogenic and rosmarinic acids, as well as quercitrin were below LOD of the applied analytical method.

3.2. Antioxidant Activity of Cotton Lavender Ethanolic Extract

The cotton lavender extract antioxidant potential is presented in Table 3. The obtained results suggest a lower potential of the extract to scavenge OH• and NO• radicals compared to DPPH radicals. Additionally, modest lipid peroxidation inhibition was noted.

Table 3. Antioxidant potential of cotton lavender ethanolic extract (expressed as RSC_{50} in μg/mL—concentrations of extract at which 50% of DPPH, OH•, and NO• radicals neutralization and lipid peroxidation inhibition were achieved).

Assay	DPPH	OH•	NO•	LP
Extract	17.38 ± 0.71 [a]	203.86 ± 1.23 [a]	233.21 ± 2.84 [a]	716.23 ± 12.73 [a]
PG	0.63 ± 0.04 [b]	10.21 ± 0.72 [b]	8.65 ± 0.63 [b]	/
BHT	/	0.04 ± 0.00 [c]	/	8.12 ± 0.71 [b]
QDH	0.99 ± 0.07 [c]	/	/	/
AA	/	2.34 ± 0.16 [d]	/	/

DPPH—2,2-diphenyl-1-picrylhydrazyl; OH•—hydroxyl radicals; NO•—nitroso radicals; LP—lipid peroxidation; PG—propyl gallate; BHT—butylated hydroxytoluene; QDH—quercetin dehydrate; AA—ascorbic acid. Different lower-case letters indicate statistically significant differences ($p < 0.05$).

3.3. Antihypergicemic Potential of Cotton Lavender Ethanolic Extract

The antihyperglycemic activity of the cotton lavender extract was evaluated in vitro as a function of enzyme inhibitory potential, correlating with the retardation of carbohydrate digestion. The results (Table 4) indicate a modest anti-α-amylase potential of the evaluated extract, but at the same time, a significant inhibition of α-glucosidase activity.

Table 4. Antihyperglycemic potential of cotton lavender ethanolic extract and acarbose (positive control)—expressed as IC_{50} values (concentrations at which 50% of α-amylase and α-glucosidase activity was inhibited).

Enzyme	Cotton Lavender Extract	Acarbose	Statistics
	IC_{50} (μg/mL)		
α-amylase	552.23 ± 12.25 [a]	4.53 ± 0.21 [b]	$z = 1.96$, $p = 0.04$
α-glucosidase	61.55 ± 1.32 [a]	42.35 ± 3.88 [a]	$z = 1.74$, $p = 0.08$

Different lower-case letters indicate statistically significant differences.

3.4. In Silico Molecular Modeling of Cotton Lavender Ethanolic Extract Potential on α-Glucosidase Inhibition

Analysis of the α-glucosidase structure in complex with the inhibitor (PDBID: 5NN5) revealed the position of the active site and its catalytic nucleophile and acid/base residues, Asp518 and Glu616. The molecular docking results identified two potential candidates that can inhibit human lysosomal α-glucosidase: rutin and quercetin (Figure 3).

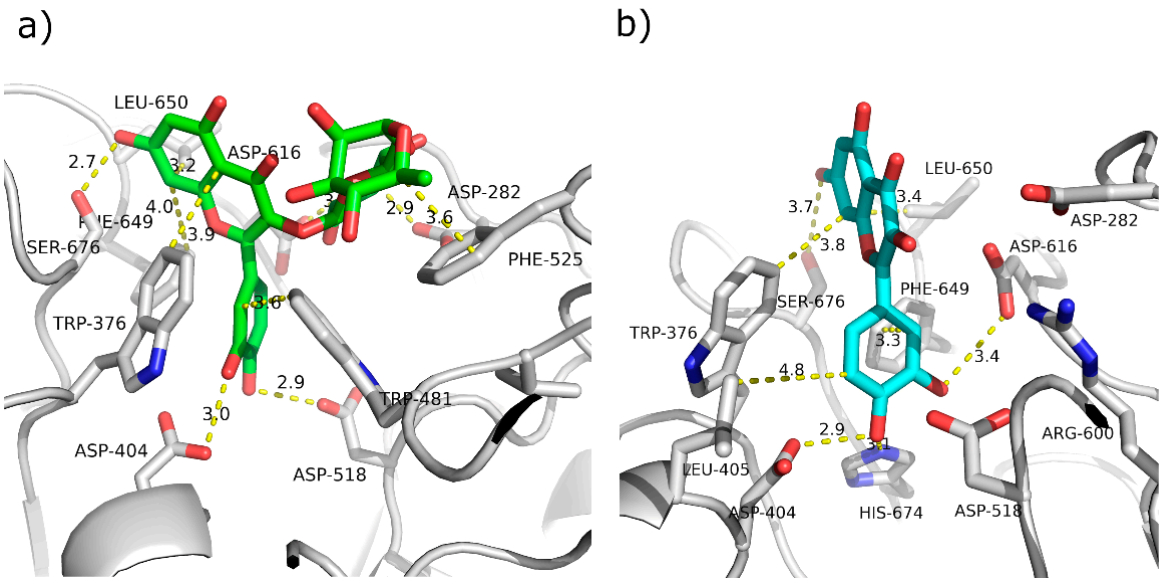


Figure 3. Molecular docking simulations of human lysosomal α-glucosidase with (**a**) rutin; (**b**) quercetin.

Among the identified compounds in the ethanolic extract, rutin has the highest predicted MMGBSA binding energy towards lysosomal α-glucosidase (−37.06 kcal/mol). According to the molecular docking simulation, it is buried deep into the active site and occupies the same space as the experimentally confirmed inhibitor 1-deoxynojirimycin. The simulation further revealed that it can make polar interactions with catalytic Asp518, as well as with Asp404, Asp282, Ser676, and Asp616. Additionally, it is able to make hydrophobic interactions with Trp376, Trp481, Phe525, Phe649, and Leu650. Another identified compound that can make favorable interactions with lysosomal α-glucosidase is quercetin, which shares the common scaffold with rutin. Quercetin can take a similar orientation in the enzyme's active site as rutin. While it cannot interact with catalytic Asp518, it can make polar interactions with another catalytic residue, Asp616, as well as with Asp404, His674, and Ser676. Hydrophobic interactions are predicted with Trp376, Phe649, Leu405, and Leu650. The predicted binding energy is −16.20 kcal/mol. Other identified compounds (trans-cinnamic acid, p-coumaric acid, and ferulic acid) had unfavorable predicted binding energies and orientations in the molecular docking simulation.

4. Discussion

A summary of literature data on the chemical composition and biological activity of various cotton lavender extracts is presented in Table 5.

Table 5. Literature review of papers dealing with cotton lavender extracts (listed from oldest to newest).

Ref.	Type of Extract	Yield (%)	Total Phenolic Content	Total Flavonoid Content	Polyphenolic Compounds	Biological Activity
[24]	hexane chloroform ethyl acetate methanol aqueous	-	-	-	-	Analgesic, anti-inflammatory, anti-cholinergic
[25]	hexane chloroform ethyl acetate methanol aqueous	2.9 3.9 1.0 4.7 6.8	-	-	-	Spasmolytic

Table 5. *Cont.*

Ref.	Type of Extract	Yield (%)	Total Phenolic Content	Total Flavonoid Content	Polyphenolic Compounds	Biological Activity
[26]	chloroform	8.2	-	-	-	Anti-inflammatory
[27]	methanol dichloromethane	-	-	-	-	Anti-inflammatory
[28]	methanol	-	-	-	-	Anti-corrosive
[29]	aqueous polyphenolic	-	132 mg GAE/g 213 mg GAE/g	4.8 mg QE/g 49.8 mg QE/g	-	Anti-inflammatory and immunomodulatory
[30]	aqueous	-	86.14 µg GAE/mg	17.10 µg QE/mg	chlorgenic acid (1958.21 mg/kg); apigenin-7-glycoside (42.44 mg/kg); gentistic acid (33.18 mg/kg); caffeic acid (31.68 mg/kg); 4-hydroxybenzoic acid (28.09 mg/kg); rutin (11.84 mg/kg); vanillic acid (10.19 mg/kg); quercitin (3.66 mg/kg); protocatechic acid (3.29 mg/kg); ferulic acid (3.02 mg/kg); gallic acid (2.72 mg/kg)	Hepatoprotective
	ethanol		108.61 µg GAE/mg	23.29 µg QE/mg	chlorgenic acid (2726.57 mg/kg); apigenin-7-glycoside (66.63 mg/kg); 4-hydroxybenzoic acid (51.91 mg/kg); caffeic acid (43.64 mg/kg); gentisic acid (19.52 mg/kg); quercitin (11.95 mg/kg); rutin (10.28 mg/kg); gallic acid (3.60 mg/kg); acide salicylique (2.33 mg/kg); acide cichorique (2.22 mg/kg); protocatechic acid (1.87 mg/kg); kampferol (1.05 mg/kg); ferulic acid (0.96 mg/kg);	
[31]	methanol	-	156 mg GAE/g	32.8 mg/g	luteolin 7-glucoside (62.97 mg/g d.e.); luteolin (18.99 mg/g d.e.); rutin (14.83 mg/g d.e.); quercitin (5.84 mg/g d.e.); p-coumaric acid (0.83 mg/g d.e.); caffeic acid (0.56 mg/g d.e.);	Antioxidant
[32]	ethyl acetate	-	-	-	-	Antidiabetic and anticancer
[33]	aqueous	-	17.28 mg GAE/g d.w.	7.28 mg CE/g d.w.	cynarin (2.0 mg/g); chlorogenic acid (0.7 mg/g); quercetin 3-O-glucoside (0.07 mg/g); isoorientin (0.04 mg/g); quercetin 3-O-galactoside (0.01 mg/g)	Antioxidant and antimicrobial
[34]	MAE	-	17.57–38.15 * mg/g	-	cynarin (8.0 mg/g d.w.); chlorogenic acid (2.7 mg/g d.w.); quercetin 3-O-glucoside (0.05 mg/g d.w.); quercetin 3-O-galactoside (0.3 mg/g d.w.); isoorientin (0.2 mg/g d.w.)	-
	UAE	-	10.35–31.39 * mg/g	-		-
[2]	SFE-CO_2	3.98	-	-	-	-
[2]	UAE	22.15–28.48 * mg/mL	1.3752–2.4477 * mg GAE/mL	0.7837–1.3104 * mg CE/mL	-	Antioxidant

Table 5. *Cont.*

Ref.	Type of Extract	Yield (%)	Total Phenolic Content	Total Flavonoid Content	Polyphenolic Compounds	Biological Activity
[35]	methanol	-	1273.2 mg GAE/100 g	-	thymol (23.6 µg/g); gallic acid (14.1 µg/g); quercitin (3.9 µ/g)	Antioxidant and antimicrobial
[36]	aqueous	-	373.0 µg/mL	71.7 µg/mL	1,3-O-di-caffeoylquinic acid (165 µg/mL); dimer of 3-O-caffeoylqunic acid (45.1 µg/mL); myricetin-O-glucuronide (38.5 µg/mL); 1,5-O-dicaffeoylquinic acid (27.0 µg/mL); 1,4-O-dicaffeoylquinic acid (13.0 µg/mL); quercetin-3-O-galactoside (12.3 µg/mL); coutaric acid hexoside (9.4 µg/mL); 4,5-O-dicaffeoylquinic acid (8.8 µg/mL); apigenin-C-hexoside-C-hexoside (8.6 µg/mL); 3-O-caffeoylquinic acid (7.7 µg/mL); chlorogenic acid (6.8 µg/mL); chlorogenic acid hexoside (6.8 µg/mL); medioresinol-O-hexoside (4.6 µg/mL); myricetin-3-O-hexoside (4.1 µg/mL); 1,3,5-O-tricaffeoylquinic acid (4.1 µg/mL); myricetin-O-malonylhexoside (3.8 µg/mL); dimer of chlorogenic acid (2.9 µg/mL); apigenin-6-C-pentoside-8-C-hexoside-7-O-hexoside (2.3 µg/mL); quercetin-3-O-glucoside (2.2 µg/mL)	Anticancer
TS	ethanol	7.08	96.04 mg GAE/g d.e.	15.82 mg QE/g d.e.	ferulic acid (1163.64 µg/g d.e.); *p*-coumaric acid (312.43 µg/g d.e.); *trans*-cinnamic acid (141.06 µg/g d.e.); rutin (95.47 µg/g d.e.); quercetin (49.71 µg/g d.e.)	Antioxidant and antihyperglycemic

Ref.—Reference; GAE—Gallic acid equivalent; CE—catechin equivalent; QE—quercitrin equivalent; d.w.—dry weight; MAE—microwave-assisted extraction; SFE-CO_2—supercritical extraction with CO_2; UAE—ultrasound-assisted extraction; * depend on solvent, temperature, time, etc.; TS—this study; d.e.—dry extract.

Different types of cotton lavender extract were investigated: hexane [24,25], chloroform [24–26], ethyl acetate [24,25,32], methanol [24,25,27,28,31,35], aqueous [24,25,29,30,33,36], dichloromethane [27], polyphenolic [29], ethanol [30], and microwave-assisted and supercritical extraction with CO_2 followed by ultrasound-assisted extraction for maximal utilization of bioactive compounds [2,34]. Additionally, yield [2,25,26], total phenolic and flavonoid content [2,29–31,33–36], as well as polyphenolic composition [30,31,33–36], were also investigated.

Moreover, biological activities such as analgesic [24], anti-inflammatory [24,26,27,29], anticholinergic [24], spasmolytic [25], anticorrosive [28], immunomodulatory [29], hepatoprotective [30], antioxidant [2,31,33,35], antimicrobial [33,35], anticancer [32,36], and antihyperglycemic potential [32] were reported.

A previously published study indicated a higher amount of extractable compounds in cotton lavender (16%) [31]. However, the extraction process used 80% methanol (v/v) as the extractant and the herbal material consisted of dried cotton lavender leaves. Therefore, it can be concluded that polar solvents are suitable for cotton lavender extraction. Furthermore, the plant part being extracted is also an important factor affecting extraction yield.

Phenolics and flavonoids are plants' secondary metabolites, playing a vital role in species survival in their natural environment. Moreover, they are considered the main compounds that contribute to the antioxidant, as well as anti-inflammatory potential of plant extracts. A previous study indicated a higher amount of phenolics (156.4 mg GAE/g d.e.) in the methanolic extract of cotton lavender leaves when compared to the results from this study (96.04 mg GAE/g d.e.) [31]. However, the ethanolic extract of the cotton lavender aerial parts contained comparable amounts of total phenolics (108.6 mg GAE/g d.e.) [30]. A similar extractability pattern was recorded for flavonoids. Namely, the available data suggest a higher flavonoid content in methanol extracts (32.8 mg QE/g d.e.) when compared to ethanol extracts analyzed in this study [31]. Disregarding the discussed variations in quantities caused by the specificity of the applied extraction processes, cotton lavender can be highlighted as a species containing significant amounts of phenolic and flavonoid compounds. Chemical profiling of cotton lavender leaf methanolic extract indicated the presence of caffeic and *p*-coumaric acids, as well as luteolin-7-O-glucoside, luteolin and quercetin. Additionally, luteolin-7-O-glucoside was declared the main constituent of this extract (62.97 mg/100 g d.e.) [31]. The current study emphasizes the presence of *trans*-cinnamic, *p*-coumaric and ferulic acids, followed by quercetin and rutin in the ethanol extract obtained from the plant's upper aerial parts. Moreover, the extract was characterized by the highest abundance of ferulic acid (1163.64 μg/g d.e. mL), while caffeic acid, previously reported in another study, was not present [31]. Furthermore, ferulic and *trans*-cinnamic acids were not found in the cotton lavender methanolic extract, while luteolin-7-O-glucoside was absent in the ethanol extract [30]. Although the unfavorable number of published studies dealing with cotton lavender chemical profiling significantly limits the drawing of comprehensive and definitive conclusions, it can be suggested that methanol is an effective extractant if the goal of the extraction is a high total content of phenolics and flavonoids, or if it is necessary to maximize the yield of caffeic acid and luteolin [31,37]. Conversely, ethanol is a more effective extraction solvent for targeting the extracts being highly abundant in ferulic and *trans*-cinnamic acids [30]. However, the solvent is just one of several key factors that influence both the extraction efficiency and the chemical composition of the extract. Other parameters, such as solvent-to-drug ratio, extraction time, temperature, pH, extraction method and herbal material particle size also play a crucial role and require optimization through comprehensive experimental design studies [38]. In addition, even if the extraction parameters are optimized, variations in chemical composition are possible due to the influence of abiotic factors characteristic of plant habitat on the secondary metabolites production. Namely, it is well known that abiotic environmental factors (light, temperature, humidity, soil nutrient and pH status, salinity, carbon dioxide concentration, mechanical stress, pollution, pesticides, etc.) influence the synthesis of secondary biomolecules in plants [39], which is of high relevance since the above-discussed published papers analyzed plant specimens collected from their natural habitat. In our research, a cultivated plant was studied. Taking into account all of the previously described aspects, the results of published studies aimed at the chemical characterization of cotton lavender, as well as the results of our study, should be considered preliminary data that provide a foundation for further, more comprehensive research into the full range of medical benefits offered by cotton lavender.

The potential to scavenge synthetic DPPH radicals is an important preliminary indicator of antioxidant activity. The current study suggests a concentration-dependent scavenging potential of cotton lavender ethanolic extract, with a recorded RSC_{50} value of 17.38 μg/mL. When compared with values obtained for positive controls (RSC_{50}(PG) = 0.63 μg/mL, RSC_{50}(QDH) = 0.99 μg/mL), this extract can be characterized as having moderate antioxidant potential. However, a previous study indicates stronger neutralization of DPPH radicals by cotton lavender methanolic extract (RSC_{50} = 8.02 μg/mL), which is expected given the higher abundance of phenolic and flavonoid compounds in methanolic extract [31]. Previously conducted studies report no data related to the potential of cotton lavender extracts to neutralize $OH^{\bullet}$ and $NO^{\bullet}$ radicals, or inhibit lipid peroxidation process.

However, the current results indicate moderate $OH^{\bullet}$ and $NO^{\bullet}$ scavenging potential of the evaluated extract (RSC_{50} = 203.86 and 233.21 μg/mL, respectively) when compared to positive controls ($OH^{\bullet}$ neutralization—RSC_{50}(PG) = 10.21 μg/mL, RSC_{50}(BHT) = 0.04 μg/mL, RSC_{50}(AA) = 2.3 μg/mL; $NO^{\bullet}$ neutralization—RSC_{50}(PG) = 8.65 μg/mL), as well as modest protective effect toward lipid components (RSC_{50} = 716.23 μg/mL) in relation to the positive control (RSC_{50}(BHT) = 8.12 μg/mL).

α-Amylase and α-glucosidase are gastrointestinal enzymes responsible for the initial breakdown of disaccharides and polysaccharides. Inhibition of their activity reduces the kinetics of intestinal carbohydrates conversion to monosaccharides, thus slowing the absorption to blood and reducing spiking glycaemia events after meals. The described mechanism is scientifically recognized and is currently targeted by many conventional drugs used in the treatment of diabetes mellitus type 2 [40]. The results of this study suggest modest anti-α-amylase activity of cotton lavender ethanolic extract (IC_{50} = 555.2 μg/mL), especially when compared to the antihyperglycemic potential of acarbose (positive control), determined under the same experimental conditions (IC_{50} = 4.53 μg/mL). A hundredfold lower activity of the cotton lavender extract is observable.

However, the available results indicate that the ethyl acetate cotton lavender extract moderately inhibits α-glucosidase (IC_{50} = 110 ± 4.25 μg/mL) [32]. This research reports promising IC_{50} values obtained for the water-ethanolic cotton lavender extract's anti-α-glucosidase potential (IC_{50} = 61.55 μg/mL), especially when comparing the obtained value to the acarbose inhibitory activity (IC_{50} = 42.35 μg/mL), determined under the same experimental conditions.

In order to further investigate the potential mechanism underpinning the recorded cotton lavender water-ethanolic extract's anti-α-glucosidase activity, the compounds identified in the extract were computationally docked into the protein active site. The output results identified rutin and quercetin as potential enzyme inhibitors (Figure 3), which is in accordance with previously published data [41,42]. Comparison of the obtained results with experimentally determined structure of well-known inhibitor acarbose in complex with α-glucosidase (PDBID: 5NN8) revealed similar binding and overlapping of the binding orientations including polar interactions with Asp404, Asp282, and Asp616, as well as hydrophobic interactions with Trp376, Trp481, Phe525, Phe649, and Leu650 [23]. While acarbose is not able to interact with Ser676, it is able to make polar interactions with Met519. The flavonoid structures of rutin and quercetin perfectly fit the active site cavity and bind to its residues through polar and hydrophobic interactions. Earlier speculation suggested that phenolic compounds might inhibit the tested enzymes. This could likely be a result of hydrogen bonds forming between the hydroxyl groups of the phenolic compounds and the catalytic residues at the enzyme's binding site. The result of this interaction is probably the stabilization of the active site through a conjugated *p*-system [43]. In particular, the chemical structures of rutin and quercetin are rich in hydroxyl groups attached to the benzene ring, which explains the potential mechanism of α-glucosidase inhibition. Although the inhibition mechanism of ferulic acid against α-glucosidase from *S cerevisie* has been proven [44], it did not show the ability to bind the active site of human lysosomal α-glucosidase. Therefore, its proven antidiabetic activity may be exerted through an alternative mechanism or metabolic pathway, such as through modulating insulin-signaling molecules [45].

This study is in line with cotton lavender's traditional use for the preparation of tea mixtures with antidiabetic effect. Moreover, cotton lavender gains the status of a potential candidate for the development of evidence-based traditional herbal medicines. Such preparations might assist as a complementary therapy in the treatment of diabetes. However, the current study results also emphasize the dependence of cotton lavender extract biological potential from the solvent used for its production.

5. Conclusions

The obtained results indicate that cotton lavender ethanolic extracts are a valuable source of phenolic and flavonoid compounds, among which a significant abundance of ferulic acid was recorded. Moreover, notable antihyperglycemic activity was demonstrated, primarily reflected through concentration-dependent anti-α-glucosidase activity, as well as modest α-amylase inhibition. Therefore, an evidence-based starting point for studying cotton lavender's beneficial effects in the prevention and support of hyperglycemia and diabetes treatment could be established. However, it should also be further developed through future preclinical and clinical trials. Additionally, the antioxidant effect of the studied extract, although classified as of moderate importance, has the potential to assist other mechanisms in mitigating elevated oxidative stress levels. As previously discussed, bioactivity-guided extraction could result in obtaining cotton lavender extracts with improved antioxidant characteristics.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/horticulturae10121247/s1, Table S1: Quantification of phenolic compounds by application of HPLC/DAD instrumental technique—supporting data.

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