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GC-MS Profiling, *in-vitro* Antioxidant, Anti-inflammatory and Anti-diabetic Activities of Petroleum Ether Extracts of *Dypsis decaryi* and *Dypsis leptocheilos* Leaves Cultivated in Egypt: Experimental and Computational Studies

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Abstract: This study aims to investigate the phytochemical composition, *in-vitro* (anti-oxidant, anti-inflammatory, anti-diabetic) activities of the lipoidal matter (petroleum ether extracts: PEE1 and PEE2) of the leaves of *Dypsis decaryi* (*D. decaryi*) and *Dypsis leptocheilos* (*D. leptocheilos*) Family Arecaceae cultivated in Egypt. The unsaponifiable and saponifiable fractions (USF and SF) of *D. decaryi* and *D. leptocheilos* were assessed using GC/MS analysis. The identified compounds in the USF of both species represented 94.63 and 92.46 %, of which squalene (18.23, 17.99 %), *α*-amyrin methyl ether (11.84 and 9.10 %) and phytol (8.97, 7.21%) were the major compounds, respectively. In the saponifiable fractions (SF), the percentage of identified saturated fatty acids were (62.49 and 79.42 %) with methyl palmitate (38.57 and 35.37%) as the major constituent, while the percentage of identified unsaturated fatty acids were (14.30 and 9.93 %) with methyl oleate (11.14 and 9.23%) as the major compound, respectively. PEE of both species exhibited significant anti-oxidant capacities in scavenging free radicals by DPPH (IC_{50}= 29.8±0.62 and 28.5±1.43 µg/mL) and ABTS (IC_{50}=173.98±8.23 and 12.68±1.08 µg/mL) methods compared to ascorbic acid (IC_{50}=38.72±0.26 and 10.65±0.81 µg/mL). PEE1 and PEE2 inhibited both COX-1 (IC_{50}= 0.67±0.06 and 0.7±0.01 µM) and COX-2 (IC_{50}= 0.049±0.001 and 0.103±0.006 µM) enzymes compared to indomethacin (IC_{50}= 0.6±0.1 and 0.079±0.001 µM). Furthermore, PEE1 and PEE2 possessed moderate anti-diabetic activity through *in-vitro* inhibition of *α*-amylase (IC_{50}=107.16±4.57 and 41.81±2.85 µg/mL) compared to acarbose (IC_{50}=14.54±0.86 µg/mL). *In-silico* study using molecular based docking of *α*-amyrin methyl ether, arundoin, cycloartenol and 24-methylenecycloartanol revealed good binding tendencies to *α*-amylase.

Keywords: *Dypsis decaryi*, *Dypsis leptocheilos*, GC/MS analysis, Anti-oxidant, Anti-inflammatory, Anti-diabetic activities, *in-silico*, Molecular based docking

1. INTRODUCTION

Arecaceae is a family of dominant perennial trees, sometimes known as palm trees. This is a family of monocots order Arecales, it includes flowering plants, and occurs in tropical, subtropical, and mild climates and has about 181 genera and 2600 species[1], [2]. The family Arecaceae comprises several species that are primarily found in tropical and sub-tropical ecological zones. These zones also include the Arabian deserts, Africa, Latin America, South and

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Southeast Asia, and South-East Asia[3]. Phenolic acids, flavonoids, tannins, amino acids, alkaloids, fatty acids, steroids, carotenoids and terpenoids are reported in Arecaceae family[4].
Many Arecaceae species are reported for their anti-oxidant, anti-inflammatory, anti-diabetic, antimalarial, anti-parasitic, anti-protozoal, antineoplastic, hepatoprotective, enzyme-inhibition, anti-fungal, anti-proliferative, and antibacterial activities[5].

Genus *Dypsis* is one of the largest genera in family Arecaceae, with over 170 species. There have been very few phytochemical and biological investigations related to *Dypsis*. Phytochemical screening of some species of *Dypsis* (*D. leptocheilos* and *D. lutescens*) revealed the presence of flavonoids, sugars, stilbenes and steroids[6,7,8]. Some studies reported that *Dypsis* species possessed different activities such as: hepatoprotective[8], anti-oxidant[9,10], cytotoxic[11], anti-diabetic[12], gastroprotective[13] and anti-obesity[14] activities. Ibrahim *et al* reported the isolation of five flavonoids along with their *in-silico* molecular based docking study and the anti-oxidant, antimicrobial and cytotoxic activities of the ethyl acetate and aqueous methanol extracts of *D. leptocheilos*[6]. A novel thermo stable lectin isolated from *D. decaryi* seeds exhibited bacteriostatic and antifungal effects[15].

Oxidative stress is a physiological imbalance between anti-oxidant scavenging mechanisms and reactive oxygen species (ROS) causing cell damage[16]. It causes the release of highly reactive free radicals[17], the onset of numerous chronic illnesses, including cancer, diabetes, autoimmune, heart disease, and neurodegenerative disorders. It also hastens human aging[18,19]. In diabetes mellitus (DM), hyperglycemia causes the glycation process to oxidize glucose to reactive oxygen species. This can damage various tissues and organs, leading to symptoms like cardiomyopathy, nephropathy, neuropathy, and retinopathy. It can also raise the body's levels of lipid peroxidation[20].

Recently, there has been a lot of interest in this medical state, and researchers have adopted numerous anti-diabetic medications to address it. But over the years, these medications haven't been able to adequately control the complications that emerge from oxidative stress. Utilizing the plant extracts is gaining attention in halting various diseases and disorders, and this is because of the appreciable phytochemicals included in them that aid in the removal of the free radicals from the body's systems[21].

The breakdown of sugars and the increase in blood glucose are aided by the digestive enzymes α-amylase and α-glucosidase. Through suppression of α-amylase and α-glucosidase activity, natural compounds with potential anti-oxidant activity can be used to treat DM. The inhibition of pancreatic α-amylase might affect the digestion and absorption of carbohydrates, hence regulating blood glucose levels. Specifically, it transforms starch into a mixture of oligosaccharides intermediates[22,23]. Numerous phytochemicals with α-amylase inhibitory action have been found in a wide range of plant species and have been suggested for the treatment of diabetes[24,25].

Not only many studies have supported that there is an interdependent relationship between oxidative stress and inflammation as oxidative stress can worsen the inflammatory process and vice versa[26], but also hyperglycemic-induced oxidative stress in diabetic patients is believed to cause local and systemic inflammation[27,28]. One of the body's natural defense mechanisms is inflammation. It displays as swelling, redness, and discomfort in the affected area in response to injury or infection. Numerous hydrolytic enzymes are released, fluids extravasate, the injured site is damaged and repaired, vasodilation occurs, blood vessel permeability increases, and blood pressure rises as a result of inflammation[29].

Such type of inflammatory responses also contributes to the activation and the release of free radicals from different cells of immune system, which causes localized tissue damage and lipid peroxidation[30]. Conventional anti-inflammatory medications have serious adverse effects that restrict their usage, including hemorrhagic gastritis, gastrointestinal toxicity (diarrhea/colitis), and hypertension [31-33]. It is crucial to discover efficient anti-inflammatory medications that both moderate inflammation and decrease the formation of ROS and free radicals; this is seen to be a promising approach for both preventing and treating conditions linked to chronic inflammation.

This is the first study of the chemical investigation of PEE of both *D. decaryi* and *D. leptocheilos* and the *in-vitro* evaluation of their anti-oxidant, anti-inflammatory and anti-diabetic activities as well as an *in-silico* molecular based docking study of anti-diabetic activity of α-amyrin methyl ether, arundoin, cycloartenol and 24-methylenecycloartanol, aiming to discover natural extracts enriched with bioactive compounds having good anti-oxidant activity and consequently could be used in the treatment of several diseases.

2. METHODS

2.1. Plant Material

The leaves of *Dypsis decaryi* (Jum.) Beentje & J. Dransf and *Dypsis leptocheilos* (Hodel) Beentje & J. Dransf were collected from Al-Abd farm at Cairo-Alexandria desert road in August 2019 following institutional, national, and international guidelines. The plants were identified by Mrs. Terase Labib, Department of Flora and Taxonomy, Al-Orman Botanical Garden, Giza, Egypt. Two voucher specimens no. (DD 719 and DL 719) were kept in the herbarium in the Department of Pharmacognosy and Medicinal Plants, Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt.

2.2. Chemicals, reagents

Petroleum ether (b.p. 60-80 °C ether (Alfa Chemika, India). Potassium hydroxide, anhydrous sodium sulfate (Research-Lab Fine Chem. Industries, Mumbai, India). DPPH (1, 1-diphenyl-2-picryl-hydrazil), ABTS (2, 2′-azino-bis-(3-ethylbenzothiazolin-6-sulfonic acid), ascorbic acid and acarbose were purchased from Sigma- Aldrich, Saint Louis, MO, USA. Indomethacin was obtained from Pharco, Egypt.

2.3. Preparation of petroleum ether extract

The leaves of both species were collected; shade dried and grinded to fine powder using a mechanical grinder. One kilogram of the plants was weighed, transferred into round flask, refluxed with petroleum ether (b.p. 60-80 °C) for 48 hours and then filtered. The filtrates were concentrated under pressure using rotary evaporator (Heidolph 4000, Germany) to obtain (65 and 59 grams) of PEE and kept at a refrigerator for further use.

2.3. a. Preparation of unsaponifiable (USF) and saponifiable (SF) fractions

This was carried out by the method described by El Sayed *et a*l [34].

2.3. b. Preparation of methyl esters of fatty acids (FAME)

This was performed according to the method adopted by El Sayed *et al* [34].

2.3. c. GC/MS analyses of USF and FAME

GC-MS analyses of the USF and FAME of both plants were carried out at National Research Center, Giza, Egypt. The analyses were performed using a TRACE GC Ultra Gas Chromatographs (THERMO Scientific Corp., USA), coupled with a thermo mass spectrometer detector (ISQ Single Quadrupole Mass Spectrometer) with TG-Wax MS non polar column (30 m × 0.25 mm ID × 0.25 µm film thickness). With an injection volume of 1µL (Split ratio 1:10) and helium gas (99.99%) utilized as the carrier gas at a constant flow rate of 1 mL/minute, the temperature program was as follows: 60 °C for 1 min; rising at 4°C /min to 300 °C and held for 15 min. The temperatures of the detector and the injection port were both set to 280°C. Diluted samples (1:10 hexane, v/v) of 0.2 µL of the mixtures were always injected. By using an electron ionization system (EI) with an ionizing energy of 70 eV and a spectral range of *m/z* 35-550, mass spectra were obtained. The compounds were identified by comparing their mass fragmentation patterns and retention times to those found in the Wiley spectral library collection, the NIST (National Institute of Standards and Technology) library, and/or published data outlined by Adams[35].

2.4. Evaluation of anti-oxidant activity of PEE (Free radicals scavenging activity)

2.4. a. DPPH scavenging activity

The DPPH radical scavenging assay was performed according to the method reported by Ibrahim *et al* [36]. Using a UV spectrophotometer (Jasco, serial No. C317961148, Japan), the absorbance was measured at 517 nm.

2.4. b. ABTS radical scavenging activity

Anti-oxidant activity was measured using the ABTS radical scavenging method in accordance with the protocols outlined by Sanchez *et al* and Ling *et al* [37, 38].

2.5. Evaluation of anti-inflammatory activity of PEE

A kit from Cayman Chemical Company (Ann Arbor, USA) was used to measure the anti-inflammatory efficacy *in-vitro*. Determination of the cyclooxygenases (COX-1 and COX-2) inhibition efficacy was performed as described by Blobaum and Marnett[39].

2.6. Evaluation of anti-diabetic activity of PEE (α-amylase inhibitory activity)

The α-amylase inhibitor screening kit (Catalog No. K482-100; Bio Vision, USA) manufacturer's protocol was followed while performing the experiment on a 96-well plate, the absorbance was measured at optical density (OD) = 405 nm using multi-well spectrophotometer (ELISA reader).

2.7. Statistical analysis and determination of IC_{50} values

Each experiment was performed three times. The data were presented as mean±SD (standard deviation), analysis of data was carried out using two-way ANOVA followed by Tukey's multiple comparisons test. The IC_{50} values were established by one-way ANOVA followed by Tukey's test as

post-hoc test and the levels of significance were determined at P<0.05. GraphPad Prism (GraphPad software Inc. version 5, USA) was used for all the statistical analysis.

2.8. *In-silico* molecular docking study of selected compounds as *α*-amylase inhibitors

The 3D crystal structure of human *α*-amylase protein was retrieved from the Protein Data Bank (http://www.rcsb.org/pdb) (PDB ID: 2qv4, resolution: 1.97 Å). All water molecules were removed from the downloaded protein structure, and the hydrogen atoms were added. The 2D structures of four selected phytoconstituents (ligands) were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov) and saved in MDL-SD file format. The four tested phytoconstituents were *α*-amyrin methyl ether (CID 612819), arundoin (CID 12308619), cycloartenol (CID 92110) and 24-methylenecycloartanol (CID 94204) with acarbose being both the reference drug (CID 41774) and the co-crystalized ligand. Energy minimization was performed by applying MMFF94 force field[40]. Then, the hydrogen atoms were hidden to make the areas of interaction clearer. The present *in-silico* molecular based docking study was performed using Autodock vina 4.2.6 version software. The molecular docking was carried out within a grid box with a number of points in *xyz* of 52 × 46 × 40 Å box, which encloses the ligand. The grid box spacing was set to 0.3 Å, and grid center designated at coordinates for the center of active site of the protein (*x, y, z*): 9.332; 42.784; 24.955. The 2D and 3D molecular docking simulation of acarbose and selected phytoconstituents were shown in Figure (5).

The binding affinity between the protein and ligands was measured in units of Gibbs free energy (ΔG) and about twenty poses were predicted then the most suitable orientations, affinity scores (Kcal/mol), and root mean square deviation (RMSD) values were captured, as shown in Table (4). Redocking of the co-crystalized ligand (acarbose) was performed for validating docking protocol (RMSD 0.78 Å). The analysis of binding interactions was performed using Discovery studio visualizer 2016.

3. RESULTS

3.1. GC/MS analyses

GC/MS chromatograms of USF and FAME of *D. decaryi* and *D. leptocheilos* leaves are represented in Figure (1) and the identified compounds are listed in Tables (1) and (2).

Unsaponifiable identified compounds.

Table 1 includes fifty-four and fifty three compounds of the USF1 and USF2 of both *D. decaryi* and *D. leptocheilos*, respectively. The total identified percentages were 94.63 % and 92.46%. Squalene was the major identified compound (18.23% and 17.99%) followed by *α*-amyrin methyl ether (11.84% and 9.10%) and phytol (8.97% and 7.21%). In addition, sterols were presented by 3.69 % and 3.71 %; *β*-sitosterol was detected in appreciable percentage in both species (3.54% and 3.05%). Triterpenes was the major class present in both USF constituting (37.02 % and 36.59 %). The USF of both species contained straight chain hydrocarbons (3.88 % and 17.97 %) and several aromatic hydrocarbons (37.15 % and 11.31 %). Butylated hydroxytoluene (4.54 %), 2, 4-bis (1, 1-dimethylethyl)-Phenol (2.93 %) and 6, 10, 14-trimethyl-2-Pentadecanone (4.33 %) were characteristic oxygenated compounds in USF of *D. leptocheilos*.

Saponifiable identified compounds.

Table 2 represents thirteen and eighteen compounds of the saponifiable fraction; FAME of *D. decaryi* and *D. leptocheilos* with a total percentage of 76.79% and 89.35%, respectively. Methyl palmitate (hexadecanoic acid, methyl ester) was the major identified compound (38.57% and 35.37%) followed by methyl oleate (9-octadecenoic acid, methyl ester; 11.14% and 9.23%). Methyl tetradecanoate was detected in considerable percentage (31%) in the saponifiable fraction of *D. leptocheilos*

3.2. Evaluation of anti-oxidant activity

3.2. a. DPPH scavenging activity

The most popular technique for quantifying free radical scavenging is DPPH radical scavenging[41]. Figure 2A illustrates the percentage inhibition of DPPH scavenging ability of PEE in comparison with ascorbic acid as a reference standard at different concentrations. Both PEE1 and PEE2 revealed an outstanding ability to eliminate the DPPH radical (92.08 and 92.93%) at concentration 1 mg/L with IC_{50} values of 29.8±0.62 and 28.5±1.43 µg/mL, respectively. Ascorbic acid exhibited 98.57% scavenging effect at concentration 1 mg/L with an IC_{50} value of 38.72±0.26 µg/mL, respectively as indicated in Table (3).

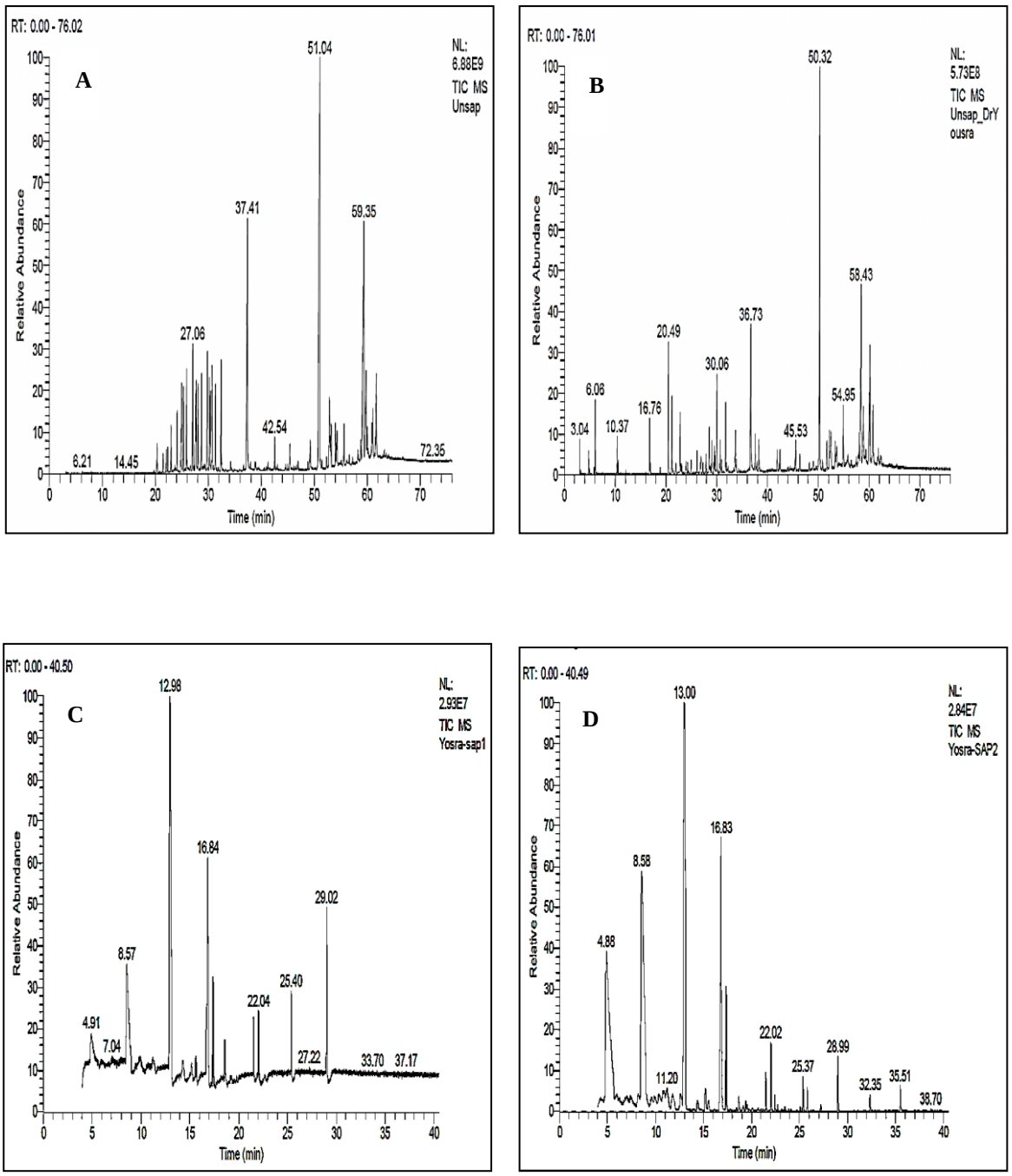

Figure 1. GC/MS chromatograms of USF and FAME of *D. decaryi* (1) and *D. leptocheilos* (2) leaves.

A: USF1, B: USF2, C: FAME1 and D: FAME2

Table1. GC/MS analysis of USF of *D. decaryi* and *D. leptocheilos* leaves.

Compounds	R_t/min	RR_t	B.p.	M.wt	M. formula	Area %	
						D. dec.	*D. lept.*
1. Aliphatic compounds							
a. Alkanes							
2 –Ethyl hexanol	6.06	0.12	57	130	$C_8H_{18}O$	-	1.56
n-Dodecane	10.57	0.21	57	170	$C_{12}H_{26}$	-	0.31
n-Tetradecane	16.93	0.34	57	198	$C_{14}H_{30}$	-	0.34
n-Hexadecane	22.93	0.46	57	226	$C_{16}H_{34}$	-	0.22
n-Heptadecane	26.68	0.53	57	240	$C_{17}H_{36}$	0.21	-
n-Octadecane	28.66	0.57	57	254	$C_{18}H_{38}$	0.15	0.19
n-Nonadecane	31.90	0.63	57	268	$C_{19}H_{40}$	0.15	-
n-Tricosane	41.00	0.81	57	324	$C_{23}H_{48}$	0.10	-
1-Eicosanol	41.25	0.82	55	298	$C_{20}H_{42}O$	0.20	-
n-Pentacosane	44.48	0.88	57	352	$C_{25}H_{52}$	0.14	0.21
1-Docosanol	45.37	0.90	55	326	$C_{22}H_{46}O$	0.64	-
n-Hexacosane	46.92	0.93	57	366	$C_{26}H_{54}$	0.20	-
n-Heptacosane	48.20	0.96	57	380	$C_{27}H_{56}$	0.20	0.31
1-Tetracosanol	49.21	0.98	55	354	$C_{24}H_{50}O$	0.77	-
n-Nonacosane	51.69	1.03	57	408	$C_{29}H_{60}$	0.32	1.18
n-Hentriacontane	54.95	1.09	57	436	$C_{31}H_{64}$	1.05	2.62
n-Dotriacontane	56.48	1.12	57	450	$C_{32}H_{66}$	-	0.36
n-Tritriacontane	58.04	1.15	57	464	$C_{33}H_{68}$	0.55	0.85
Subtotal						**4.68**	**8.15**
b. Alkenes							
1-Decene	4.79	0.095	55	140	$C_{10}H_{20}$	-	0.47
1-Dodecene	10.37	0.21	55	168	$C_{12}H_{24}$	-	0.88
1-Tetradecene	16.76	0.33	55	196	$C_{14}H_{28}$	-	1.72
1-Hexadecene	22.79	0.45	55	224	$C_{16}H_{32}$	-	2.11
1-Octadecene	28.55	0.57	55	252	$C_{18}H_{34}$	0.11	1.89
1-Eicosene	33.68	0.67	55	280	$C_{20}H_{40}$	0.17	1.71
1-Docosene	38.28	0.76	55	308	$C_{22}H_{40}$	0.21	1.12
1-Tetracosene	42.47	0.84	55	336	$C_{24}H_{48}$	0.15	0.82
9-Hexacosene	46.34	0.92	55	364	$C_{26}H_{52}$	-	0.66
1-Dotriacontene	57.21	1.14	55	448	$C_{32}H_{64}$	0.17	-
Subtotal						**0.81**	**11.38**
2. Aromatic hydrocarbons							
5-Phenyl decane	22.06	0.43	91, 147	218	$C_{16}H_{26}$	0.47	-
4- Phenyl decane	22.36	0.44	91, 133	218	$C_{16}H_{26}$	0.59	-
3- Phenyl decane	22.95	0.45	91, 119	218	$C_{16}H_{26}$	0.94	-
2-Phenyl decane	23.15	0.46	105	218	$C_{16}H_{26}$	1.26	0.16
6- Phenyl undecane	23.87	0.47	91, 161	232	$C_{17}H_{28}$	0.92	0.17
5- Phenyl undecane	23.99	0.48	91, 147	232	$C_{17}H_{28}$	1.84	0.36
4- Phenyl undecane	24.29	0.48	91, 133	232	$C_{17}H_{28}$	1.94	0.34
3- Phenyl undecane	24.93	0.49	91, 119	232	$C_{17}H_{28}$	2.46	0.52
2- Phenyl undecane	26.13	0.52	105	232	$C_{17}H_{28}$	3.68	0.82

6- Phenyl dodecane	26.75	0.53	91, 161	246	$C_{18}H_{30}$	1.95	0.37
5- Phenyl dodecane	26.88	0.53	91, 147	246	$C_{18}H_{30}$	1.81	0.49
4- Phenyl dodecane	27.25	0.54	91, 133	246	$C_{18}H_{30}$	1.93	0.42
3- Phenyl dodecane	27.90	0.55	91, 119	246	$C_{18}H_{30}$	2.39	0.74
2- Phenyl dodecane	29.05	0.58	105	246	$C_{18}H_{30}$	3.47	1.18
6- Phenyl tridecane	29.50	0.59	91, 161	260	$C_{19}H_{32}$	2.43	0.99
5- Phenyl tridecane	29.68	0.59	91, 147	260	$C_{19}H_{32}$	1.69	0.78
4- Phenyl tridecane	30.72	0.61	91, 133	260	$C_{19}H_{32}$	2.46	-
3- Phenyl tridecane	31.35	0.62	91,119	260	$C_{19}H_{32}$	1.98	1.14
2- Phenyl tridecane	31.76	0.63	105	260	$C_{19}H_{32}$	2.94	2.83
Subtotal						**37.15**	**11.31**
3. Aromatic compounds							
Butylated hydroxyanisole	20.31	0.40	165	180	$C_{11}H_{16}O_2$	0.67	-
Butylated hydroxytoluene	20.49	0.41	205	220	$C_{15}H_{24}O$	0.39	4.54
2,4-bis(1,1-dimethylethyl)- Phenol	21.17	0.42	191	206	$C_{14}H_{22}O$	-	2.93
Dihydroactinidiolide	21.93	0.44	111	180	$C_{11}H_{16}O_2$	-	0.56
Vitamin E	55.83	1.11	165	430	$C_{29}H_{50}O_2$	0.22	0.35
Subtotal						**1.28**	**8.38**
4. Sterols							
2-Methylene-cholestane-3-oL	57.45	1.14	69	400	$C_{28}H_{48}O$	-	0.41
Stigmasterol	57.83	1.15	55	412	$C_{29}H_{48}O$	-	0.25
Campesterol	58.32	1.16	105	400	$C_{28}H_{48}O$	0.15	-
β-Sitosterol	58.87	1.17	43	414	$C_{29}H_{50}O$	3.54	3.05
Subtotal						**3.69**	**3.71**
5. Terpenes							
Neryl acetone	18.88	0.38	69	194	$C_{13}H_{22}O$	-	0.24
6,10,14-trimethyl-2-Pentadecanone	30.06	0.59	58	268	$C_{18}H_{36}O$	-	4.33
5E, 9E-Farnesyl acetone	31.91	0.63	69	262	$C_{18}H_{30}O$	0.14	0.31
Phytol	36.72	0.73	71	296	$C_{20}H_{40}O$	8.97	7.21
Isophytol	37.94	0.75	71	296	$C_{20}H_{40}O$	0.13	-
4,8,12,16-Tetramethylheptadecan-4-olide	41.94	0.83	99	324	$C_{21}H_{40}O_2$	0.76	0.85
Squalene	50.32	1	69	410	$C_{30}H_{50}$	18.23	17.99
2,6,10,15,19,23-hexamethyl-1,6,10,14,18,22-Tetracosahexaen-3-ol	52.19	1.04	69	426	$C_{30}H_{50}O$	1.92	1.23
α-Amyrin methyl ether	58.43	1.16	218	440	$C_{31}H_{52}O$	11.84	9.10
Cycloeucalenol	59.35	1.18	69	426	$C_{30}H_{50}O$	0.15	0.51
Lupeol	59.99	1.19	69	426	$C_{30}H_{50}O$	0.52	-
3β-Methoxyfern-9(11)-ene (arundoin)	60.15	1.20	71	440	$C_{31}H_{52}O$	-	5.44
Cycloartenol	60.78	1.21	69	426	$C_{30}H_{50}O$	0.79	2.32
Betulin	61.05	1.21	189	442	$C_{30}H_{47}O_3$	1.20	-
3-β-24-Methylenecycloartanol	61.72	1.23	55	440	$C_{31}H_{52}O$	2.37	-
Subtotal						**46.26**	**48.44**
Total identified compounds						**94.63%**	**92.46%**

*RR_t: Retention time relative to Squalene

Table 2. GC/MS analysis of FAME of *D. decaryi* and *D. leptocheilos* leaves

Compounds	R_t/min	RR_t	B.p.	M.wt	M. formula	Area %	
						D. dec.	*D. lept.*
a. Saturated FAME							
Methyl dodecanoate	4.90	0.38	74	214	$C_{13}H_{26}O_2$	2.19	2.55
Methyl tetradecanoate	8.58	0.66	74	242	$C_{15}H_{30}O_2$	8.95	31.00
Methyl pentadecanoate	11.67	0.89	74	256	$C_{16}H_{32}O_2$	0.29	-
Methyl hexadecanoate (methyl palmitate)	12.98	1.00	74	270	$C_{17}H_{34}O_2$	38.57	35.37
Methyl heptadecanoate	15.20	1.17	74	284	$C_{18}H_{36}O_2$	0.87	1.09
Methyl octadecanoate (methyl stearate)	17.37	1.34	74	298	$C_{19}H_{38}O_2$	-	4.47
Methyl eicosanoate	21.52	1.66	74	326	$C_{21}H_{42}O_2$	2.54	0.99
Methyl-4-methoxy-4,8,12,16-tetramethylheptadecanoate	22.43	1.73	145	370	$C_{23}H_{46}O_3$	-	0.40
Methyl heneicosanoate	23.48	1.81	74	340	$C_{22}H_{44}O_2$	-	0.10
Methyl docosanoate	25.40	1.96	74	354	$C_{23}H_{46}O_2$	3.21	0.80
Methyl tricosanoate	27.22	2.09	74	368	$C_{24}H_{48}O_2$	-	0.18
Methyl tetracosanoate (methyl lignocerate)	29.02	2.24	74	382	$C_{25}H_{50}O_2$	5.87	1.27
Methyl hexacosanoate	32.35	2.49	74	410	$C_{27}H_{54}O_2$	-	0.44
Methyl octacosanoate	35.51	2.74	74	438	$C_{29}H_{58}O_2$	-	0.71
Methyl triacontanoate	38.71	2.98	74	466	$C_{31}H_{62}O_2$	-	0.05
Subtotal						**62.49**	**79.42**
b. Unsaturated FAME							
Methyl tridecenoate	5.96	0.46	55	226	$C_{14}H_{26}O_2$	1.01	0.52
Methyl heptadecenoate	14.34	1.10	55	282	$C_{18}H_{34}O_2$	1.41	-
Methyl-7,10-octadecadienoate	16.68	1.28	67	294	$C_{19}H_{34}O_2$	0.46	0.18
Methyl-9-octadecenoate (methyl oleate)	16.84	1.29	55	296	$C_{19}H_{36}O_2$	11.14	9.23
Methyl-10-nonadecenoate	20.06	1.55	55	310	$C_{20}H_{38}O_2$	0.28	-
Subtotal						**14.30**	**9.93**
Total identified compounds						**76.79%**	**89.35%**

*RR_t: Retention time relative to Squalene

3.2. b. ABTS scavenging activity

A decolorization assay called the ABTS scavenging capacity method assesses the antioxidants' ability to react directly with ABTS radicals produced by a chemical process[42]. PEE2 showed an impressive ability to scavenge the ABTS radical with IC_{50} value of 12.68±1.08 µg/mL with 91.76 % scavenging effect at concentration 1 mg/L compared to ascorbic acid (IC_{50} value of 10.65±0.81 µg/mL) (Figure 2B; Table 3). PEE1 showed a moderate activity with IC_{50} value of 173.98±8.23 µg/mL with 79.48 % scavenging effect at concentration 1 mg/L.

3.3. Evaluation of anti-inflammatory activity of PEE via inhibition of COX-1 and COX-2 enzymes

The anti-inflammatory activity of PEE was *in-vitro* evaluated by inhibiting the cyclooxygenases enzymes COX-1 and COX-2, which catalyze the

conversion of free arachidonic acid to prostaglandin H2 (PGH2), the committed step in prostaglandin (PG) formation. PGH2 is converted into the other PGs or thromboxane (TxA2) by specific synthases. NSAIDs inhibit both forms of COX at approximately equivalent concentrations[43, 44].

PEE1 and PEE2 exhibited dose-dependent inhibition effect on these two cyclooxygenases enzymes, the highest inhibition capacities of COX-1 were 74% and 75% at 100 µM and COX-2 was 77% at 100 µM for both extracts, additionally the IC_{50} values of COX-1 and COX-2 were 0.67±0.06, 0.7±0.01 µM and 0.049±0.001, 0.103±0.006 µM for PEE1 and PEE2 in comparison with the reference drug indomethacin which exhibited 74% inhibition activity for both cyclooxygenases and with IC_{50} values of 0.6±0.1 and 0.079±0.001 µM for COX-1 and COX-2, respectively (Figure 3; Table 3).

3.4. Evaluation of anti-diabetic activity through α-amylase inhibition activity

PEE1 and PEE2 inhibited α-amylase enzyme with inhibitory property 68.27 and 76.02% at conc. 1mg/mL and with IC_{50} values of 107.16±4.57 and 41.81±2.85 µg/mL. Acarbose revealed 96.73% inhibitory property of α-amylase enzyme at conc. 1 mg/mL (IC_{50} value of 14.54±0.86 µg/mL) (Figure 4; Table 3).

3.5. Molecular docking study

The binding energy of acarbose was -8.98 Kcal/mol, against human α-amylase protein. Thirteen hydrogen bonds were observed by interaction with Ala106, Asn105, Thr163, Gln63, Trp59, His299, Asp300, Glu233, Arg195, and His201 (Figure 5A). α-Amyrin methyl ether exhibited a binding energy -6.61 Kcal/mol, with 13 hydrophobic π-interactions were observed with Trp59, Leu162, His305, Ile235, His201 and Ala198 (Figure 5B).

Moreover, arundoin exhibited a binding energy of -6.32 Kcal/mol. Seven hydrophobic π-interactions were observed with Trp59, His305, Leu165, and Val107 (Figure 5C). Cycloartenol showed a binding energy -7.55 Kcal/mol. It formed 10 hydrophobic π-interactions with Tyr62, Leu165, Trp59, Val107, Ala106, Leu162 and His305, moreover, it formed couple of hydrogen bonds with Asp300 and Glu233 at distances of 2.94 and 2.41 Å, respectively (Figure 5D), while 24-methylenecycloartanol exhibited a binding energy -7.10 Kcal/mol. It formed 15 hydrophobic π-interactions with Ala198, Leu162, His305, Ile51, Val107, His101, Trp58, Tyr62, Trp59, and Leu165, additionally a hydrogen bond was obtained by interaction with Glu233 with a distance of 2.20 Å (Figure 5E).

4. DISCUSSION

Free radicals are highly unstable and include reactive chemical units with a specific property having one or more unpaired electrons[45]. Sources of free radicals in cells and their surroundings include a variety of substances such as ROS, smoking, chemicals, radiations, the creation of neutrophils and macrophages and industrial effluents. Numerous studies have demonstrated the significant role free radicals play in causing damage to DNA, lipids, and proteins, which can lead to a variety of diseases such rheumatoid arthritis, diabetes mellitus, and cancer[46]. Oxidative stress takes place when there is an imbalance between the body's antioxidant capacity and the quantity of free radicals.

A class of metabolic diseases known as diabetes mellitus (DM) is characterized by hyperglycemia (increased blood glucose levels) and deficiency in the pancreatic synthesis or activity of insulin[47]. In general, Type 2 diabetes mellitus (T2DM) is the diagnosis for 90–95% of diabetic cases[48]. Obesity, insulin resistance and pancreatic β-cell dysfunction are the major signs of T2DM[49,50]. In addition to the pancreas, other organs were affected including the kidneys, liver, brain, stomach and eyes [51].

During the first stages of the illness, the pancreatic β-cells produce more insulin to counteract insulin resistance, which weakens and malfunctions the β-cells and impairs insulin secretion, resulting in hyperglycemia[52]. It is becoming more obvious that oxidative stress and inflammation are the primary processes causing cellular damage in T1DM and T2DM diabetic complications[53]

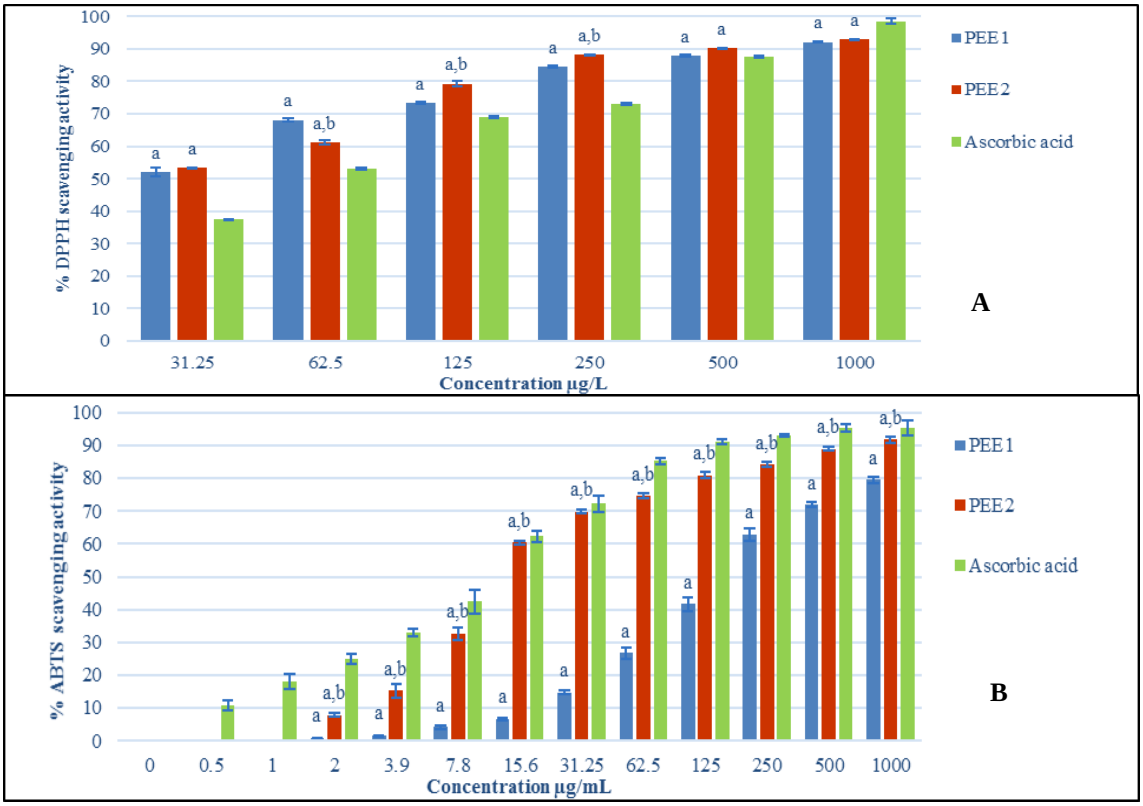

Figure 2. *In-vitro* antioxidant activity of PEE1, PEE2 of *D. decaryi* and *D. leptocheilos* leaves and ascorbic acid (reference drug) using: DPPH radical scavenging activity (A) and ABTS radical scavenging activity (B). The results are expressed as mean ± SD (n=3). a: Statistically significant from the standard drug, b: PEE2 statistically significant from PEE1 at P < 0.05.

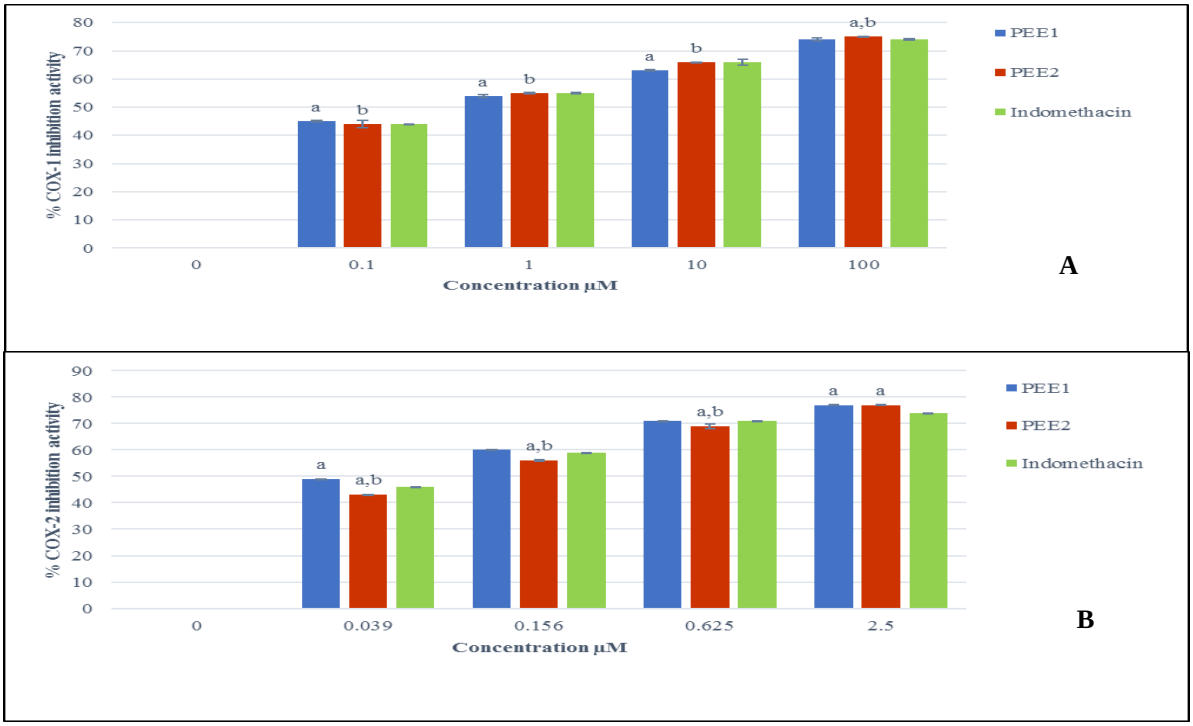

Figure 3. *In-vitro* anti-inflammatory activity of PEE1, PEE2 of *D. decaryi* and *D. leptocheilos* leaves and indomethacin (reference drug) using: COX-1 (A) and COX-2 (B) inhibition activities. The results are expressed as mean ± SD (n=3). a: Statistically significant from the standard drug, b: PEE2 statistically significant from PEE1 at P< 0.05.

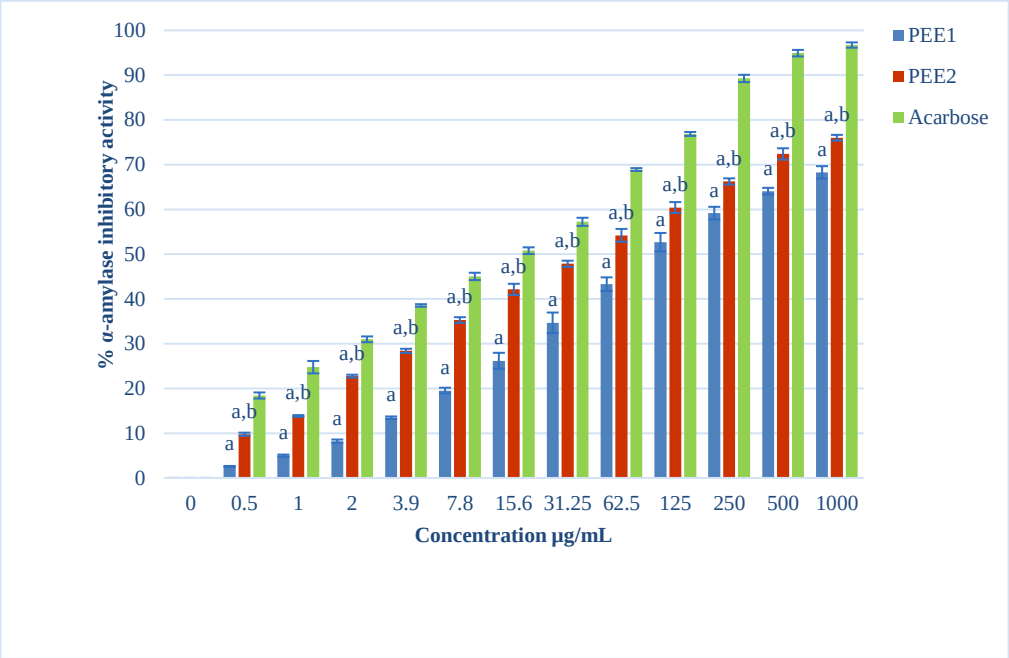

Figure 4. *In-vitro* α-amylase inhibitory activity of PEE1, PEE2 of *D. decaryi* and *D. leptocheilos* leaves and acarbose (reference drug). The results are expressed as mean ± SD (n=3). a: Statistically significant from the standard drug, b: PEE2 statistically significant from PEE1 at $P < 0.05$.

Table 3. IC_{50} values of PEE1, PEE2 of *D. decaryi* and *D. leptocheilos* leaves against DPPH, ABTS, COX-1, COX-2, and α-amylase inhibition.

Activity	**IC_{50} of Plant extract/ Standard**		
1.Anti-oxidant	**PEE1**	**PEE2**	**Standard**
a. DPPH	29.8±0.62[a] µg/mL	28.5±1.43[a] µg/mL	38.72±0.26 µg/mL (Ascorbic acid)
b. ABTS	173.98±8.23[a] µg/mL	12.68±1.08[b] µg/mL	10.65±0.81 µg/mL (Ascorbic acid)
2. Anti-inflammatory			
a. COX-1	0.67±0.06 µM	0.7±0.01 µM	0.6±0.1 µM (Indomethacin)
b. COX-2	0.049±0.001[a] µM	0.103±0.006[a,b] µM	0.079±0.001 µM (Indomethacin)
3. Anti-diabetic			
α-amylase inhibitory activity	107.16±4.57[a] µg/mL	41.81±2.85[a,b] µg/mL	14.54±0.86 µg/mL (Acarbose)

[a] Statistically significant from the standard drug, [b] PEE2 statistically significant from PEE1 at $P < 0.05$ using one-way ANOVA followed by Tukey's multiple comparisons test. ANOVA: analysis of variance; SD: standard deviation.

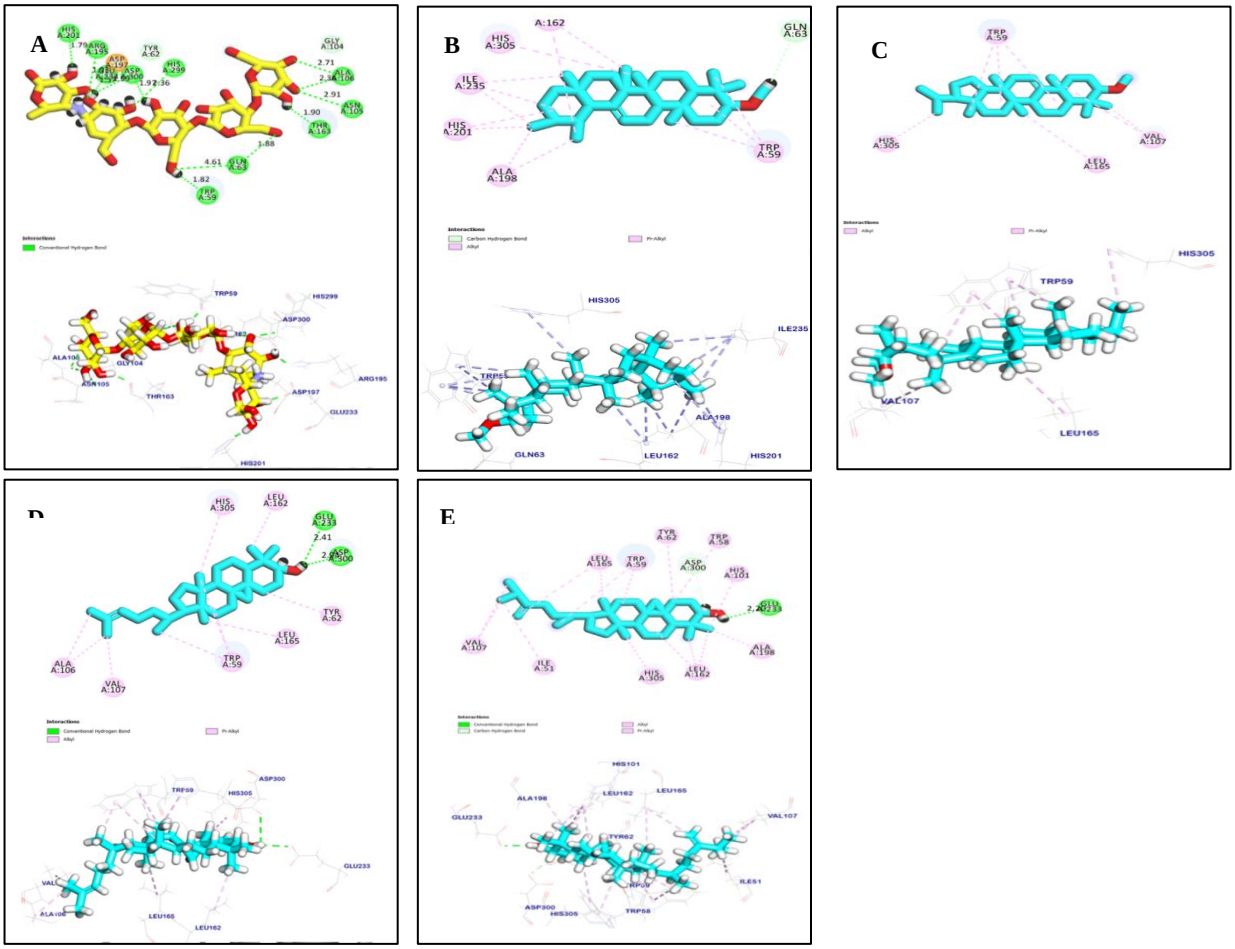

Figure 5. 2D and 3D orientations of docking simulation for reference drug: Acarbose (A), α-Amyrin methyl ether (B), Arundoin (C), Cycloartenol (D) and 24-Methylenecycloartanol (E) against human α-amylase protein (PDB 2qv4).

Oxidative stress is a significant component in the development of insulin resistance and β-cell dysfunction[54]. Not only diabetes-related oxidative stress alters an enzymatic system, results in lipid peroxidation, impairs glutathione (GSH) metabolism and reduces vitamin C levels[55], but also elevates the levels of pro-inflammatory proteins with infiltrated macrophages releasing inflammatory cytokines which in turn causes both local and systemic inflammation[56] and is a known mechanism in the development of diabetes complications[57].

Non-steroidal anti-inflammatory drugs (NSAIDs) are used routinely in clinical management of inflammation[58]. It is believed that these drugs' mode of action is dependent on COX enzyme inhibition[59]. The cyclooxygenase enzyme (COX) has two primary isoforms: COX-1 and COX-2. Normal tissues contain the structural enzyme COX-1, which is responsible for preserving fundamental physiological processes like the stomach's cytoprotection and the kidneys' vasodilation. Conversely, COX-2 is an inducible enzyme; it is rarely produced in normal physiological conditions but is overexpressed in inflammation and tumors. COXs are key enzymes in the conversion of arachidonic acid to the pro-inflammatory mediators, prostaglandins and other eicosanoids. It was hypothesized that if COX-2 could be inhibited without inhibiting COX-1, many of the side effects associated with NSAIDs use could be avoided[60]. Furthermore, it has been documented that expensive and selective COX-2 inhibitors have side effects. Alternatively, medicinal plants can be used to create safer and less expensive medications[61].

It is commonly known that DPPH scavenging radicals have extraordinary scavenging power. The

current study found that the two species under investigation had a higher degree of DPPH quenching potential. This suggests that PEE might have advantageous antioxidants that can eliminate free radicals from the body and minimize the potential of oxidative stress.

Terpenes, for example, are recognized components of plant tissues that possess remarkable biological activities, including anti-inflammatory, anti-viral, anti-bacterial, antifungal, anti-hyperglycemic, spermicidal, anti-allergic, and cardiovascular protective properties[62]. They are classified based on the number of carbons to monoterpenes, sesquiterpenes, diterpenes, tri- and tetraterpenes. They are highly effective in treating disorders linked to oxidative stress through the modulation of the endogenous antioxidant system and control ROS scavenging pathway[63].

Numerous *in-vivo* and *in-vitro* investigations have confirmed their multidirectional features: anti-oxidant[64], anti-inflammatory[65], anti-diabetic[66], anti-cancer[67], anti-atherosclerotic[68] and antiviral[69]. Since triterpenes represent the majority of the USF in this investigation, their presence in the extracts may have contributed to the biological activities that were examined. Squalene, one of the identified constituents, is the biological precursor for the synthesis of secondary metabolites such as sterols, hormones, or vitamins[70] and other triterpenes[71,72].

Squalene -the most abundant constituent in USF1and USF2 (18.23 % and 17.99 %)- possessed a strong antioxidant activity which was attributed to the abundance of double bonds in its structure[73]. It was also found that squalene exerted an anti-inflammatory effect and could be used as UV protective agent in cosmetic products by the reduction of ROS levels[74]. Widyawati *et al* stated the *in-vivo* and *in-silico* assays of the anti-diabetic activity of squalene[75,76].

Phytol, is an acyclic diterpene that possessed strong anti-oxidant activity that may be due to the hydroxyl group (OH) present in the molecule which transforms free radicals into less reactive species by donating hydrogen atoms with an unpaired electron ($H^{\cdot}$)[77,78]. Silva *et al* suggested that phytol reduced inflammation by preventing neutrophil migration, which was partially attributed to decreased levels of TNF-α and IL-1β as well as oxidative stress[79]. It might be useful in treating metabolic diseases and insulin resistance that co-exist with diabetes and/or obesity, using an insulin-resistant diabetic rat model, the *in-vivo* effect of phytol and its modulatory activity on pioglitazone was evaluated[80].

Additionally, the anti-diabetic biological action of phytol was validated by molecular docking studies of phytanic acid, an active metabolite of phytol, which demonstrated good alignment with the experimental results. Lower dosages of anti-diabetic medications, such as thiazolidinediones (TZDs), could be used with phytol to preserve the entire therapeutic efficacy with fewer side effects[80]. Several agonists commonly used to treat T2DM was shown to be activated by phytanic acid in previous *in-vitro* investigations[81-83]. β-sitosterol, stigmasterol, campesterol, stigmastanol, and campestanol are some of the major phytosterols that have been researched for their pharmacological relevance. A study found that β-sitosterol had an anti-inflammatory effect when BV2 cells were exposed to LPSby lowering the production of pro-inflammatory markers as cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), inducible nitric oxide (*i*NOS), and interleukin-6 (IL-6)[84]. Additionally, it was discovered to be a strong α-amylase inhibitor in the treatment of diabetes mellitus[85].

Cycloartenol possessed numerous pharmacological properties such as anti-oxidant, anti-inflammatory, antitumor, antibiosis and anti-Alzheimer's disease[86]. According to Nair *et al*, cycloartenol and 24-methylenecycloartanol had the ability to lower blood sugar levels. Even at greater dosages, they did not cause hypoglycemia shock and instead kept blood sugar levels near to normal control levels. Additionally, they possessed the ability to restore the altered serum biochemical parameters of diabetic animals to a normal state[87].

The computational (*in-silico*) technique has been widely employed as an effective tool for virtual biological screening during the drug design and discovery phases. Using this procedure, natural compounds' estimated biological activities and affinities are assessed. Through a number of recent applications, the nature of targeted locations and the identification of various compounds as activators or inhibitors have been better understood. In this study, some of the identified components were evaluated for their anti-diabetic activity through molecular docking simulation with human α-amylase protein. AutoDock Vina, molecular docking software, was used to simulate the binding modes of human α-amylase protein with some selected phytoconstituents (ligands) based on their abundances in both USF, acarbose the anti-diabetic

standard drug and the co-crystalized ligand was used for comparison.

Acarbose (ΔG = -8.98 Kcal/mol) formed 13 hydrogen bonds with Ala106, Asn105, Thr163, Gln63, Trp59, His299, Asp300, Glu233, Arg195, and His201. Docking interaction revealed cycloartenol and 24-methylenecycloartanol were the most well nested compounds into the active site of human *α*-amylase protein. Cycloartenol with binding energy (ΔG = -7.55 Kcal/mol) formed 10 hydrophobic π-interactions with Tyr62, Leu165, Trp59, Val107, Ala106, Leu162 and His305, moreover it formed couple of hydrogen bonds with Asp300 and Glu233 at distances of 2.94 and 2.41 Å, while 24-methylenecycloartanol exhibited a binding energy (ΔG = -7.10 Kcal/ mol) formed 15 hydrophobic π-interactions with Ala198, Leu162, His305, Ile51, Val107, His101, Trp58, Tyr62, Trp59, and Leu165, additionally a hydrogen bond was obtained by interaction with Glu233 with a distance of 2.20 Å, respectively.

The present *in-silico* molecular based docking study matches the previous study that took place by Nair *et al* and can give attention to these two compounds and their probable efficacy in the treatment of T2DM[87]. Both *α*-amyrin methyl ether and arundoin exhibited a binding energy -6.32 Kcal/mol that revealed the good binding affinities of them to human *α*-amylase protein giving them a chance for further investigation for their anti-diabetic activity. *α*-Amyrin methyl ether showed 11 π-hydrophobic interactions with Ala106, Leu165, Trp59, Trp58 and His305, while arundoin showed 7 π-hydrophobic interactions were observed with Trp59, His305, Leu165, and Val107.
Several studies indicated that fatty acids anti-inflammatory capabilities were connected to the reduction of TNF-*α*, IL-1*α*, IL-1*β*, and IL-6 levels[88]. It was established that the saturated fatty acid palmitic acid could affect T cells in particular or inhibit phospholipase A2, which was responsible of releasing lysophospholipids and arachidonic acid, the precursor to potent inflammatory mediators like prostaglandins and leukotrienes[89]. Oleic acid, sometimes referred to as Omega 9, is a fatty acid that had the ability to reduce the expression of inflammatory molecules and inhibited endothelial cell stimulation[90]. Furthermore, in LPS-stimulated microglial cells, oleic acid suppressed the release of pro-NO and prostaglandin E2 mediators as well as the synthesis of NOS and COX-2. The anti-inflammatory effect of oleic acid may be due to its role in ROS suppression [91]. *In-silico* molecular docking and dynamics studies indicated that palmitic and oleic acid are potential *α*-amylase enzyme inhibitors[92].

Another saturated fatty acid, tetradecanoic acid showed maximum of 83% inhibition towards *α*-amylase enzyme at 1.12 μM[93], so its presence in an appreciable amount in PEE2 (31%), in-addition to arundoin (5.44%) and cycloartenol (2.32%) could be one of the reasons of its higher anti-diabetic activity than PEE1. PEE1 exhibited significant COX-2 inhibitory activity than PEE2 and indomethacin which gives a chance for this extract to be further analyzed.

5. CONCLUSIONS

This study revealed that petroleum ether extracts of the studied plants possess secondary metabolites, which are possibly responsible for its anti-oxidant, anti-inflammatory and anti-diabetic properties. The *in-silico* molecular docking study showed that *α*-amyrin methyl ether, arundoin, cycloartenol and 24-methylenecycloartanol, can inhibit *α*-amylase enzyme, so these compounds can be used in developing new drugs that can aid in the treatment of T2DM. Further studies including *in-vivo* studies are essential to assess the efficacy of the bioactive compounds as drug candidates for T2DM.

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Ethical Statement: NA

Author Contribution: Yousra M. El -Dakroury and Reda S. Mohammed: Conceptualization, collecting the data and plant material, running laboratory works, investigation, software, formal analysis and interpretation of data, writing & editing the manuscript, Aisha H. Abou Zeid: Supervision, proposed the conception of the study designed the experiments, interpretation of data, critical revision and final editing of the manuscript; Reda S. Mohammed: Validation, visualization and supervision, Atef A. El-Hela: Supervision, worked on the overall planning, critical revision and final editing of the manuscript; Abeer S. Temraz: Supervision, worked on the overall planning, critical

revision and final editing of the manuscript. The final version of the manuscript has been reviewed and approved by all authors.

List of Abbreviations:
USF: Unsaponifiable fraction
SF: Saponifiable fraction
ROS: Reactive Oxygen Species
DM: Diabetes Mellitus
SD: Standard deviation
Rt: Retention time
RRT: Relative retention time
GSH: Glutathione
COX-1 & COX-2: Cyclo-oxygenases ½

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