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# Anti-Alzheimer potential of *Solanum lycopersicum* seeds: in vitro, in vivo, metabolomic, and computational investigations

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## Abstract

**Background** *Solanum lycopersicum Linn.* (Tomato, Family Solanaceae) is one of the fruits that are most consumed worldwide. The current research intends to emphasise the possibility of positive and therapeutic effects of *S. lycopersicum* seed extract (SLSE) on Alzheimer's disease's neurodegeneration effects being reversed in a study utilising rats exposed to aluminium chloride. Investigations were done on the cholinesterase and antioxidant in vitro activity of SLSE. Rats with Alzheimer's disease were given SLSE, and donepezil (500, and 10 mg/kg.b.wt., daily for six weeks, respectively) to test SLSE biological activity. Beam-balance and T-maze tests, as well as serum levels of AChE, norepinephrine, dopamine, serotonin, IL-6, glycated end product, BDNF, MDA, TAC, and GSH were assessed, accompanied with histological investigation. To impact the effectiveness of this extract, bioinformatics study was validated.

**Results** Crude SLSE showed in vitro DPPH scavenging and AChE inhibition activities, indicating the extract might have anti-Alzheimer potential, which was validated using an aluminium-intoxicated rat model, in vivo. In Alzheimer's rats, in vivo studies showed considerable improvements, as seen by improved beam balance, and T-maze tests and decreased serum levels of AChE, norepinephrine, dopamine, serotonin, IL-6, glycated end product, BDNF, and MDA, with increasing in TAC, and GSH levels. Brain tissue histological tests revealed a largely typical pattern of collagen fibre distribution. LC–HRESIMS metabolomic profiling of crude SLSE identified 33 compounds. Furthermore, the bioinformatics study discovered 378 targets related to the major identified compounds, of which only 133 were related to Alzheimer's and memory disorders, with APP, AChE, and PSEN2 targets which were marked as the top genes. Gene enrichment analysis identified the arachidonic acid metabolism and PPAR signalling pathway as the biological pathways enriched by all the gene sets under investigation.

**Conclusion** As a result, the study findings are expected to pave the way for the creation of dietary supplements for Alzheimer's disease management.

**Keywords** AChE, Alzheimer, Metabolomics, Tomato seeds

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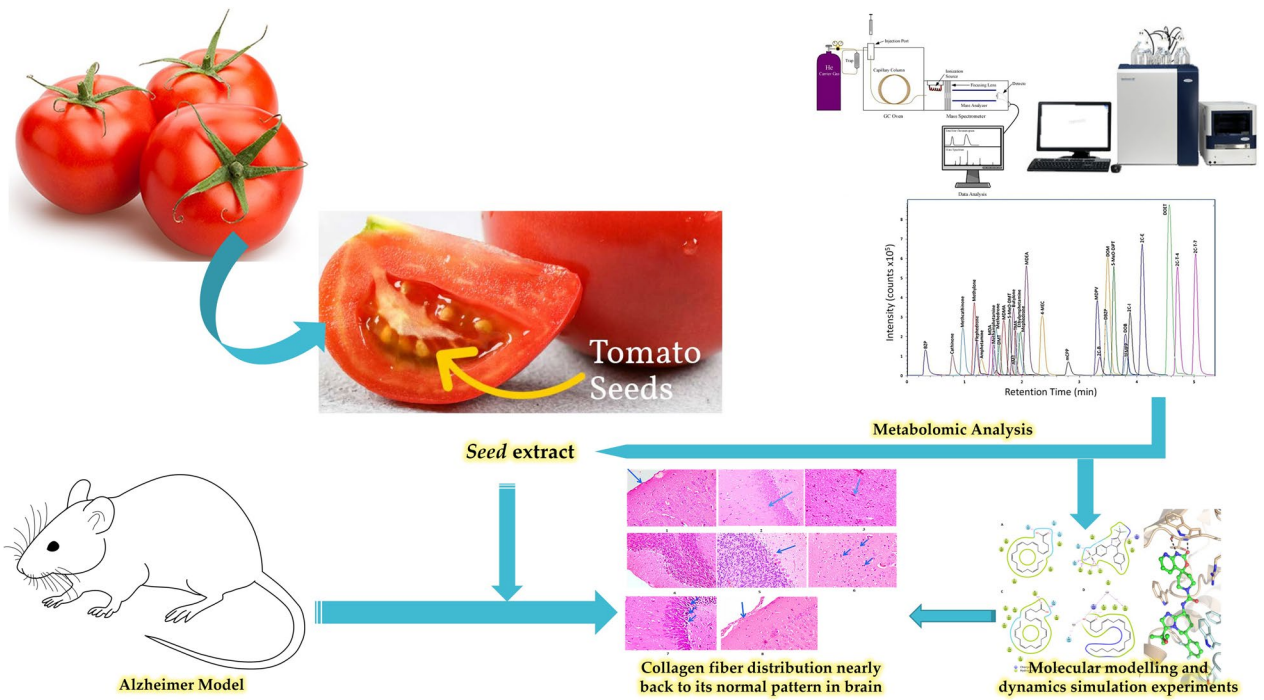
**Graphic abstract**




## 1 Background

The slow deterioration of neuronal structure or function that characterises neurodegenerative illnesses can result in neuronal death [1]. Progressive cognitive, functional, and behavioural alterations brought on by neurodegenerative diseases frequently manifest as dysfunctional motor and cognitive impairments. Many studies have been conducted on the most prevalent neurodegenerative conditions, including Alzheimer's disease (AD) [1]. Over the world, neurodegenerative disorders place a significant economic burden. With age, the likelihood of developing a neurodegenerative disease rises sharply [1]. As a result, as the population ages, it is anticipated that more people will become impacted, necessitating therapy development options that can prevent or delay the degenerative process. Brain derived neurotrophic factor (BDNF) is necessary for the formation and survival of neurons. The main controllers of synaptic plasticity, which is crucial for learning and memory formation, are BDNF and its receptors [1]. Many neurodegenerative illnesses have been found to alter BDNF levels and signalling pathways [1]. Moreover, the creation of medications to treat neurological illnesses uses BDNF as a key biological target [1].

Interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) are inflammatory mediators that have been linked to AD. TNF-α has been shown to mediate memory impairment and peripheral glucose intolerance in AD mouse models by interfering with insulin signalling and turning on cellular stress pathways [2]. In AD brains, IL-6 contributes to the development of early-stage amyloid plaques and has been linked to tau phosphorylation, synapse loss, and learning deficits in mice [2]. Despite some disagreement in the published works, past meta-analyses have discovered that patients with moderate cognitive impairment and AD have higher levels of IL-6 in their cerebrospinal fluid (CSF) and plasma compared to controls [2]. A causal relationship between IL-6, cognitive impairments, and peripheral metabolic abnormalities in AD has not yet been established, even though this supports a linkage between IL-6 and AD pathogenesis.

The amyloid peptide (Aβ), which results from the modification of the amyloid precursor protein (APP) by β- and ɣ-secretase, builds up inside neuronal cells as an amyloid deposit. A pathologic feature of Alzheimer's disease is the brain deposit [3]. Glyceraldehyde-derived advanced glycated end products (AGEs) have been recognised as a key source of neurotoxicity in AD. Oxidative stress controls the formation of Aβ and APP processing [3]. Moreover, Aβ causes the death of brain cells through reactive oxygen species (ROS) [3]. AGEs control amyloid buildup

and Aβ aggregation [3]. Our prior research indicated that AGEs formed from glyceraldehyde boost the production of APP and Aβ through ROS, which ultimately results in cell death [3]. Yet, it is still unknown what role AGEs play in the onset of Alzheimer's disease.

Patients experience a deterioration in their physical and cognitive abilities as they age, which may be related to a higher vulnerability to the cumulative effects of oxidative stress and inflammation [4]. Only symptomatic treatments are available for AD as of now. Three AChE inhibitors, donepezil, rivastigmine, galantamine, and memantine, are currently available and approved for the treatment of mild to moderate AD, however they come with a number of side effects [5]. The "one change, one disease, one drug" paradigm is no longer appropriate because AD is a typical example of a complicated multifactorial disease [6]. There is a high demand for the discovery of novel natural products with the potential to protect against or even prevent this neurodegenerative disease, slow down or even stop the disease's progression and deterioration in its early stages, and/or lessen its side effects, all of which could promote healthy ageing [7].

Given the critical functions of antioxidant chemicals in the treatment and prevention of illnesses connected to oxidative stress that is produced by free radicals, research on plants with antioxidative potential has gained growing attention [8, 9]. Antioxidants do, in fact, serve to scavenge free radicals that can interfere with cellular genetic material and destroy cellular membranes [8]. Natural products provide excellent chances to slow the progression and symptoms of AD [8–12]. The antioxidant, anti-inflammatory, anticholinesterase, and anti-amyloidogenic properties of the plants as *Curcuma longa*, *Bacopa monnieri*, *Convolvulus pluricaulis*, *Centella asiatica*, *Ginkgo biloba*, *Zingiber officinaleis*, *Allium sativum* or their plant-derived natural compounds such quercetin, berberine, epigallocatechin-3-gallate, huperzine A, resveratrol, and luteolin are of particular interest [13, 14].

Nonetheless, the seeds of tomato plants (*S. lycopersicum* L., also known as *Lycopersicon esculentum*) are a valuable source of nutrients, including proteins, amino acids, fatty acids, fibre, and active substances with noteworthy nutraceutical qualities [1]. Phytochemicals such as gallic acid, *trans*-cinnamic acid, and quercetin are abundant in tomato seeds. Using an ethanolic extract and lycopene by hexane extraction, it was possible to acquire a significant amount of total phenolic components, total flavonoids, and increased antioxidant activity. It was discovered that a small dose of 500 ppm tomato by-product extract was sufficient to regulate lipid peroxidation and could improve oil stability [1]. Moreover, tomato seeds contain unsaponifiable substances such as desmethyl-sterols and α- and ɣ-tocopherols. Along with the tocopherols, delta-5-avenasterol, the desmethyl sterols, and citrostadienol exhibit considerable tomato seed antioxidant activity. The results of investigations conducted on tomato seeds in vitro and in vivo using animal models and human cell lines support their potential health advantages, including their usage as potent antioxidant, antiplatelet, anticancer, antibacterial, neuroprotective, and antimutagenic agents. Because of their outstanding nutritional and nutraceutical foundation, tomato seeds can be used as a functional food ingredient [1]. Further, it was declared that tomato seed can attenuate neurotoxicity and rotenone (mitochondrial complex I blocker) induced oxidative stress in mice [15]. The oral dose of tomato seed in mice offset rotenone-induced oxidative deterioration, reinstated glutathione levels and stimulated the antioxidant defence system (glutathione peroxidase, superoxide dismutase). It also lowered the activity of rotenone-induced acetylcholinesterase and revived dopamine in the striatum [15]. Intriguingly, tomato seed was shown to effectively restore mitochondrial complex activities and maintain their redox state. Researchers have indicated that oral administration of tomato seed exhibits a high propensity to offer neuroprotection against neurotoxicants and other neurodegenerative ailments, such as Parkinson's disease [15].

Bioinformatics is a cutting-edge tool that helps with the development of new drugs based on virtual genetic and pathway enrichment analysis. This technique allows researchers to directly target a particular pathway, thus reducing the need for blind trials on different pathways. So, bioinformatics research should be incorporated into every scientific study to identify the top pathway responsible for the treatment of a specific disease [16–18].

An important risk factor for a number of age-related neurological diseases, including AD, is aluminium (Al) [19]. Aluminium chloride, a neurotoxic substance, builds up in the brain, where it damages ionic, cholinergic, and dopaminergic neurotransmission [19]. To open the door for potential early therapeutic applications, the current research intends to emphasise the possibility of positive and therapeutic effects of SLSE on the reversal of the neurodegenerative symptoms of Alzheimer's disease in a model of Al-intoxicated rats. This could result in a simple, noninvasive, dependable, inexpensive, and reproducible blood-based panel of circulating diagnostic biomarkers. Additionally, metabolomic analysis and a bioinformatic study of the extract were performed to pinpoint the chemical constituents that are responsible for the anti-Alzheimer action.

## 2 Methods

### 2.1 Chemicals, reagents, extraction of SLSE

Solvents were purchased from El-Nasr Company for pharmaceuticals and chemicals for use in this work (Egypt). Donepezil, reagents, and all of the kits for the biological study were bought from Sigma Company in the United States. Aluminium chloride ($AlCl_3$) was acquired from CDH, India. 100 g of the seeds were macerated in 200-mL portions of 70% ethanol over the course of 3 days at room temperature before being concentrated and dried in a rotary evaporator (Buchi Rotavapor R-300, Vernon Hills, USA) under vacuum at 50 °C to yield twenty-gram dry extract, which was then stored at 4 °C for further research [9, 12, 20–26].

### 2.2 SLSE in vitro DPPH radical scavenging activity assay

The radical scavenging activity of SLSE was tested using the stable radical DPPH assay [27]. Specifically, two mL of DPPH solution, freshly prepared in a concentration of 20 µg/mL, were combined with 1 mL of SLSE at various concentrations as follow 0.01, 0.05, and 0.1 µg/mL dissolved in $C_2H_5OH$ absolute, and then for 30 min, the mixture was incubated at room temperature in the dark. The absorbance at 517 nm was measured using a UV–Vis Jenway 6003 spectrophotometer. Absolute ethanol served as a blank, while ascorbic acid served as a positive control. To calculate the DPPH radical scavenging activity, the following equation was utilised:

$$\%\text{DPPH scavenger activity} = \frac{\text{absorbance of blank} - \text{absorbance of tested sample}}{\text{absorbance of blank}} \times 100.$$

### 2.3 SLSE in vitro cholinesterase activity assay

In accordance with the directions provided by the manufacturer, the cholinesterase activity of SLSE was calculated [28]. A 0.2 mL solution of SLSE was quickly combined with 3 mL distilled water. The solutions were made at various concentrations as follows 10, and 20 µg/mL dissolved in absolute ethanol. A 3 mL addition of phosphate solution followed. A pH metre was used to measure the pH (pH-1). Then, 0.12 mL of a 7.5% acetylcholine iodide solution was added. The mixture was placed in a water bath set at 37 °C and allowed to incubate for 30 min. Subsequently, the pH values (pH-2) were determined for the mixtures. The pH change within 30 min was then estimated by comparing pH-1 and pH-2. The difference indicates the level of cholinesterase activity in the sample, i.e. ΔpH/30 min = pH1–pH2/(pH of blank*).

### 2.4 In vivo anti-Alzheimer activity

#### *2.4.1 Animals*

The male Wistar albino rats (150 ± 10 g), were housed in groups of ten rats per cage and kept in a controlled environment at 26–29 °C. To help them adjust to life under normal conditions, for one week, they had a set schedule of light and dark, along with unlimited access to food and water (ethical approval no: 022–370).

#### *2.4.2 Induction of $AlCl_3$-induced Alzheimer's disease*

$AlCl_3$ was dissolved in water for oral delivery, 100 mg/kg of $AlCl_3$, and rats received orally each day for eight weeks a dose of 0.5 mL/100 g b.wt. [29].

#### *2.4.3 Acute toxicity study*

To determine the acute toxicity of crude SLSE, serial concentrations of five hundred to five thousand mg/kg b.wt. in four rats per group (24 rats in all, across all groups) were utilised.

#### *2.4.4 Experimental design, brain tissue sampling preparation*

Four groups of ten rats each were formed from a random division of 40 rats. Group 1 consisted of healthy rats. Rodents in Group 2 were used as AD models, and rodents received $AlCl_3$ orally. Group 3: For 6 weeks (1/10 $LD_{50}$), the AD rats were given crude SLSE (500 mg/kg.b.wt.), daily. The AD rats in Group 4 were given the conventional medication donepezil (10 mg/kg b.wt., daily for 6 weeks) [30].

Under a light thiopental anaesthetic, animals that had been fasting overnight were sacrificed [31]. In a nutshell, rats were anaesthetised by being injected with thiopental (30 mg/kg b.wt. of container volume) before being slaughtered by decapitation under light anaesthesia. The brains of each rat were rapidly dissected, washed with isotonic saline solution, and dried out on filter paper for drying. The brain was weighed and homogenised in an ice-cold solution of 50, 300 mM-Tris–HCl, with sucrose, respectively (pH 7.4) to produce a 10%w/v, homogenate [29, 32]. For 10 min, this homogenate was centrifuged at 4 °C, 1400 g. The resulting solution was maintained at 80 °C for subsequent biological processes.

#### *2.4.5 Behavioural assessment*

Evaluation of Motor Coordination and Cognitive Capabilities T-Maze is built locally at the National Research

Centre (NRC). When the therapy period is over, rats cognitive function and spatial memory damage were assessed after two months of chronic $AlCl_3$ exposure [33]. The beam balancing test was used to evaluate motor skills [34].

#### *2.4.6 Estimation of brain neurotransmitters*

A quantitative enzyme-linked immunosorbent assay (ELISA) was used to quantify serum acetylcholine esterase (AChE), according to Engvall E. Perlman, 1971 [35]. According to Giday et al., 2009, the quantities of norepinephrine, serotonin (5-HT), and dopamine (DA) in the brain were evaluated using HPLC-ED [36]. The amounts of IL-6, aglycated end products, with BDNF were assessed using kits of ELISA as directed by the producer [36]. Serum TAC was assessed using the colorimetric method developed by Koracevic et al., 2009 [37]. MDA, and GSH were determined according to published literature [38, 39].

#### *2.4.7 Histopathological studies*

All of the animals in each group had their brains removed, and they were all fixed in neutral 10% buffered formalin. 5 mm thick paraffin slices were created for histological examination under a light microscope (Olympus BX43), stained with H&E, and photographed using the cellsSens Dimension program (Olympus) attached to an Olympus DP27 camera [40]. The histological investigation was performed by an expert pathologist, who was not aware of the treatments. The following neuropathologic damage was graded (0–4): (0) indicated no changes, (1) suggested a 10% impacted region, (2) indicated a 20–30% affected area, (3) indicated a 40–60% affected area, and (4) indicated a 60% or greater affected area [41].

### 2.5 Metabolomic analysis procedure

For mass spectrometry analysis, SLSE was produced (1 mg/mL). As stated by Abdelmohsen et al. 2014, LC–HRESIMS was used to perform a metabolic study on the obtained extract [42]. For this purpose, a quadrupole time-of-flight hybrid mass spectrometer Waters Synapt G2 HDMS linked to an Acquity Ultra Performance Liquid Chromatography system was used. High-resolution mass spectrometry was carried out utilising both positive and negative ESI ionisation modes, a spray voltage of 4.5 kV, a capillary temperature of 320 °C, and a mass range of *m/z* 150–1500. The MS dataset was analysed, and the data were obtained using MZmine 2.20 and the predefined parameters [43]. A chromatogram builder and chromatogram deconvolution were used to identify mass ion peaks. The local minimum search algorithm was taken into consideration, and grouper's isotopic peaks were used to identify isotopes. To display missing peaks, the gap-filling peak finder was utilised. An adduct search as well as a complex search were carried out. Afterwards, peak identification and the prediction of the chemical formula were applied to the processed data set. The corresponding extract positive and negative ionisation mode data sets were replicated against the DNP (Dictionary of Natural Products) databases [44, 45].

### 2.6 Bioinformatic study

#### *2.6.1 Plant-metabolite network*

A plant-metabolite network was built based on the metabolomic profiling of *S. lycopersicum* seeds using LC–HRESIMS, which dereplicated 33 compounds.

#### *2.6.2 Metabolite-target network*

The databases PubChem [11, 46], which was last accessed on November 11, 2022, while Swiss Target Prediction, which was last retrieved on November 16, 2022, were used to determine the targets of the major metabolites in *S. lycopersicum* [47, 48].

#### *2.6.3 Protein–protein interactions*

The functional association between all identified targets (genes) was predicted in a network form and visualised using the online database STRING (https://string-db.org/cgi/network?taskId=bgI0vTh97E1E&sessionId=bYFdOL7xOkeV) with a median confidence of 0.4 [49], last accessed on 17–11-2022.

#### *2.6.4 Targets-Alzheimer and memory disorders network*

DisGeNet was used to gather the genes linked to Alzheimer's and memory issues [50]. The genes linked to Alzheimer's disease and memory issues were found using the DisGeNet database. All targets were used (by common names). We focussed on the search keywords on Alzheimer diseases and memory loss disorders, filter keywords of "Alzheimer's disease, focal onset", "Alzheimer disease", "Age-Related Memory Disorders", "Alzheimer disease, familial, type 3", "Alzheimer disease, late onset", "Alzheimer Disease, Early Onset", "Memory Disorders", "Memory Impairment", "Memory Dysfunction", "Familial Alzheimer Disease (FAD) ", "Memory Impairment, CTCAE 3.0", "Memory Loss".

#### *2.6.5 Building of networks and visualisation*

Using the Cytoscape programme (a platform for visualising complicated networks and integrating the results), networks of plant-metabolites, metabolite-target, PPI, and target-Alzheimer and memory disorders were constructed [51]. In the graphical network, nodes stand in

for plants, metabolites, targets, Alzheimer's, and memory diseases, while edges signify appropriate interactions.

#### *2.6.6 Analysis of gene enrichment*

The FunRich programme 3.1.3 maintained the represented gene enrichment analysis circuits of targets relevant to Alzheimer's and memory disorders in terms of biological processes, cellular components, molecular activities [52], and Bionformatics database was used for biological pathways https://www.bioinformatics.com.cn/en [53].

### 2.7 Statistical analysis

All data sets were reported as mean ± standard deviations (SD). The data were statistically tested for normal distribution using Co-State for Windows, version 8, and One-Way ANOVA software. At $p < 0.05$. Statistics show that different letter values are significant.

$$\%\text{change} = \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

$$\%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

## 3 Results

### 3.1 DPPH radical scavenging activity test conducted in vitro for SLSE

The extreme scavenging behaviour of SLSE was tested utilising the stable-radical DPPH-assay (Table 1). The findings revealed that SLSE is a strong DPPH scavenging activity that is dosage-dependent relationship vs ascorbic acid.

### 3.2 In vitro SLSE AChE inhibition activity

SLSE cholinesterase inhibitory activity was assessed against the AChE enzyme in contrast to the standard medication donepezil, and the outcomes were stated as $IC_{50}$ (µg/mL) values in Table 2. With an $IC_{50}$ value of 0.036 µg/mL, SLSE demonstrated a significant inhibitory effect.

**Table 1** In vitro SLSE's DPPH scavenging effectiveness

| | 0.01 µg/mL | 0.05 µg/mL |
|---|---|---|
| Crude extract | 50.2 ± 2.22[a] | 84.1 ± 5.9[b] |
| Ascorbic acid | 81.3 ± 4.76[b] | 90.0 ± 6.1[d] |

Data are presented as the mean ± SD ($n = 3$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$

**Table 2** In vitro SLSE AChE inhibition activity

| | $IC_{50}$ µg/mL |
|---|---|
| Crude extract | 0.036 ± 0.004 |
| Donepezil | 0.025 ± 0.003 |

Data are presented as the mean ± SD ($n = 3$). With the help of Co-State for Windows, version 8, and one-way ANOVA software, the variations between the treatment groups were examined. A $p < 0.05$ difference was regarded as statistically significant when compared to the vehicle-treated control group. As a positive control, donepezil was used. $IC_{50}$ is the concentration (µM) that inhibits cell growth by 50% in vitro

### 3.3 Anti-Alzheimer activity

A crude extract of SLSE was employed for further in vivo investigations to estimate the anti-Alzheimer activity based on in vitro DPPH radical scavenging and cholinesterase activity testing.

#### *3.3.1 Acute toxicity study*

Acute toxicity was determined using serial concentrations of SLSE. Up to 3000 mg/kg.b.wt., there were no signs of mortality or toxicity, for 48 h, in addition to the absence of toxicity or behavioural problems. The dosage used for this study was 500 mg/kg.b.wt [54].

#### *3.3.2 SLSE's potential impacts in the T-maze test*

The results showed that rats took significantly longer (in seconds) to get to the food in the T-maze for AD group, showing reduced neurocognitive function (an increase of 233.8%) (Table 3). Rats given SLSE showed greater cognitive capacity as they required considerably less time to get to their meal than the AD-induced group. This difference was most pronounced when compared to rats treated with donepezil (181.9%) (Table 3).

#### *3.3.3 Potential-effects of SLSE utilising the beam balance test*

The findings of the beam balancing test revealed that $AlCl_3$ induced a 70.6% decline in brain cognitive functioning in AD group (Table 4). Treatment of rats with SLSE or donepezil, on the other hand, brought about a change in behavioural status, as shown by enhanced motor coordination and thinking, with a % of improvement reaching

**Table 3** Effect of SLSE utilising the T-maze test in Alzheimer's disease-induced rats

| | Baseline | Induction (2 months) | Treatment (6 weeks) |
|---|---|---|---|
| Control | $14.3 \pm 1.2^{a}$ | $15.8 \pm 1.2^{a}$ | $14.9 \pm 0.9^{a}$ |
| $AlCl_3$-AD<br>% change | | $52.9 \pm 3.6^{b}$<br>+233.8 | – |
| Crude extract<br>% of improvement | – | – | $29.2 \pm 1.6^{c}$<br>151.1 |
| Donepezil drug<br>% improvement | – | – | $24.1 \pm 0.7^{d}$<br>181.9 |

Data are presented as mean ± SD ($n = 10$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$. The

$$\%\text{change} = \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100,$$

$$\%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

**Table 4** Effect of *SLSE* utilising the beam balance test in Alzheimer's disease-induced rats

| | Baseline | Induction (2 months) | Treatment (6 weeks) |
|---|---|---|---|
| Control | $10.6 \pm 0.8^{a}$ | $10.1 \pm 0.4^{a}$ | $11.1 \pm 0.2^{a}$ |
| $AlCl_3$-AD<br>% change | | $2.9 \pm 0.6^{b}$<br>70.6 | – |
| Crude extract<br>% improvement | – | – | $8.8 \pm 1.1^{c}$<br>58.1 |
| Donepezil drug<br>% improvement | – | – | $10.0 \pm 0.5^{d}$<br>69.0 |

Data are presented as mean ± SD ($n = 10$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$. %chan $= \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$,

$$\%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

**Table 5** Effect of SLSE on the levels of AChE in rats with induced Alzheimer's disease

| Parameters | Control | $AlCl_3$-AD | Extract | Donepezil |
|---|---|---|---|---|
| AChE (U\L)<br>% change<br>% improvement | $215.0 \pm 11.00^{a}$ | $419.0 \pm 10.00^{b}$<br>+94.80 | $285.8 \pm 11.00^{c}$<br>61.90 | $240.0 \pm 9.70^{c}$<br>83.20 |

Data are presented as mean ± SD ($n = 10$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$. AChE in serum: Acetylcholine esterase.

$$\%\text{change} = \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100,$$

$$\%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

58.11% for SLSE compared to the donepezil group, which recorded 69.0%.

#### *3.3.4 SLSE's potential impact on AChE*

AChE significantly rises in the AD group, up to 94.8%, as shown in Table 5. AChE levels improved in AD rats treated with SLSE by 61.9% as compared to donepezil (83.2%).

#### *3.3.5 Potential effects of SLSE on brain levels of norepinephrine, dopamine, and serotonin*

The AD-group showed a significant increase in norepinephrine levels with a % that reached 723.0% compared to normal rats (Table 6), with a significant reduction in both levels of dopamine and 5-HT, with % of 68.94 and 65.6%, respectively. SLSE -treated AD rats showed marked improvement in levels of neurotransmitter, reaching 448.0, 34.4, and 36.6%, compared to donepezil (Table 6).

**Table 6** Effect of SLSE on the levels of dopamine, norepinephrine, and serotonin in Alzheimer's -affected rats

| | Norepinephrine (µg/g tissue) | Dopamine (µg/g tissue) | Serotonin (5-HT) (µg/g tissue) |
|---|---|---|---|
| Control | $2.0 \pm 0.10^{a}$ | $3.2 \pm 0.20^{a}$ | $2.9 \pm 0.20^{a}$ |
| $AlCl_3$-AD<br>% change | $16.4 \pm 0.90^{b}$<br>+723.0 | $1.0 \pm 0.10^{b}$<br>-68.9 | $1.0 \pm 0.10^{b}$<br>-65.6 |
| Crude extract<br>% improvement | $7.5 \pm 0.50^{a}$<br>448.0 | $2.1 \pm 0.20^{c}$<br>34.4 | $2.1 \pm 0.20^{c}$<br>36.6 |
| Donepezil drug<br>% improvement | $5.30 \pm 0.50^{c}$<br>558.0 | $2.7 \pm 0.50^{c}$<br>55.2 | $2.6 \pm 0.10^{c}$<br>54.8 |

Data are presented as mean ± SD ($n = 10$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$. The

$$\%\text{change} = \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100,$$

$$\%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

**Table 7** Effect of SLSE on IL-6, glycated end product, and BDNF levels in rats with Alzheimer disease

| | BDNF (Pg/g tissue) | Glycated end product (µg/g tissue) | IL-6 (Pg/mL) |
|---|---|---|---|
| Control | $343.0 \pm 10.20^{a}$ | $12.7 \pm 1.20^{a}$ | $39.6 \pm 3.00^{a}$ |
| $AlCl_3$-AD<br>% change | $167.0 \pm 10.90^{b}$<br>-50.3% | $40.8 \pm 3.10^{b}$<br>221.2% | $130.0 \pm 8.00^{b}$<br>227.7% |
| AD crude extract<br>% improvement | $230.0 \pm 3.50^{c}$<br>18.3% | $26.0 \pm 2.50^{c}$<br>116.6 | $66.5 \pm 4.00^{c}$<br>160.1 |
| Donepezil drug<br>% improvement | $288.0 \pm 16.00^{e}$<br>35.2 | $12.9 \pm 1.10^{a}$<br>219.6 | $39.0 \pm 2.80^{a}$<br>229.4 |

Data are presented as mean ± SD ($n = 10$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$.

$$\%\text{change} = \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100,$$

$$\%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$$

#### *3.3.6 Potential effects of SLSE on brain levels of IL-6, glycated end product, and BDNF*

Comparing the AD-rats to the control rats, Table 7 shows a significant drop in brain tissue BDNF levels as well as a large rise in serum IL6 levels and brain tissue glycated end product. When compared to donepezil, AD rats treated with SLSE showed significant improvements in all measured parameters (Table 7).

#### *3.3.7 SLSE's potential effects on MDA, TAC, and GSH*

Comparing to the control group, there was a significant reduction in TAC of 74.1%. GSH also indicated a considerable decline in brain tissue, with a % reduction of 60.9%, whereas MDA levels increased significantly, reaching 451.7%. The AD group treated with SLSE had a higher % of improvement in antioxidant and oxidative stress levels, reaching 38.2, 340.4, and 30.1% for TAC, MDA, and GSH compared to donepezil (Table 8).

### 3.4 Histopathological investigations

Histopathological examinations revealed AD rat brains with neuronal degeneration, meningeal blood congestion, Purkinje cell degeneration, and hippocampus neurodegeneration (Photomicrographs 3–4, Fig. 1) compared to the normal control group (Photomicrographs 1–2, Fig. 1). The AD rat brain, after treatment with SLSE, showed a degeneration of some neurons in the cerebral cortex, and hippocampus and a degeneration of a few Purkinje cells in the cerebellum (Photomicrographs 5–7, Fig. 1). Donepezil treated group brains demonstrated meningeal haemorrhage and a small number of deteriorated neurons (Photomicrographs 8, Fig. 1).

The scoring system was designed as follows: score 0 = no lesion in all rats in the group (n = 5), score 1 = < 30%, score 2 = 30%-50%, and score 3 = > 50%. G1 is the control group, G2 is the AD group, G3 is the AD group treated with SLSE, and G4 is the donepezil-treated group.

Group 2 (AD-rats) demonstrated more pronounced histological alterations in the brain than Group 1 (normal group). Group 3: Alzheimer disease group treated with SLSE against donepezil as the conventional management (Table 9).

The score system was designed as: score 0 = absence of the lesion in all rats of the group ($n = 5$), score 1 = (< 30%), score 2 = (30% – 50%), score 3 = (> 50%). G1: control group, G2: Alzheimer-induced group, G3: AD group treated with SLSE, and G4: donepezil-treated AD group

### 3.5 Chemical dereplication of SLSE

Several hits were found when analysing SLSE (Additional file 1: Table S1, Fig. 2, Additional file 1: S1A and B). At *m*/*z* 207.1385, 271.06065, 287.09225, and 287.22263, the mass ion peaks were corresponding to the suggested molecular formulas $C_{13}H_{18}O_2$, $C_{15}H_{12}O_5$, $C_{16}H_{16}O_5$, and $C_{16}H_{32}O_4$ $[M+H]^+$, and $[M\text{-}H]^+$ (Additional file 1: Table S1), fitting with polyphenolics, and acid derivatives like aureonitol (**1**), 2′,4,4′,6′-tetrahydroxychalcone (**2**), 2′,4,4′,7-tetrahydroxyisoflavan 4′-methyl ether (**3**), and 10,16-dihydroxyhexadecanoic acid (**4**). These compounds had previously been isolated from endophytic *Chaetomium globosum* [55], *Solanum lycopersicum* [56], *Solanum lyratum* [57], and *Solanum lycopersicum* [58]. At *m*/*z* 291.19463, 293.2114, 299.1497, 305.16085, 328.11915, and 329.2325 $[M+H]^+$, and $[M\text{-}H]^+$ (Additional file 1: Table S1), the molecular ion mass peaks were corresponding to the anticipated molecular compositions $C_{18}H_{26}O_3$, $C_{18}H_{30}O_3$, $C_{15}H_{24}O_6$, $C_{15}H_{20}N_4O_3$, $C_{18}H_{19}NO_5$, and $C_{18}H_{34}O_5$, gave hits at fatty acids like chromomoric acid C (**5**), 13-oxo-9,11-octadecadienoic acid (**6**), at the lignan syringolide 2 (**7**), at the alkaloidal derivatives cernumidine (**8**), *N*-(4-hydroxy-3-methoxy-*E*-cinnamoyl octopamine) (**9**), and at the unsaturated fatty acid, 9,10,11-trihydroxy-12-octadecenoic acid (**10**), respectively, which had previously been isolated from *Lycopersicon esculentum* [59], *Solanum lycopersicum*

**Table 8** Effect of SLSE on TAC, MDA, and GSH levels in rats with induced Alzheimer disease

| | Control rats | Intoxicated rats | Crude extract | Standard drug |
|---|---|---|---|---|
| TAC (mM/L)<br>% change<br>% improvement | $0.8 \pm 0.3^{a}$<br>– | $0.2 \pm 0.2^{d}$<br>– 74.1 | $0.5 \pm 0.5^{c}$<br>38.2 | $0.7 \pm 0.2^{b}$<br>52.8 |
| MDA (nmol/g tissue)<br>% change<br>% improvement | $26.1 \pm 2.1^{d}$ | $144.0 \pm 6.1^{a}$<br>+451.7 | $55.1 \pm 3.0^{c}$<br>340.4 | $41.1 \pm 2.5^{b}$<br>394.2 |
| GSH (tissue) (mg/g tissue)<br>% change<br>% improvement | $25.0 \pm 1.0^{a}$ | $9.7 \pm 3.0^{d}$<br>60.9 | $17.3 \pm 1.1^{c}$<br>30.1 | $23.1 \pm 2.2^{b}$<br>53.4 |

Data are presented as mean ± SD ($n = 10$). The groups that share an identical letter do not differ considerably. Conversely, those that have various letters are, at $p \leq 0.05$.
$\%\text{change} = \frac{\text{mean of negative control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100, \%\text{improvment} = \frac{\text{mean of positive control} - \text{mean of treatment group}}{\text{mean of negative control}} \times 100$

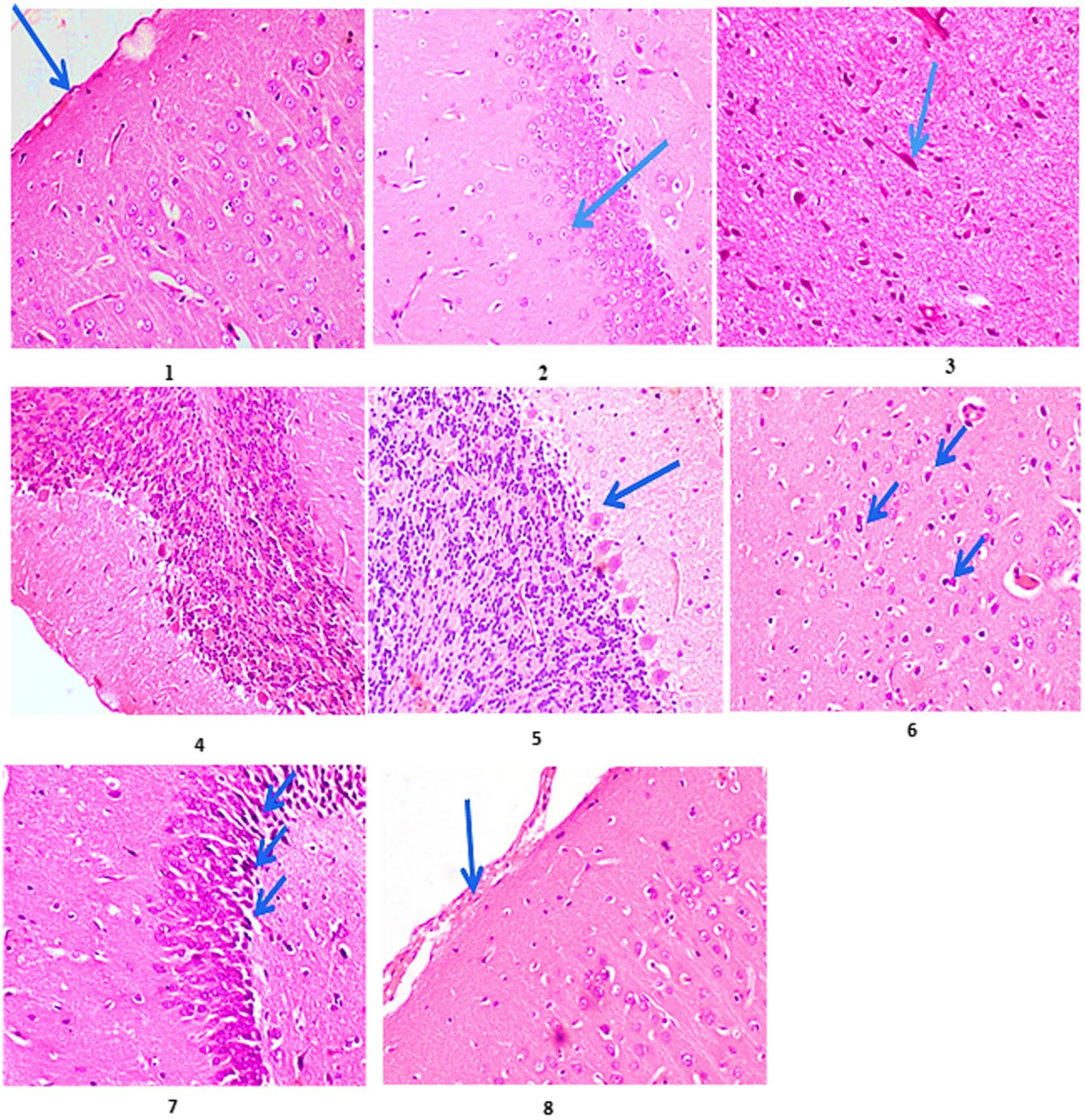



**Fig. 1** H&E-stained rat cerebral brain slices photomicrographed: 1. In a controlled rat brain, the cerebral meninges have a typical histological anatomy (arrow). 2. In a controlled rat brain, the hippocampus has a typical histological structure (arrow). 3. Neurofibrillary tangles (NFT) are present together with neuronal degeneration in the Alzheimer's disease-induced rat brain (arrow). 4. Rat brain deterioration brought on by Alzheimer's disease with lessened granular layer density. 5. Few Purkinje cells in the cerebellum in the AD rat brain treated with SLSE are displaying signs of degradation. 6. A loss of certain neurons in the cerebral cortex is highlighted in the AD rat brain treated with SLSE (arrows). 7. SLSE-treated AD rat brain with damaged hippocampus neurons (arrows). 8. Meningeal bleeding in an Alzheimer's disease-affected rat brain after treatment with donepezil (arrow)

[60], *Pseudomonas syringae pv. tomato* [61], *Solanum cernuum* [62], *Solanum khasianum* [63], *and Solanum melongena* [64].

The *m*/*z* 331.04684, 335.09183, 339.07247, 341.13862, 355.1023, and 359.1495 (Additional file 1: Table S1), with anticipated chemical compositions $C_{16}H_{12}O_8$, $C_{20}H_{16}O_5$, $C_{15}H_{16}O_9$, $C_{20}H_{20}O_5$, $C_{16}H_{18}O_9$, and $C_{20}H_{22}O_6$ gave hits of polyphenolics nucleus of 3′,4′,5,5′,7-pentahydroxy-3-methoxyflavone (**11**), solalyratin A (**12**), 6,7-dihydroxy-2H-1-benzopyran-2-one, 7-*O*-*β*-D-glucopyranoside (**13**), lyratin B (**14**), 3-*O*-caffeoylquinic acid (**15**), and lyratin B, 3′,4′-dihydro, 3′Ξ-hydroxy (**16**), which had earlier been isolated from *Solanum spp.* [65], *Solanum lyratum* [66], *Solanum pinnatisectum* [67], *Solanum lyratum* [68], *Solanum melongena* [69], and *Solanum lyratum* [68]. Six *m*/*z* values of

**Table 9** Histopathological changes in the brain of all treated groups scored

| Lesions | G1 control | G2 AD | G3 crude extract | G4 drug |
|---|---|---|---|---|
| Neuronal degeneration with NFT | 0 | 3 | 2 | 1 |
| Congestion of meningeal blood vessels | 0 | 2 | 0 | 0 |
| Meningeal haemorrhage | 0 | 2 | 1 | 1 |
| Degeneration of hippocampus neurons | 0 | 3 | 2 | 1 |
| Degeneration of Purkinje cells in cerebellum | 0 | 2 | 1 | 0 |
| Decreased granular layer density in cerebellum | 0 | 2 | 1 | 0 |

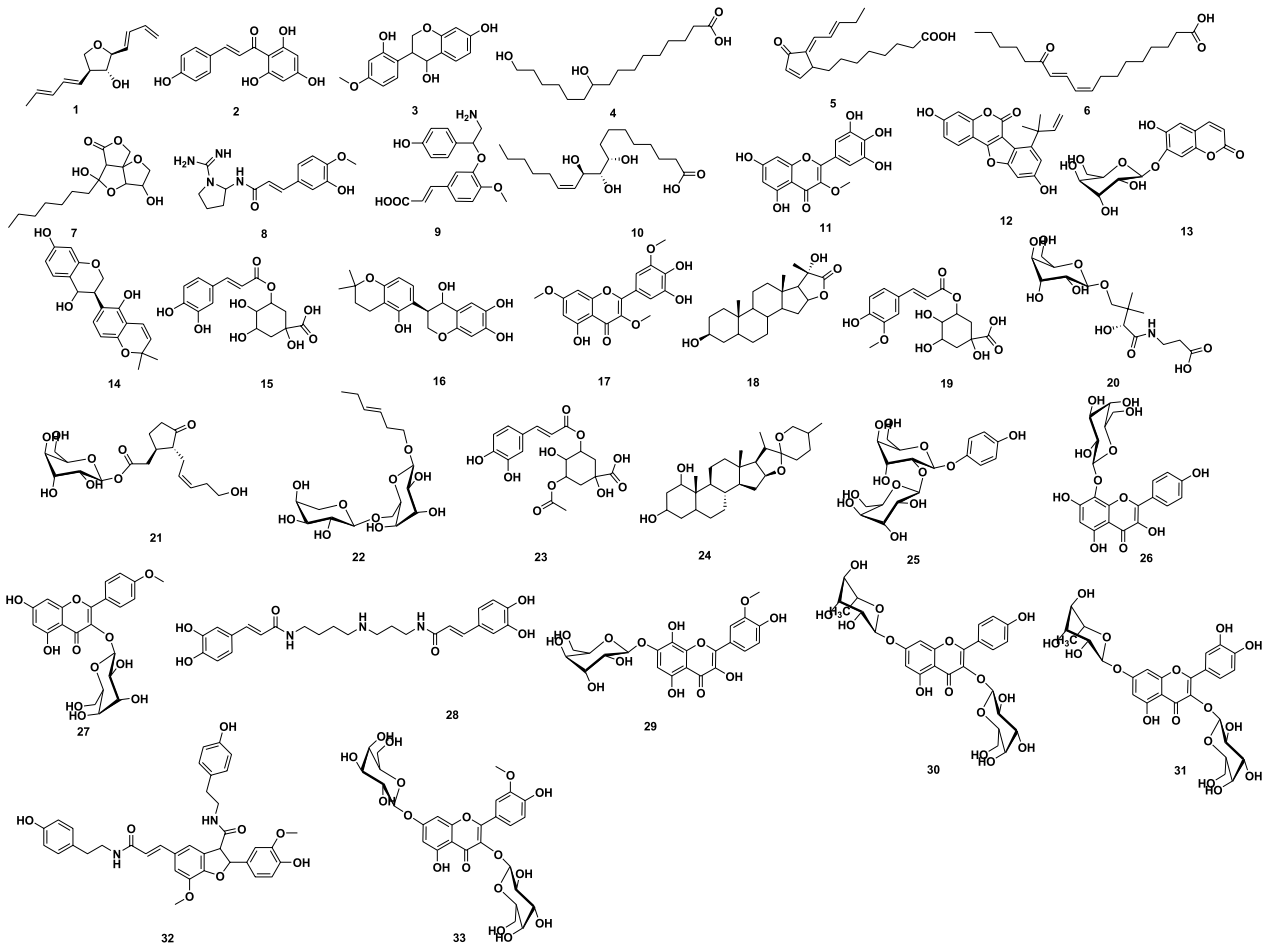


**Fig. 2** Dereplicated compounds found in SLSE after LC–HRESIMS investigation

359.07626, 363.2527, 367.10312, 380.15605, 387.16678, and 393.1763 $[M+H]^+$, and $[M\text{-}H]^+$ (Additional file 1: Table S1), with the anticipated molecular compositions $C_{18}H_{16}O_8$, $C_{22}H_{34}O_4$, $C_{17}H_{20}O_9$, $C_{15}H_{27}NO_{10}$, $C_{18}H_{28}O_9$, and $C_{17}H_{30}O_{10}$, were detected and dereplicated as polyphenolics and triterpene derivatives (Fig. 2), 3,3′,4′,5,5′,7-hexahydroxyflavone, 3,3′,7-trimethyl ether (**17**), lycopersiconolide (**18**), 3-*O*-caffeoylquinic acid, 3′-methyl ether (**19**), pantothenic acid, 4′-*O*-*β*-D-glucopyranoside (**20**), jasmonic acid, 12-hydroxy, *O*-*β*-D-glucopyranoside (**21**), and 3-hexen-1-ol, *O*-[*α*-L-arabinopyranosyl-(1 → 6)-*β*-D-glucopyranoside] **22**), respectively, which had previously been isolated from *Solanum torvum* [70], *Solanum lycopersicum* [71], *Lycopersicon esculentum* [72], *Lycopersicon esculentum* [72],

*Solanum tuberosum* [73], and *Lycopersicon esculentum* [72].

Also, the mass ion peaks at *m*/*z* 395.09763, 433.33111, 433.13426, 447.09317, 463.12307, and 470.22904, corresponding to the suggested molecular formulas $C_{18}H_{20}O_{10}$, $C_{27}H_{44}O_4$, $C_{18}H_{26}O_{12}$, $C_{21}H_{20}O_{11}$, $C_{22}H_{22}O_{11}$, and $C_{25}H_{31}N_3O_6$ $[M+H]^+$, and $[M\text{-}H]^+$ (Additional file 1: Table S1), which fit with the compounds 3-*O*-caffeoylquinic acid, 5-*O*-acetyl (**23**), spirostane-1,3-diol (**24**), arbutin, 2-*O*-*β*-D-glucopyranosyl (**25**), 8-*β*-D-galactopyranosyl-3,4′,5,7-tetrahydroxyflavone (**26**), 3,5,7-trihydroxy-4′-methoxyflavone, 3-*O*-*β*-D-glucopyranoside (**27**), and spermidine, *N*,*N*″-bis(3,4-dihydroxycinnamoyl) (**28**), which had also been isolated from *Solanum melongena* [74], *Solanum polyadenium* [75], *Solanum lycopersicum* [76], *Solanum elaeagnifolium* [77], *Solanum spp.* [78], and *Solanum melongena* [79], respectively.

Moreover, the *m*/*z* 477.10499, 593.14981, 609.1466, 625.25509, and 639.15639 $[M+H]^+$, and $[M\text{-}H]^+$ (Additional file 1: Table S1), for the anticipated molecular compositions $C_{22}H_{22}O_{12}$, $C_{27}H_{30}O_{15}$, $C_{27}H_{30}O_{16}$, $C_{36}H_{36}N_2O_8$, and $C_{28}H_{32}O_{17}$ gave hits of the flavones and alkaloid derivatives 4′,5,7,8-tetrahydroxy-3′-methoxyflavone, 7-*O*-*β*-D-glucopyranoside (**29**), kaempferol 3,7-diglycoside, 3-*O*-*β*-D-galactopyranoside, 7-*O*-*α*-L-rhamnopyranoside (**30**), quercetin 3,7-diglycosides, 3-*O*-*β*-D-galactopyranoside, 7-*O*-*α*-L-rhamnopyranoside (**31**), grossamide (**32**), and isorhamnetin 3,7-diglycosides, 3,7-Di-*O*-*β*-D-glucopyranoside (**33**), which has previously been isolated from *Solanum grayi* [80], *Solanum spp.* [65], and *Solanum tuberosum* [81] (Additional file 1: Table S1).

## 3.6 Bioinformatic study

### 3.6.1 Plant-metabolite network

A simple network was formed to show the tentatively identified compounds from SLSE (Additional file 1: Fig. S2).

### 3.6.2 Metabolite-target network

Cytoscape software was used to create and visualise a network to display the targets related to the major identified compound of SLSE. With 392 nodes and 636 edges, the built network had a network centralisation of 0.249 and a typical path length of 3.479, the nodes represented the major metabolites (14) and the targets (378) (Additional file 1: Fig. S3).

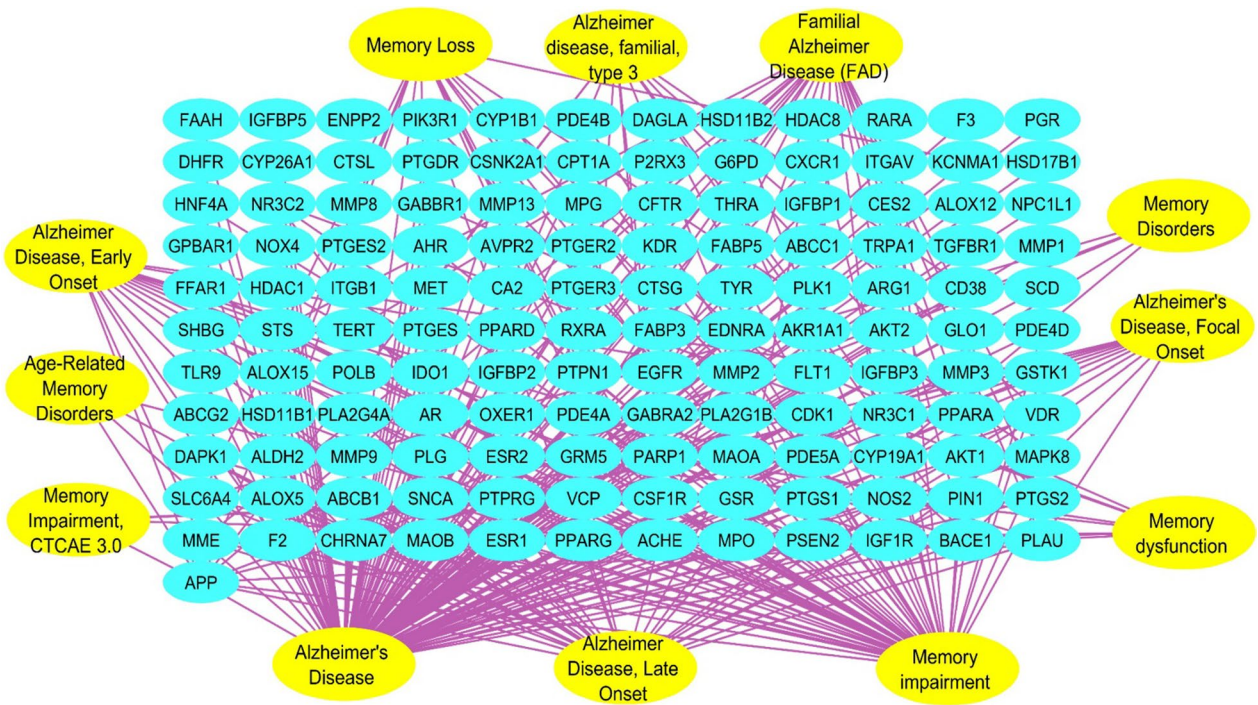



**Fig. 3** Targets-Alzheimer and Memory Disorders Network: a network describing the targets of major identified metabolites that correlate with different types of Alzheimer and memory disorders, yellow oval shapes represent the types of Alzheimer's and memory disorders, blue oval shapes represent the targets

#### *3.6.3 Protein–protein interactions*

The protein–protein interaction (PPI) was shown in five clusters by the String database, the shown network is a physical protein subnetwork, where interacted proteins correspond to protein complexes (Additional file 1: Fig. S4). The formed network is composed of 378 nodes and 932 edges, with a local clustering coefficient of 0.461.

#### *3.6.4 Targets: AD and Memory Disorders Network*

From the DisGeNET database, targets of major metabolites linked to Alzheimer and memory disorders were 133. These results were summarised in a network (Fig. 3), the formed network consisted of 145 nodes and 314 edges, with a network centralisation of 0.864. APP, AChE, and PSEN2 genes were the top genes correlated to different types of Alzheimer and memory disorders with 12, 11 and 10 edges, respectively (Additional file 1: Table S2).

#### *3.6.5 Study of functional enrichment and gene ontology*

All the targets were used as input data in the FunRich software to find the gene enrichment analysis in terms of biological processes, cellular components, molecular functions, and biological pathways. The most important biological processes discovered were signal transduction and cell communication according to the number of genes (Additional file 1: Fig. S5). The top cellular component terms were cytoplasm and plasma membrane (Additional file 1: Fig. S6). The top molecular function terms were catalytic activity and G-protein-coupled receptor activity (Additional file 1: Fig. S7). The top biological pathways were Arachidonic acid metabolism and PPAR signalling pathway. All biological were arranged in descending order according to the enrichment score (Fig. 4).

The bioinformatics study was designed to find out the genes that are responsible for performing activity towards Alzheimer's disorders. The major identified compounds were selected for this study. The study identified 378 genes related to the major metabolites, and from DisGeNET analysis, a network of metabolites related to Alzheimer's and memory disorders was constructed. As the top genes related to most types of Alzheimer's and memory disorders, the APP, AChE, and PSEN2 genes were determined. Dementia in the elderly is caused in large part by the improper processing of amyloid precursor protein (APP) [82]. The aetiology of cognitive failure seen in Alzheimer disease (AD) is associated with a reduction in brain acetylcholine

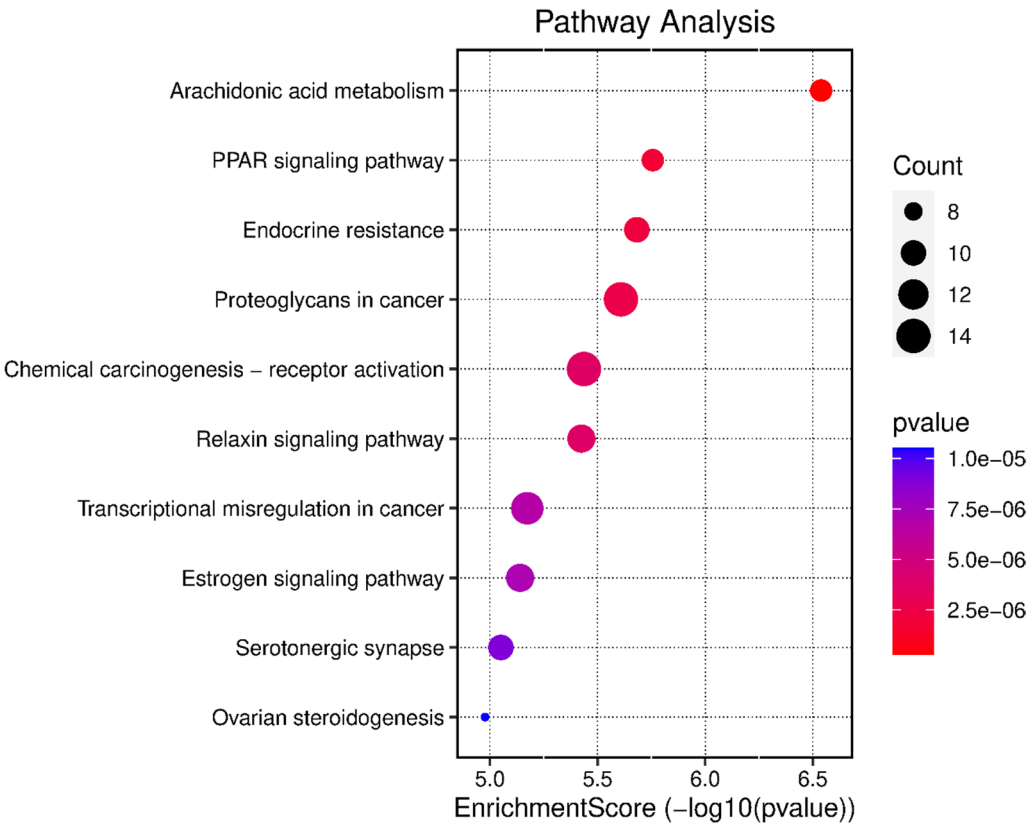



**Fig. 4** The top biological KEGG pathways, arranged according to the enrichment score

(ACh) levels [83]. Previous research has shown that some mutations in the PSEN2 gene result in an augmented synthesis of Aβ42, a prominent pathological feature seen in the brains of individuals affected with (AD). This finding has been established by investigations conducted using cell-based experiments and mice models [84]. Based on these findings, the activity of *S. lycopersicum* as anti-Alzheimer could be attributed to the combination of the APP, AChE, and PSEN2 genes. The gene enrichment analysis determined the top biological pathways as Arachidonic acid metabolism and PPAR signalling pathway. According to the above results, *S. lycopersicum* possessed anti-Alzheimer activity through one of the mentioned biological pathways.

## 4 Discussion

In vitro results showed high DPPH inhibitory activity of SLSE with dose dependent relationship comparing with ascorbic acid (Table 1). In a parallel line with Kumar et al. 2021 [85] results who declared that tomato seeds have been reported to contain antioxidant molecules such as phenols, flavonoids, condensed tannins, ascorbic acid (vitamin C), tocochromanols, and carotenoids. Antioxidants exert their effects by interacting with free radicals that could otherwise damage vital molecules in the body. These interactions include decomposition of peroxides, scavenging of radicals and binding to metal ions. Although the antioxidant activity of the whole tomato, pomace or peel has been evaluated by several authors [86–88], less attention has been given to the isolated seed extract. Valdez-Morales et al. [2014] [89] determined the antioxidant activity and phenolic content of seeds and peel of tomato cultivars from Sinaloa, Mexico. These compounds primarily included caffeic acid, ferulic acid, chlorogenic acids, quercetin-3-β-*O*-glycoside, and quercetin. The peel and seeds showed higher antioxidant potential for all tested tomato varieties. Variation in antioxidant activities was also observed in tomatoes at different maturation stages [90]. The total antioxidant activity and phenolic content were higher in red tomato seeds than in green ripe tomato ones.

Our results declared also, AChE inhibitory activity of SLSE with $IC_{50} = 0.036 \pm 0.004$ µg/mL as compared with standard drug donepezil ($0.025 \pm 0.003$ µg/mL). In this aspect, Kumar et al. 2021 [85], illustrated that, despite the presence of a diverse group of antioxidant compounds, the neuromodulatory effects of SLSE have not been extensively investigated. The authors reported SLSE evaluated for its neuroprotective effect by its ability to attenuate neurotoxicity and rotenone (mitochondrial complex I blocker)-induced oxidative stress in mice [91]. The oral dose of SLSE in mice offset rotenone-induced oxidative deterioration, reinstated glutathione levels and stimulated the antioxidant defence system (glutathione peroxidase, superoxide dismutase). It also lowered the activity of rotenone-induced acetylcholinesterase and revived dopamine in the striatum. Intriguingly, SLSE was shown to effectively restore mitochondrial complex activities and maintain their redox state.

The in vivo study, the behavioural T-maze test (Table 3) reflected previous findings that $AlCl_3$-neurointoxicated rats took longer to gather food inside a T-maze, indicating impaired neurocognitive function [92]. In contrast to the standard drug, SLSE demonstrated improved cognitive abilities. In addition, a beam balance examination was used to assess the ability of rats to maintain their balance while crossing a high beam having a small diameter. The beam balance test results demonstrated that $AlCl_3$ severely deteriorated cognitive performance in the AD group (Table 4). However, when rats were administered donepezil or SLSE, their behavioural states were improved indicating amelioration in cognitive brain function.

The current data, (Table 5), demonstrates a significant rise in the activity of AChE in the serum of AD group. According to previous research, $AlCl_3$ is a cholinotoxin that alters cholinergic, dopaminergic, and noradrenergic neurotransmission activities [9]. Furthermore, the current findings show a large increase in norepinephrine and a significant decrease in DA, and serotonin in AD group. The outcomes run concurrently with Kaur et al. (2019) [93], who stated that $AlCl_3$ has a negative impact on memory performance. This might be connected to the function of $AlCl_3$ in the dopaminergic system, as well as its capacity to generate oxidative stress which causes deficiencies in several important neurotransmitters, including DA and ACh. Additionally, increased production of $O_2$ and $H_2O_2$ may be linked to the large changes in brain neurotransmitters observed in AD group, raising the risk of neurodegenerative disorders [94]. Additionally, $AlCl_3$ suppresses DA β-hydroxylase and tryptophan decarboxylase activity, promotes α-synuclein aggregation, and lowers DA-binding receptors (D1 and D2) in $AlCl_3$-exposed cerebral cortex and striatum (responsible for DA formation) [9]. Increased monoamine oxidase (MAO) activity, which resulted in enhanced dopamine breakdown, may potentially be responsible for the lower DA level and altered cholinergic function. When compared to untreated AD rats, neurotransmitter levels in SLSE treated AD rats improved (Tables 5–6).

The current investigation shows that BDNF is significantly depleted in the AD group (Table 7). The recent findings and the connection between AD's disease and BDNF have been supported by several investigations. The neocortex and hippocampus of brain tissue had reduced amounts of BDNF protein and mRNA, indicating that

BDNF is important in Alzheimer's disease [1]. The connection between BDNF tau phosphorylation, neuroinflammation, neurodegeneration and Aβ accumulation may help to explain this depletion [1]. If the effects of tau pathology on neurotrophic pathways are not considered, treating Alzheimer disease with a solely Aβ-centred approach may not be beneficial, as tau contributes to the downregulation of BDNF caused by Aβ [95]. It should be noted that BDNF overexpression or gene transfer can aid in the management of behavioural problems, neural abnormalities, neuronal loss, and synaptic degeneration.

The current findings demonstrate a considerable increase in AGEs in the Alzheimer's disease group (Table 7). This rise in AGEs may be explained by the alteration of the APP by α- and β-secretase, which results in amyloid deposits (plaques) in brain cells [3]. Glyceraldehyde-derived AGEs have been identified as a major source of neurotoxicity in AD. It was discovered that AGEs formed from glyceraldehyde enhance APP and Aβ through ROS. It has been demonstrated that adding AGEs and Aβ increases neurotoxicity [3]. Furthermore, IL-6 levels in the serum of AD group were significantly elevated (Table 7). Lyra e Silva et al. (2021) [96] stated that IL-6 has been negatively implicated in memory formation, as blocking IL-6 enhances long-term potentiation and improves long-term memory in a hippocampus-dependent task. AD rats treated with SLSE improved in BDNF, glycated end product, and IL6 by 18.3, 116.6, and 160.1%, respectively, compared to the standard drug (Table 7).

The current investigation shows that AD-induced rats had significantly lower levels of TAC and GSH and significantly higher levels of MDA (Table 8). Excessive production of reactive oxygen species (ROS) and disruption of the antioxidant defence system are thought to be the primary causes of intracellular damage because of mitochondrial dysfunction [97]. Our findings are consistent with Aly et al. (2018) [97], who stated that lipid peroxidation may increase because of the neurotoxicity associated with $AlCl_3$. The current study also demonstrates a relationship between an increase in MDA and the decline in TAC and GSH, i.e. two molecules involved in removing ROS from brain tissue, showing that $AlCl_3$ has prooxidant properties. Instead, Sumathi et al. (2013) [98] stated that when exposed to $AlCl_3$, neuronal lipids are more likely to be destroyed, and changes to the enzymatic antioxidant defence mechanism of the body are also observed. Also, the brain tissues of $AlCl_3$-induced rats exhibited a considerable reduction in GSH levels, which may be explained by the fact that brain endothelial cells experienced a high level of $H_2O_2$-induced cytotoxicity because of glutathione reductase inhibition [97]. Long-term $AlCl_3$ exposure produces an increase in lipid peroxidation as well as the depletion and exhaustion of numerous antioxidant enzymes, which may explain the significant decline in brain TAC in $AlCl_3$-induced AD rats [9]. It could be illustrated that according to our results, SLSE have antioxidant molecules such as phenols, flavonoids, condensed tannins, ascorbic acid (vitamin C), tocochromanols, and carotenoids, the SLSE exerts its effects by interacting with free radicals that could otherwise damage vital molecules in the body. These interactions include decomposition of peroxides, scavenging of radicals and binding to metal ions [88]. Also, Gharbi et al. [99] stated that due to the presence of tocopherols, higher values of free radical inhibition were found in the SLSE than in other parts. The primary contributing to the antioxidant potential of include lycopene, β-carotene, polyphenols, and tocopherols. The bioactive compounds in tomato seed oil and phytosterols also synergistically contribute to antioxidant activities by acting as proton donors. Metal ions such as ($Fe^{2+}$) can instigate the production of ROS, which can harm living systems. Metal chelators can therefore inhibit ROS production and prevent damage to vital macromolecules. Although several preclinical and clinical studies have demonstrated the positive role of tomato and its bioactive compounds, such as phenolics and lycopene, in the management of different metabolic syndromes, such as obesity, Alzheimer disease, cardiovascular diseases, diabetes and inflammation [100–102].

In concomitant with our results revealed the improvements in antioxidant status, the study of Liu et al. [2017] [103] demonstrated that tomato seed oil can reduce the blood sugar content and improve the glucose tolerance in diabetic mice associated with neurodegeneration, potentially by regulating the levels of MAD, SOD, and GSH-PX. Diverse phenolic compounds in tomato seeds, including chlorogenic acid, naringenin, isorhamnetin, kaempferol, and quercetin, exhibit anti-obesity and hypocholesterolaemic properties by regulating lipid metabolism-related hepatic gene expression [104]. The primary mechanism of defatted tomato seed-mediated cholesterol reduction, specifically (low-density lipoprotein cholesterol and hepatic cholesterol), relies on the faecal excretion of lipids and cholesterol [105].

The oral administration of SLSE exhibits a high propensity to offer neuroprotection against neurotoxicants and other neurodegenerative ailments, such as Parkinson's disease [139]. The disease is associated with midbrain basal ganglia dopaminergic malfunctioning, which results in motor impairment ultimately causing gait and neurobehavioural abnormalities. Flavonoids such as myricetin, kaempferol, and quercetin present in SLSE are metabolised through the intestinal microflora to produce hydroxyphenyl acetic acid which display anxiolytic effects. Additionally, lycopene in SLSE alleviates oxidative

dysfunction of the mitochondria. Also, the neuroprotective effects of tomato seeds extract on rotenone-induced neurotoxicity in *Drosophila*, tomato seeds extract was found to protect flies against death, oxidative stress, neurotoxicity and locomotory defects [106].

Our histopathological investigation (Fig. 1) showed neurofibrillary tangles (NFT) are present together with neuronal degeneration in the Alzheimer disease-induced rat brain and brain deterioration brought on by Alzheimer's disease with lessened granular layer density. Clark, 1998 [107] reported, histopathologically, Alzheimer's patients have a loss of neurons, neurofibrillary tangles, and senile plaques containing extracellular amyloid β (Aβ) [108]. Besides, a hyperphosphorylated form of microtubular protein tau is also encountered. Pathologically, AD has two distinctive features, which have a toxic effect on nerve cells and consist of abnormal proteins. Of these, Aβ neuritic plaques are protein aggregates outside nerve cells in the brain, whereas neurofibrillary tangles are found inside cells [108, 109]. Studies showed that the main component of amyloid plaques is Aβ, and the main component of neurofibrillary tangles is tau protein [110]. These abnormal proteins cause toxic effects on nerve cells, damaging their functions and eventually causing cell death. This can cause memory loss, behavioural disorders (as illustrated in our results in beam balance and T-maze test, showed decline in brain cognitive functioning, Tables 3, 4), decreased confusion, agitation, and hallucination, which are common symptoms of AD [111], while our results showed few Purkinje cells in the cerebellum in the AD rat brain treated with SLSE are displaying signs of degradation. Also, a loss of certain neurons in the cerebral cortex is highlighted in the AD rat brain treated with SLSE and damaged hippocampus neurons while meningeal bleeding in an Alzheimer's disease-affected rat brain after treatment with donepezil. The well-accepted therapeutic method in AD is based on the principle of restoring cholinergic function using compounds that block enzymes that break down acetylcholine (as presented in the in vitro AChE, Table 2). Cholinesterase inhibitors, which are designed to maintain activation of cholinergic synapses by preventing the breakdown of acetylcholine, are generally considered a symptomatic treatment for AD [112, 113], even though the fact that clinical evidence and guidelines support the using cholinesterase inhibitors at all levels of AD. Studies showed that there is an association between the neurofibrillary pathology of AD and cholesterol metabolism. Cholesterol and its transport maintain amyloid plaques production and hyperphosphorylation of the tau in the brain. Furthermore, these studies revealed that aside from AD, cholesterol metabolism contributes to intracranial vascular diseases and cerebral ischaemia [114]. SLSE catalyses the rate-limiting step during cholesterol biosynthesis. Thus, it inhibits HMG-CoA reductase, one of the enzymes in the pathogenesis of AD. SLSE was found to enhance β-oxidation by increasing the expression of CPT1A, ACADL and PPAR-α, subsequently reducing plasma lipid levels [105, 115]. Phytosterols present in tomato seed also suppressed cholesterol absorption due to their structural similarity with cholesterol and reduces cholesterol levels by indirectly modulating the activity of HMG-CoA reductase through sterol regulatory element-binding protein-2 (SREBP-2) [105, 115]. SLSE, their specific bioactive compounds showed prevention of CVDs and antiplatelet activities [116]. During ischaemic injury due to SLSE block platelet aggregation, which adhere to the endothelial cell lining by P-selectins, preventing recruitment of leukocytes through intercellular adhesion molecule 2. This subsequently results in prevention the local vascular inflammation causing permanent or intermittent obstruction of blood flow, causing organ dysfunction, ischemic injury, so improving brain tissue architecture [116].

As a result, the current research adequately demonstrates the therapeutic effects of SLSE on inflammatory and neurotransmitter markers.

An examination of the metabolome of the SLSE was done to find out more about the chemical molecules that may support-the-activity-treated for Alzheimer-related syndromes. Using LC–HRESIMS, dereplication of 33 compounds from the metabolic profile of the SLSE succeeded. These metabolites were discovered to belong to a variety of chemical classes, including flavonoids, triterpenes, fatty acids, alkaloids, and polyphenolics (Fig. 2). Furthermore, the bioinformatics study discovered 378 targets related to the major identified compounds, and determined the APP, AChE, and PSEN2 targets as the top genes among 133 genes related to Alzheimer. Gene enrichment analysis identified Arachidonic acid metabolism and PPAR signalling pathway as the biological pathways enriched by all the gene sets under investigation. This study was designed to uncover the possible action of *S. lycopersicum* seed extract (SLSE) on Alzheimer disease by the in vivo and in vitro studies, which was able to prove this activity, the pharmacology network was able correlate this anti-Alzaheimer activity and correlated degenerative disorders with specific human genes affected by the compounds identified in the extract and suggested the possible pathways (PPAR signalling pathway) related to the identified genes by the compounds of the *S. lycopersicum* seed extract. This workflow allows the future researchers to focus on the correlation of this extract on the mentioned pathway on a molecular level.

## 5 Conclusion

In this study, SLSE showed neuroprotective, antiapoptotic, and anti-amnesic effects against brain damage and cognitive decline brought on by $AlCl_3$. The anti-AChE and antioxidant activities of SLSE may be responsible for this effect. Using LC–HRESIMS, thirty-three compounds were dereplicated. Furthermore, the bioinformatics study discovered 378 targets related to the major identified compounds, of which only 133 were related to Alzheimer's and memory disorders, with APP, AChE, and PSEN2 targets identified as the top genes. Gene enrichment analysis identified the TRAIL signalling pathway and the glypican pathway as the biological pathways enriched by all the gene sets under investigation. This study suggests the use of SLSE as a promising therapeutic approach in the management of AD disease. To verify the findings, future detailed mechanistic studies and secondary metabolites quantification in the extract are still required to confirm the results.

**Abbreviations**

| | |
|---|---|
| Aβ | Amyloid peptide |
| AChE | Acetylcholine esterase |
| AD | Alzheimer's disease |
| APP | Amyloid precursor protein |
| BDNF | Brain-derived neurotrophic factor |
| CHRNA7 | Alpha7 neuronal nicotinic acetylcholine receptor gene |
| CSF | Cerebrospinal fluid |
| DA | Dopamine |
| DPPH | 2,2-Diphenyl-1-picrylhydrazyl |
| GSH | Glutathione |
| H&E | Hematoxylin and eosin |
| HPLC-ED | High performance liquid chromatography with electrochemical detection |
| 5-HT | 5-Hydroxytryptamine |
| IGF-I | Insulin-like growth factor-1 |
| IL-6 | Interleukin-6 |
| LC–HRESIMS | Liquid chromatography–high-resolution electrospray ionisation mass spectrometry |
| MDA | Malondialdehyde |
| PPI | Protein protein interaction |
| PSEN2 | Presenilin 2 |
| ROS | Reactive oxygen species |
| SLSE | Solanum lycopersicum seed extract |
| TAC | Total antioxidant capacity |
| TNF-α | Tumour necrosis factor-α |
| U/L | Units per litre |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43088-023-00453-x.

**Additional file 1: Table S1.** Dereplicated metabolites from LC-HRESIMS analysis of the seed extract of Solanum lycopersicum. **Table S2.** Targets related to Alzheimer and memory disorders; targets arranged according to number. of edges in descending order. **Figure S1A.** LC-HRESIMS chromatogram of the dereplicated metabolites of Solanum lycopersicum seed extract (positive). **Figure S1B.** LC-HRESIMS chromatogram of the dereplicated metabolites of Solanum lycopersicum seed extract (negative). **Figure S2**. Plant-metabolite network; a network connecting the plant species (Solanum lycopersicum) in blue circle to the identified metabolites in pink triangles. **Figure S3** Metabolite-target network; a network of the correlations between major metabolites and targets, oval blue shapes represent the major metabolites (in number), the diamond violet shapes represent the targets. **Figure S4.** PPI of gene set correlated to major identified compounds from Solanum lycopersicum seeds.

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**Author contributions**
Conceptualization: HTB, OHA, URA, GB, FAM; methodology: HFA, EAY, MAA, FHA; software: NAA, MM, FA, URA; formal analysis: HTB, OHA, URA, GB, FAM; investigation: HTB, OHA, URA, FAM; resources: FA, HFA, EAY, MAA; data curation: HFA, EAY, MAA, FHA; writing—original draft: AHE, HFA; writing—review and editing: HTB, OHA, URA, GB, FAM. All authors have read and agreed to the published version of the manuscript.

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**Availability of data and materials**
Data are contained within the article.

## Declarations

**Ethics approval and consent to participate**
The study was approved by Beni-Suef University, Egypt's Ethics Committee (ethical approval no: 022–370). The National Research Centre (NRC) Animal House is the place where the male Wistar albino rats were taken.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no conflicts of interest.

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