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ORIGINAL ARTICLE

Possible Ameliorative Effect of Dandelion Plant Leaf Extract on Paclitaxel Drug Induced Peripheral Neurotoxicity in Adult Male Albino Rats

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ABSTRACT

Background: Paclitaxel induced peripheral neurotoxicity (PIPN) is a dose limiting toxicity, which can compromise patient's outcome. Dandelion leaves have been reported to possess antioxidant and anti-inflammatory activities. So, we aimed to evaluate the protective effect of dandelion leaf extract against the PIPN on sciatic nerves in adult male albino rats after analysis of its components by GC/MS.

Methods: Dandelion leaves methanolic extraction was done then the extract was processed to GC/MS analysis. This 6-week study involving 45 adult male albino rats, five groups were formed: Group I (Control, 9 rats) received regular diet and tap water. Group II (vehicle, 9 rats) received intraperitoneal injection of 1 ml normal saline twice weekly. Group III (Dandelion Leaf Extract, DLE, 9 rats) received DLE orally at 500 mg/kg daily. Group IV (Paclitaxel, PTX, 9 rats) received paclitaxel at 2 mg/kg IP twice weekly. Group V (PTX & DLE, 9 rats) received both treatments. Serum Neurotensin, serum TNFα, tissue oxidative stress markers (MDA, GSH and SOD) was measured. The sciatic nerve was examined microscopically after H&E staining.

Results: The GC/MS analysis of DLE revealed presence of 55 vital compounds. Neurotensin, TNFα and Malondialdehyde increased in Paclitaxel group and decreased in DLE-treated groups. While SOD and GSH activity were reduced in paclitaxel group, both markers improved in DLE-treated groups. Paclitaxel caused Wallerian degeneration with axonal and myelin fragmentation. In the Paclitaxel & DLE group, partial axonal regeneration was noted.

Conclusion: Paclitaxel induces peripheral neuropathy with inflammation and oxidative stress. DLE demonstrates neuroprotective effects against PIPN.

Keywords: Dandelion Leaf Extract; Paclitaxel; Peripheral Neurotoxicity; GC/MS analysis; Ameliorative Effect.

INTRODUCTION

Paclitaxel (PTX) is a chemotherapeutic agent, sold under several trade names, including Taxol. It is a mitotic inhibitor drug used to treat a number of cancers. In 1971, it was initially isolated from the Pacific yew tree's bark., which contain endophytic fungus that produce paclitaxel [1].

By targeting microtubules from β-tubulin heterodimers and promoting their stable assembly, paclitaxel inhibits the microtubule's depolymerization, this eventually causes apoptosis and lead to stoppage of cell division. Furthermore, PTX suppresses tumor angiogenesis and triggers the production of cytokines and genes that prevent cell division and lead the cells to death [2]. Even though PTX is effective against a variety of cancers, its effectiveness can be somewhat overshadowed by its potential neurotoxic side effects, which can lead to peripheral neuropathy and other complications. The majority of patients experience an immediate painful condition with each PTX injection, which can be exacerbated by a much more severe chronic sensory polyneuropathy. This is part of the complex neurotoxicity profile of PTX. Although managing paclitaxel-induced peripheral neurotoxicity (PIPN)

can be difficult, PIPN can be persistent even after treatment ends [3].

The Asteraceae family subdivided into a diverse range of plants, including, the common dandelion (*Taraxacum officinale)* This is a common perennial herbaceous plant. It is an edible vegetable. It is a common weed in Egypt and grows wild in the fields. As a folk remedy, dandelion is well-known as a traditional medicine. This herb is non-toxic and has anti-inflammatory, anti-rheumatic, and maybe antioxidative properties [4].

The basis for dandelion's antioxidant properties is its bioactive components, which include flavonoids and phenolic acids. These substances can effectively prevent the production of free radicals and eradicate the excess of them from the body. Furthermore, in both people and animals, dandelion extract has been demonstrated to enhance the activity of antioxidant enzymes like superoxide dismutase and reduce intracellular oxidative processes [5].

In addition to identifying the active ingredients in dandelion leaf extract using GC-MS, using biochemical and histological analysis, the study aimed to evaluate the protective effect of dandelion leaf extract against the neurotoxic effect of paclitaxel on sciatic nerves in adult male albino rats.

METHODS

I. Material:

Chemicals:

1- Paclitaxel (PTX): Paclitaxel was purchased as pharmaceutical preparation **(Taxol: 100 mg vial, 6mg/ml)** from Elezaby pharmacy in Zagazig. Corden Pharma Latina S.P.A., located in Sermoneta, Latina, Italy, was the manufacturer. It was in the form of clear, colorless to slightly yellow viscous solution.

2- Dandelion leaf methanolic extract: Dandelion leaves were acquired from Zagazig University's Faculty of Agriculture, Egypt. The leaves were large, long, polished, hairless, and light to dark green with deep dental borders (5-40 cm long and 1–10 cm wide). The extraction process of Dandelion leaves was done at Plant Protection Research Institute, Pest Physiology department, Sharkia Branch, Egypt. Three kilograms of dandelion leaves were grounded into a fine powder using a mortar after being cleaned with water and allowed to air dry for three days. The resultant powder was macerated in 2 liters of methanol with shaking. Every day, the mixture was filtered, the collected fractions were put together and two liters of fresh methanol added to the residual pulp for 5 days. A dark green semisolid mass was obtained by evaporating the methanolic extract using a rotary evaporator. This mass was then stored at -20°C until it was needed.

Analysis of Dandelion leaf extract by Gas chromatography/mass spectrometry (GC/MS) [6]**:** GC/MS was used to identify the main active components in Dandelion leaf extract at the Faculty of Medicine's Forensic Medicine & Clinical Toxicology research lab at Zagazig University. A 300 m x 0.25 mm x 1 m df capillary column, an Elite-1 (100% Dimethyl Ply Siloxane) mass detector, and a Clarus 500 Perkin-Elmer (Auto System XL) gas chromatograph are connected to a Turbomas 5.2 spectrometer.

A starting temperature of 110°C was established for the instrument, and it was kept there for two minutes. At the end of this time, the oven temperature was increased to 280°C at a rate of 5°C per minute and kept there for nine minutes. A 250°C injection port temperature and a 1 ml/min helium flow rate were guaranteed. Seventy eV was the ionization voltage. In split mode, the samples were injected 10:1. The range of the mass spectral scan was 45–450 MHz. By using GC/MS, the chemical components were determined. The fragmentation patterns of mass spectra were compared with those stored in the spectrometer database using the National Institute of Standards and Technology Mass Spectral database (NIST-MS). Each component's proportion in the chromatogram was calculated using its relative peak area.

Kits: Rat {neurotensin (NT) kit, tumor necrosis factor alpha (TNFα) kit, Malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD) ELISA kits were purchased from MyBiosource biotechnological company, San Diego, United States.

Animals:

45 adult male albino rats weighing 180–200 grams and approximately 6 weeks of age were acquired from Zagazig University's Faculty of Medicine's Animal House. The sample size was determined using the (open-EPi) system in the Community Medicine department of Zagazig University's Faculty of Medicine. All animals underwent a seven-day period of passive preliminaries prior to the experiment in order to establish their physical well-being, acclimate to their new surroundings, and rule out any ill animals. The animals were housed in individual plastic cages that were free of any chemical pollution sources. They were kept under controlled conditions with a 12-hour light cycle, an ambient temperature range of 22 ± 2 ºC, and a relative humidity of 50 ± 5%. In order to keep the animals clean and prevent overcrowding and isolation, soft wood shavings were used for bedding and replaced when the cages were washed

on other days. Before and throughout the drug administration, the rats were fed a well-balanced diet that was full of all the nutrients they needed to stay healthy. It was made of barley and bread. The water was served in separate, hygienic containers. As stated in "The Guide for the Care and Use of Laboratory Animals," all animals were treated in accordance with the Ethical Regulations and Animal Care Guidelines. [7]. The Institutional Animal Care and Use Committee (IACUC) of Zagazig University awarded ethical approval for all the experimental procedures (ZU-IACUC/3/F/110/2023).

II. Methods:

Experimental design:

Rats were randomly divided into five groups following housing acclimation:

- **Group I (control group)** (9 rats)**:** For six weeks, each rat was given only Tap water and a typical diet are used to measure the fundamentals.
- **Group II (vehicle group)** (9 rats)**:** For six weeks, each rat was given a twice-weekly intraperitoneal (IP) injection of one millilitre of paclitaxel's vehicle, regular saline solution.
- **Group III (Dandelion leaf extract) (DLE)** (9 rats)**:** The extract from dandelion leaves was diluted in normal saline and administered orally by gavage every day for six weeks at a dose of 500 mg/kg body weight dissolved in 1 ml normal saline for each rat.
- **Group IV (Paclitaxel group)** (9 rats)**:** Paclitaxel was dissolved in normal saline. It was IP injected at a dose of a 2 mg/ kg body weight (about 1/16 of LD50), twice a week for six consecutive weeks according to **[8]**. LD50 of paclitaxel in rats by IP route is 32.5 mg/kg**.**
- **Group V (Paclitaxel & DLE)** (9 rats)**:** In addition to paclitaxel injection (2mg/kg, IP, twice/week), Dandelion leaves extract was administrated orally (500 mg/kg/day) for six consecutive weeks. In days which both were administrated Dandelion leaves extract was received first, then after 3 hours paclitaxel was injected.

− Following an IP injection of sodium pentobarbital (50 mg/kg body weight) to anaesthetize the rats in each group, venous blood samples were obtained from the retro-orbital plexus of the animals by capillary glass tubes and each rat was then pinned to a dissecting board in a prone position. A midline incision was made from the neck to the sacral region then longitudinal postero-lateral incision in both thighs, from the great trochanter until the region next to the femur lateral condyles to dissect the sciatic nerve. The nerve was released from surrounding soft tissue (Mid- thigh incision approach). Left sciatic nerves were first washed with 0.9% saline, then homogenized and centrifuged pending the biochemical analysis. Right sciatic nerves were fixed in 10% neutral formalin for histopathological examination (hematoxylin & eosin) at the end of the experiment.

Biochemical studies:

1- Assessment of Serum Neurotensin (pg /ml): Neurotensin was assayed by ELISA Double Antibody Sandwich technique **[9]** according to the instructions of the manifacture catalog number (MBS267436).

2- Assessment of serum tumor necrosis factor alpha (pg/ml): Tumor necrosis factor alpha was assayed by ELISA Double Antibody Sandwich technique **[9]** according to instruction of the manufacture Catalog number (MBS700574).

3- Tissue oxidative stress parameters: Each rat's left sciatic nerve homogenate underwent the following tests:

a. Malondialdehyde (MDA) (nmol/ml): Malondialdehyde was assayed by ELISA Double Antibody Sandwich technique **[9]** according to instruction of the manufacture catalog number (MBS268427).

b. Superoxide dismutase (SOD) (U/ml): Superoxide dismutase was assayed by ELISA Double Antibody Sandwich technique **[9]** according to instruction of the manufacture catalog number (MBS266897).

c. Reduced glutathione (ng/ml): Reduced glutathione was assayed by ELISA Double Antibody Sandwich technique **[9]** according to instruction of the manifacture catalog number (MBS8807501).

Histopathological studies:

Hematoxylin and Eosin (H & E).

Samples of tissue from the right sciatic nerve were preserved, dried, cleaned, and embedded in paraffin wax. Blocks were sectioned and stained by hematoxylin and eosin following the common procedures **[10].** Slides were examined under the light microscope.

Statistical analysis

The data was verified, entered, and analyzed using the Statistical Package of Social Science (SPSS) software, version 27.0. The least significant difference (LSD) and one-way analysis of variance (ANOVA) tests were used.

RESULTS

The Phytochemical analysis of dandelion leaf methanolic extract by GC/MS revealed the presence of 55 vital compounds. These compounds include 26 fatty acid esters (47%), 9 fatty acids

(16%), 4 steroids (7%), 4 alkanes (7%), 4 alkene (7%), 3 alcohols (6%), 2 Phthalates (4%), 1 phenol (2%), 1 Vitamin (2%) and 1 carbonyl ketone (2%). The identified compounds have multiple pharmacological actions, including anti-inflammatory, anti-bacterial, anti-oxidant, anti-cancer, anti-rheumatic, etc. Hexadecanoic acid, methyl ester (13.61%), n-hexadecanoic acid (13.16%), 10-octadecenoic acid, methyl ester (12.46%), and octadecanoic acid, methyl ester (9.89%) have the largest relative area percent (Table 1, Figure 1).

No statistically significant difference was observed between the biochemical findings of control "I", vehicle "II" and DLE "III" groups as regard values of Neurotensin, TNF-α and oxidative stress markers (MDA, SOD & GSH) at the end the study by ANOVA test (Table 2). So, the control group (I) was used for comparison with other treated groups.

Each group's neurotensin levels were measured for assessment of neuronal impairment. Serum neurotensin levels were significantly elevated after paclitaxel administration compared to control groups (I) ($p<0.001$). Serum neurotensin levels in the Paclitaxel & DLE treated group (V) were significantly lower than those in the Paclitaxel treated group (IV) ($p<0.001$), but they were still significantly higher than those in the control group (I) ($p<0.001$) (Table 2).

Each group's levels of tumor necrosis factor-α were measured for assessment of inflammation. Serum TNF-α levels increased significantly after paclitaxel administration compared to the control group (I) ($p<0.001$). Serum TNF-α levels in the Paclitaxel & DLE treated group (V) were significantly lower than those in the Paclitaxel treated group (IV) ($p<0.001$), but they were still significantly higher than those in the control group (I) ($p<0.001$) (Table 2).

Each group's sciatic nerve malondialdehyde levels were assessed to determine the degree of lipid peroxidation. When compared to the control group, paclitaxel administration resulted in a very high and significant rise in the MDA levels of sciatic nerve tissues ($p<0.001$). In comparison to the Paclitaxel-treated group (IV), the Paclitaxel & DLE-treated group (V) displayed considerably reduced levels of MDA in the sciatic nerve tissues ($p<0.001$), but they also showed a significant rise ($p<0.001$) in comparison to the control groups (I) (Table 2).

When compared to the control group (I), the sciatic nerve tissues' SOD and GSH enzyme activity levels were significantly reduced after 6 weeks of paclitaxel administration ($p<0.001$). SOD and GSH enzyme levels were significantly greater in the Paclitaxel & DLE treated group (V) than in the Paclitaxel treated group (IV) ($p<0.001$), although they were still significantly lower in the control group (I) ($p<0.001$) (Table 2).

Sections taken from the right sciatic nerves of control (I), vehicle (II) and dandelion leaf extract (III) groups revealed normal histological nerve fiber architectures made up of Schwann cells and myelin sheaths encircling central axons (Figures 2A, B & C).

Paclitaxel administration revealed Wallerian degeneration of sciatic nerve that represented by irregularity of axonal thickness with diffuse fragmentation of both axons and myelin sheath, accompanied with presence of empty spaces (Figure 2D).

Sections from the right sciatic nerves of rats from Paclitaxel & DLE treated group (V) show axonal regeneration that represented by proliferated Schwann cells with preserved structures of majority of axons beside mild demyelinated fibers (Figure 2E).

Table (1): Major compounds identified in dandelion leaf methanolic extract by GC/MS showing their retention time (RT) in minutes, molecular formula, area percent, category and activity.

RT (min)	Compound Name	Molecular Formula	Area %	Category	Activity
4.35	Phenol, 2-methyl-5-(1-methylethyl)-	C10H14O	0.62	Phenol	Anti-inflammatory, antioxidant, antitumor, antimicrobial, fungicidal, insecticidal activity [11]
12.21	Undecanoic acid, 10-methyl-, methyl ester	C13H26O2	1.49	Fatty acid methyl ester	Anti-oxidant anticancer [12]
17.20	Dodecanoic acid, 3-hydroxy-	C12H24O3	0.59	Fatty acid	Antifungal activity against molds and herbicides [13]

RT (min)	Compound Name	Molecular Formula	Area %	Category	Activity
17.45	Methyl tetradecanoate	C15H30O2	1.49	Fatty acid	Antioxidant, Cancer-preventive, Hypercholesterolemic, Lubricant, Nematicide [14]
18.51	Oleic Acid	C18H34O2	0.92	Fatty acid	Antibacterial, cancer preventive, anemiagenic, insectifuge, antiandrogenic, and dermatitigenic activities [15]
19.76	12,15-Octadecadiynoic acid, methyl ester	C19H30O2	0.48	Fatty acid methyl ester	Anti-inflammatory [16]
20.74	Phthalic acid, isobutyl octadecyl ester	C30H50O4	1.77	Phthalates	Antimicrobial plasticizer [17]
21.40	9-Hexadecenoic acid	C16H30O2	0.59	Fatty acid	Anti-inflammatory and improve insulin Synthesis [18]
21.74	Pentadecanoic acid, 14-methyl-, methyl ester	C17H34O2	0.60	Fatty acid methyl ester	Anti-inflammatory, antiandrogenic, antioxidant, hypercholesterolemic, and antimicrobial activities [19]
21.88	Hexadecanoic acid, methyl ester	C17H34O2	13.61	Fatty acid methyl ester	Antioxidant Free radical scavenger Peroxidase substrate Reductant Lipid peroxidase inhibitor Antiviral Anticancer [20]
22.26	Estra-1,3,5(10)-trien-17á-ol	C18H24O	0.76	Steroid	Steroid, anti-inflammatory [21]
22.74	n-Hexadecanoic acid	C16H32O2	13.16	Fatty acid	Antioxidant, pesticide, hypocholesterolemic, nematicide, lubricant, and antiandrogenic [18]
23.24	l-(+)-Ascorbic acid 2,6-ihexadecanoate	C38H68O8	0.65	Vitamin Derivative	Anti-inflammatory, hypocholesterolemic, cancer preventive, hepatoprotective and antiarthritic [22]
23.31	Hexadecanoic acid, 2-hydroxy-1,3-propanediyl ester	C35H68O5	0.33	Fatty acid ester	Antimicrobial [23]
23.89	Oxiraneundecanoic acid, 3-pentyl-, methyl ester, trans-	C19H36O3	0.57	Fatty acid methyl esters	Antioxidant and anticancer [24]
24.86	E-8-Methyl-9-tetradecen-1-ol acetate	C17H32O2	0.35	Alcohol	Insect pheromone [25]

RT (min)	Compound Name	Molecular Formula	Area %	Category	Activity
25.23	9,12-Octadecadienoyl chloride, (Z,Z)-	C18H31ClO	3.21	Fatty acid	Antioxidant, anti-cancerous and thyroid inhibiting [26]
25.33	10-Octadecenoic acid, methyl ester	C19H36O2	12.46	Fatty acid methyl ester	Antibacterial, antifungal, antioxidant, decrease blood cholesterol [27]
25.44	11-Octadecenoic acid, methyl ester	C19H36O2	2.97	Fatty acid methyl ester	Antioxidant Free radical scavenger Peroxidase substrate Reductant Lipid peroxidase inhibitor Antiviral Anticancer [20]
25.80	Octadecanoic acid, methyl ester	C19H38O2	9.89	Fatty acid methyl ester	Antioxidant Free radical scavenger Peroxidase substrate Reductant Lipid peroxidase inhibitor Antiviral Anticancer [20]
26.20	9-Hexadecenoic acid	C16H30O2	4.01	Fatty acid	Anti-inflammatory, and improve insulin Synthesis [18]
26.55	Octadecanoic acid	C18H36O2	4.17	Fatty acid	Antiviral, anti-inflammatory, cure skin lesions, antioxidant, hypocholesterolemic, nematicide, pesticide, anti-androgenic, hemolytic, 5-alpha reductase inhibitor [28]
26.97	17-Pentatriacontene	C35H70	0.32	Alkene	Anti-inflammatory, anticancer, antibacterial, and antiarthritic [29]
27.08	1-Hexadecanol, 2-methyl-	C17H36O	0.72	Alcohol	Antimicrobial [30]
27.74	Oleic acid, eicosyl ester	C38H74O2	0.52	Fatty acid ester	Anti-inflammatory, cancer preventive, dermatitigenic Hypocholesterolemic and anemiagenic Insectifuge [31]
28.49	Oleic acid, 3-(octadecyloxy)propyl ester	C39H76O3	0.33	Fatty acid ester	Antifungal [18]
28.83	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	C26H54	0.47	Alkane	Antioxidant and anti-inflammatory [32]
28.94	22-Tricosenoic acid	C23H44O2	0.32	Fatty acid	lipid anchor in bio membranes, Anti xiokytic.

RT (min)	Compound Name	Molecular Formula	Area %	Category	Activity
					[33]
29.05	7-Methyl-Z-tetradecen-1-ol acetate	C17H32O2	0.84	Fatty acid ester	Anticancer, Antifungal, anti-inflammatory, hepatoprotective [34]
29.36	Cyclopropanedodecanoic acid, 2-octyl-, methyl ester	C24H46O2	1.23	Fatty acid methyl ester	Antimicrobial [24]
29.91	Oleic acid, 3-(octadecyloxy)propyl ester	C39H76O3	0.93	Fatty acid ester	Antifungal [18]
30.06	Oleic acid, eicosyl ester	C38H74O2	0.27	Fatty acid ester	Anti-inflammatory, cancer preventive, dermatitigenic Hypocholesterolemic and anemiagenic Insectifuge [31]
30.51	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	C26H54	0.48	Alkane	Antioxidant and anti-inflammatory [32]
30.65	17-Pentatriacontene	C35H70	0.27	Alkene	Anti-inflammatory, anticancer, antibacterial, and antiarthritic [29]
31.08	Oleic acid, 3-(octadecyloxy)propyl ester	C39H76O3	0.79	Fatty acid ester	Antifungal [18]
31.99	Oleic acid, eicosyl ester	C38H74O2	0.18	Fatty acid ester	Anti-inflammatory, cancer preventive, dermatitigenic Hypocholesterolemic and anemiagenic Insectifuge [31]
32.13	Z-5-Methyl-6-heneicosen-11-one	C22H42O	1.06	Carbonyl Ketone	AntiMycobacterium tuberculosis Activity, anti-inflammatory, analgesic and antimicrobial activities [35]
32.25	17-Pentatriacontene	C35H70	0.64	Alkene	Anti-inflammatory, anticancer, antibacterial, and antiarthritic [29]
32.65	Cyclopropanedodecanoic acid, 2-octyl-, methyl ester	C24H46O2	1.37	Fatty acid methyl ester	Antimicrobial [24]
33.02	1,2-Benzenedicarboxylic acid, diisooctyl ester	C24H38O4	4.47	Phthalate esters	Antimicrobial, antifouling [36]
33.61	Oleic acid, 3-(octadecyloxy)propyl ester	C39H76O3	0.22	Fatty acid ester	Antifungal [18]
33.68	Oleic acid, eicosyl ester	C38H74O2	0.27	Fatty acid ester	Anti-inflammatory, cancer preventive, dermatitigenic Hypocholesterolemic and anemiagenic Insectifuge [31]
34.18	17-Pentatriacontene	C35H70	0.48	Alkene	Anti-inflammatory, anticancer, antibacterial, and antiarthritic [29]

RT (min)	Compound Name	Molecular Formula	Area %	Category	Activity
35.17	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	C26H54	1.18	Alkane	Antioxidant and anti-inflammatory [32]
35.67	Docosanoic acid, 1,2,3-propanetriyl ester	C69H134O6	0.69	Fatty acid ester	Antioxidant, hypocholesterolemic, nematicide, pesticide, flavouring agent, lubricant and anti-androgenic [37]
36.63	Ethyl iso-allocholate	C26H44O5	1.64	Steroid compound	Antimicrobial Antiasthma Anti-inflammatory Anticancer Diuretic [38]
36.91	1-Monolinoleoylglycerol trimethylsilyl ether	C27H54O4Si2	0.39	Steroid	Antimicrobial Antioxidant Antiinflammatory Antiarthritic Antiasthma, Diuretic [39]
37.29	9-Octadecenoic acid, (2-phenyl-1,3-dioxolan-4-yl) methyl ester, cis-	C28H44O4	0.60	Fatty acid ester	Antimicrobial, anti-inflammatory [40]
40.12	Ethyl iso-allocholate	C26H44O5	0.30	Steroid compound	Antimicrobial Antiasthma Anti-inflammatory Anticancer Diuretic [38]
40.22	7,8-Epoxylanostan-11-ol, 3-acetoxy-	C32H54O4	0.37	Alcohol	Antimicrobial, antioxidant, anti-inflammatory and anticancer [41]
40.32	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	C26H54	1.42	Alkane	Antioxidant and anti-inflammatory [32]
40.43	9-Octadecenoic acid, (2-phenyl-1,3-dioxolan-4-yl) methyl ester, cis-	C28H44O4	0.37	Fatty acid ester	Antimicrobial, anti-inflammatory [40]
44.46	9,12,15-Octadecatrienoic acid, 2,3-bis[(trimethylsilyl)oxy] propyl ester, (Z,Z,Z)-	C27H52O4Si2	0.69	Fatty acid ester	Hepatoprotective, anti-inflammatory and anti-cancer [42]
44.80	Stearic acid, 3-(octadecyloxy)propyl ester	C39H78O3	0.65	Fatty acid ester	Antifungal [43]
44.95	2,3-bis[(trimethylsilyl)oxy] propyl ester, (Z,Z,Z)-	C27H52O4Si2	0.85	Fatty acid ester	Antioxidant, anti-inflammatory, antimicrobial, antipyretic, anticancer [44]

Table (2): Statistical comparison among control (I), vehicle (II), DLE (III), Paclitaxel (IV) and Paclitaxel & DLE (V) groups as regard levels of serum neurotensin, serum TNF-α, tissue MDA, SOD and GSH at the end of the study by ANOVA & LSD test.

n=9 / Biochemical parameter	Control (I) Mean ± SD	Vehicle (II) Mean ± SD	DLE (III) Mean ± SD	Paclitaxel (IV) Mean ± SD	Paclitaxel & DLE (V) Mean ± SD	F	P
Neurotensin pg/ml	40.11±7.76	36.55±6.9	33.75± 2.4	231.6±37. 06^{abce}	131.85±15. 56 ^{abcd}	196.494	<0.001***
TNF-α pg/ml	18.13±1.88	17.31±1.93	16.68± 1.32	159.17±1 4.94 ^{abce}	79.02±10.4 4 ^{abcd}	514.773	<0.001***
MDA nmol/mL	2.30±0.48	2.10±0.41	1.91±0 .08	8.58±1.11 ^{abce}	4.33±0.45 ^{abcd}	192.505	<0.001***
SOD U/mL	226.28±21.2 7	233.66±17.7 3	235.76 ±6.20	51.15±4.9 1 ^{abce}	95.14±4.21 ^{abcd}	414.916	<0.001***
GSH ng/mL	67.51±5.55	68.66±4.18	71.14± 2.23	27.16±3.0 6 ^{abce}	43.00±4.69 ^{abcd}	426.428	<0.001***

N.B: Values are expressed as Mean±SD. (SD: standard deviation). n: number of sacrificed rats in each group. DLE: dandelion leaf extract. pg/ml: picogram per milliliter. nmol/mL: nanomole per milliliter. U/mL: unit per milliliter

***** very high significant (P <0.001).**

a = significant with group I, **b**= significant with group II, **c**= significant with group III, **d** = significant with group IV, **e** = significant with group V

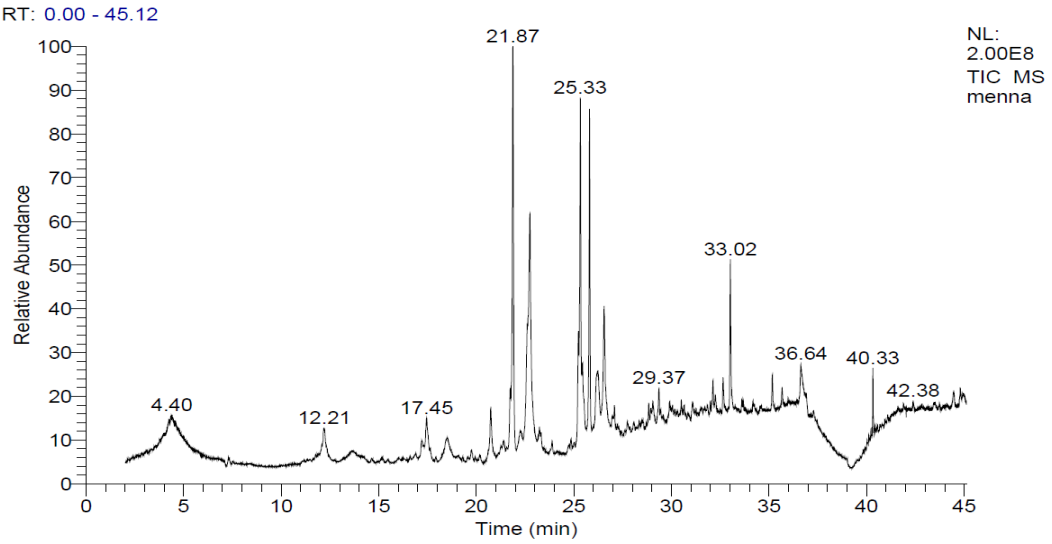

Figure (1): GC/MS total ionic chromatogram of dandelion leaf methanolic extract.

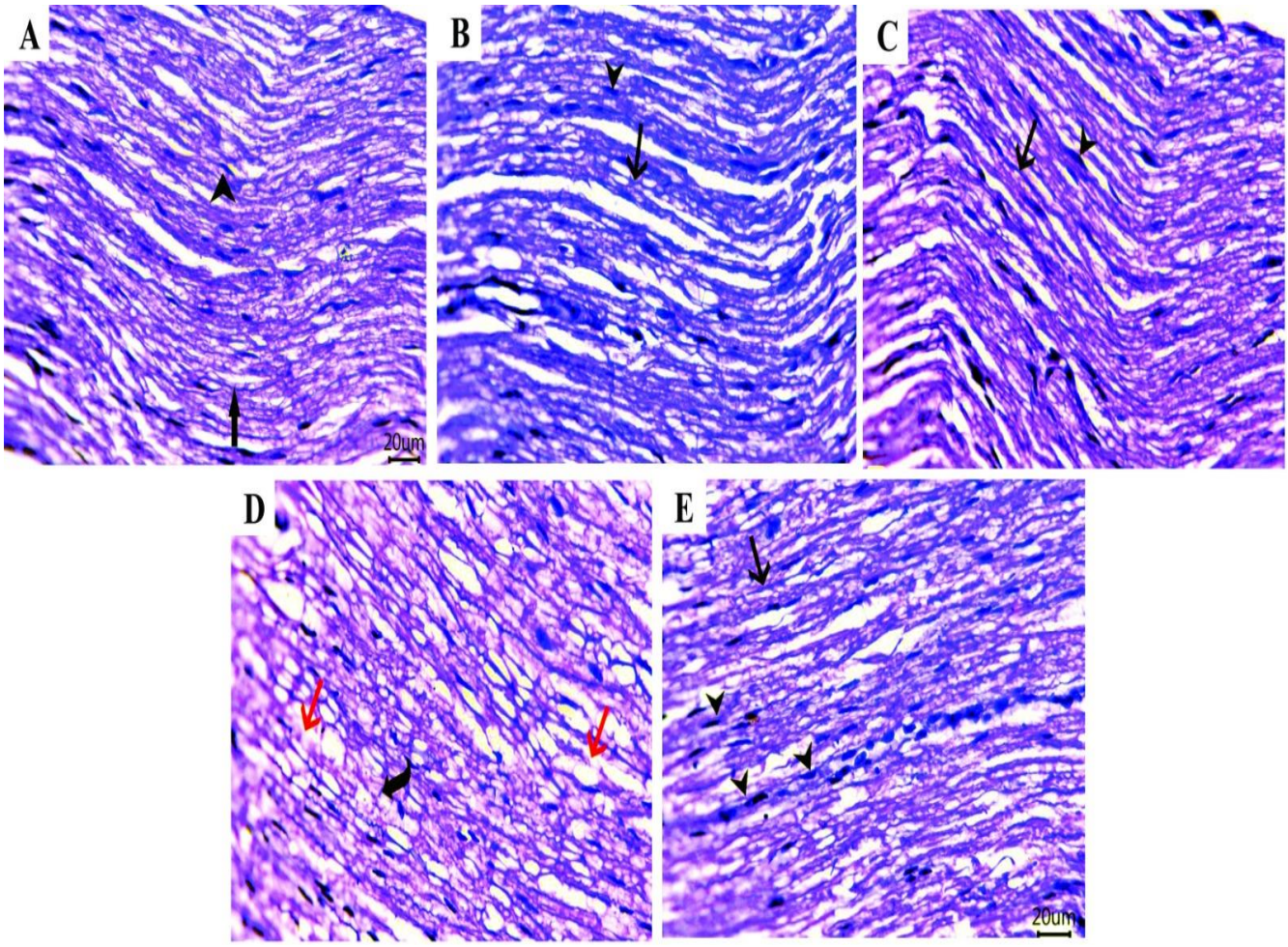

Figure (2): Representative photomicrograph of a section from the sciatic nerve of a rat from control group (A), vehicle group (B) and dandelion group (C) showing normal histological architectures of central axons (arrows) surrounded by myelin sheath and Schwann cells (arrowheads). Paclitaxel group (D) showing Irregularity of axonal thickness with diffuse fragmentation of both axons and myelin sheath (Red arrows) accompanied with presence of empty spaces (curved arrow). Paclitaxel & DLE group (E) showing proliferated Schwann cells (arrowheads) with preserved structures of majority of axons (arrow) (H&E x 400) Scale bar 20µm.

DISCUSSION

Analysis of dandelion leaf extract by GC/MS revealed the identified compounds including fatty acid esters which was the major compounds, fatty acids, steroids, alkanes, alkene, alcohols, Phthalates, phenol, Vitamin and carbonyl ketone. The four major fatty acids recognized were Hexadecanoic acid, methyl ester; n-Hexadecanoic acid; Octadecanoic acid, methyl ester and 10-Octadecenoic acid, methyl ester.

Studies on *Taraxacum officinale* have shown that different extraction methods and plant parts yield a variety of bioactive compounds. In the study by Razak et al. [45], A wide variety of active metabolites were identified by GC-MS analysis of the methanol extract of the entire Taraxacum officinale plant. The plant's rich phytochemical profile is highlighted by the 19 chemicals that have been found in several classes, including phenols, terpenes, fatty acids, and alkanes. Hexadecanoic acid, methyl ester of hexadecanoic acid (2.78%), hydroxy-benzeneacetic acid, b-amyrin, eicosane, Lup-20(29)-en-3-ol, hentriacontane, 3-methyl-2-pentanone, lupeol, and tritetracontane were the main active compounds based on percentage peak area and retention duration.

The study by Díaz et al. [46], provides valuable insights into the phytochemical constituents of dandelion leaves, especially by use GC-MS to analyse extracts of hexane and ethyl acetate. The richness of the dandelion's chemical composition is highlighted by the detection of several chemicals in these extracts. They discovered that the hexane

extract contained 40 different components:Triterpenoids made up 72.46%, followed by terpenes (16.56%), phthalate ester (4.25%), fatty acids and derivatives (1.46%), aldehydes and ketones (1.42%), alcohols (1.81%), and unknown chemicals (0.55%). The ethyl acetate extract, on the other hand, included 80 different components: 37.86% unknown chemicals, 3.04% fatty acids and derivatives, 17.08% terpenes, 1.50% ketones and alcohols, and 37.06% triterpenoids.

The results of the present study showed a significant increase in the level of NT in serum of paclitaxel treated group as compared to their corresponding values in control group.

This result goes along with the study done by Werida et al. [47] They discovered that NT levels in the blood significantly increased in breast cancer patients who got paclitaxel at a dose of 80 mg/m2 IV, every week for six months. Furthermore, Bakry et al. [48] revealed a significant increase in serum NT in breast cancer patients received paclitaxel at dose of 175 mg/m2 biweekly for 4 cycles.

Neurotensin is increasingly recognized for its role in neuroinflammatory and neurodegenerative processes due to its interactions with neurotransmitter systems, immune responses, pain perception and modulation. inflammatory pain induced by paclitaxel has been associated with enhanced release of neurotensin (NT). Though, Paclitaxel can trigger neuroinflammation, leading to increased levels of NT. This release can sensitize neurons and contribute to the development of neuropathic pain associated with chemotherapy [49].

Rats treated with dandelion leaf extract and paclitaxel in the current study had significantly lower NT levels than the group treated with paclitaxel which still not returned to levels of control group indicating partial improvement.

Dandelion leaf extract has been shown to contain various constitutions that have anti-inflammatory properties like 9-Hexadecenoic acid, Octadecanoic acid, Phenol, 2-methyl-5-(1-methylethyl)- and l-(+)-Ascorbic acid 2,6- ihexadecanoate which helped in prevention and recovery of inflammatory neuropathic pain caused by paclitaxel.

When compared to control group, paclitaxel treatment significantly raised TNF-α mean values in the current study. The elevated levels of this inflammatory marker indicated that the activation of the inflammatory cascade and increased production of pro-inflammatory cytokines, such as tumour necrosis factor-α, are the causes of paclitaxel-induced peripheral neuropathy. The results of the present study are correlating with the results of Semis et al. [50], in which paclitaxel was administrated to rats in a dose of 2 mg/kg/day for 5 days, led to elevation of TNF-α level in serum of treated rats. Similarly, in a study done by Miao et al. [51] on Sprague Dawley rats, PTX was administrated in a dose of 1 mg/kg/one injection every two days and a total of four injection, the level of TNF-α was elevated than control group.

In agreement with this study, Zhao et al. [52] who discovered that male Sprague-Dawley rats given PTX on alternate days (days 0, 2, 4, and 6) at a dose of 2 mg/kg showed elevated levels of serum TNF-α in comparison to control group. In another study done by Okkay et al. [53] In order to cause acute paclitaxel toxicity in adult male Wistar rats, a single intraperitoneal dose of 8 mg/kg paclitaxel was administered at the start of the experiment. The results of the investigation showed that the levels of TNF-α in the rats' plasma were noticeably higher.

Tumor necrosis factor-alpha (TNF-α) is an essential pro-inflammatory cytokine that plays a role in a number of physiological and pathological processes, including infection, inflammation, and the development of tumors. [54]. Immune system cells such mast cells, lymphoid cells, and macrophages are the main producers of TNF-α. [55].

In the present study, the mean serum TNF-α levels in the dandelion leaf extract+ paclitaxel-treated rats were significantly lower than those in the paclitaxel-treated group, although they had not yet reached the control group's level, suggesting a partial improvement. The observations of the present work were in line with the results of Hamza et al. [56] who found that Adult male albino rats pretreated with dandelion in a dose of (500 mg/kg body weight orally) for 8 weeks before CCL4 led to restoration of TNF-α which indicate partial improvement. Şükran et al. [57] also mentioned dandelion's protective properties. TNF-α immunoreactivity in liver tissue was significantly reduced in male rats given dandelion (2.4 g/kg body weight) orally for 14 days following streptozotocin-induced diabetes.

Hu et al. [58] demonstrated that dandelion administration at doses of 10.0, 100.0, and 200.0 µg/ml decreased TNF-α levels in rats' mammary microvascular endothelial cells treated with lipopolysaccharide.

The decrease in TNF-α observed in this study could be attributed to the presence of bioactive compounds in dandelion leaf extract (DLE) such as phenols and alkaloids. According to studies Sterols and fatty acids are also present in DLE which may be able to treat inflammation. Widely present in the plant, fatty acids are frequently recognized as the primary constituents that give them their anti-inflammatory properties. Additionally, it has been demonstrated that steroids are effective inhibitors of inflammation [59].

The results of this investigation showed that the sciatic nerve tissue of rats treated with PTX had significantly lower levels of GSH and SOD and significantly greater levels of MDA compared to the control group. This suggests that oxidative stress, a significant contributing factor to the development of peripheral neuropathy, is present in sciatic nerve tissue.

Our obtained data were in accordance with the results of Semis et al. [50] They discovered that, in comparison with the control group, the sciatic nerve tissue homogenate's MDA level significantly increased and its GSH and SOD levels significantly decreased after receiving PTX intraperitoneally for five days at a dose of 2 mg/kg body weight. Furthermore, Rahman et al. [60] discovered that, when compared to the control group, giving White Sprague-Dawley male rats PTX intravenously once a week for eight weeks at a dose of 10 mg/kg raised the sciatic nerve level of MDA and decreased the sciatic nerve level of GSH and SOD.

In a study done by Singh et al. [61], Male Wistar rats were given PTX intraperitoneally every other day for 28 days at a dose of 1 mg/kg body weight. the sciatic nerve tissue homogenate showed a marked rise in MDA levels and a decrease in GSH and SOD levels when compared to the control group.

Zafar et al. [62] discovered that administering PTX intraperitoneally four times a week to male mice at a dose of 2 mg/kg body weight raised MDA levels in the spinal cord and sciatic nerve tissue while markedly reducing GSH and SOD levels. Increased H2O2 and ROS production may be the cause of this impact, which in turn promotes oxidative stress.

When cells and tissues produce too many reactive oxygen species (ROS) and the antioxidant system is unable to eliminate them, this is known as oxidative stress. As a result, the nervous system is easily attacked by excessive oxidative damage due to its high energy requirements, rich lipid content, and limited antioxidant capacity. As a result, the increase in ROS is a cellular danger that can seriously harm neurons, if it exceeds or bypasses counteracting mechanisms [63].

It is true that one popular technique for determining oxidative stress is to evaluate the end products of lipid oxidation. When lipids undergo oxidative damage, they generate various byproducts that can serve as biomarkers for oxidative stress levels in biological systems. The term "lipid peroxidation" is commonly used to describe the chemical reaction between ROS and lipids [64]. Zhang et al. [5] claimed that MDA is a marker that is frequently used to measure the levels of oxidative stress and lipid peroxidation.

However, one of the most prevalent antioxidants in a variety of organisms, including bacteria and eukaryotes, is the tripeptide glutathione (GSH), which is known for its reductive properties [65].

Khawaja et al. [66] asserted that endogenous antioxidants like superoxide dismutase (SOD) offer the primary defence against cellular damage caused by reactive oxygen species (ROS). Superoxide radicals are dismutated into hydrogen peroxide, a less dangerous form, by SOD.

Anti-cancer medications work by leading cancer cells to produce ROS, which triggers apoptosis. However, by targeting both cancer cells and other cells, these generated ROS can be hazardous to different tissues and organs, particularly the nervous tissue. The peripheral nervous system is significantly more susceptible to toxins than the others due to its structural characteristics and ineffective vascular barrier. The body possesses both enzymatic and non-enzymatic antioxidant defence systems against ROS under normal conditions. Nevertheless, the peripheral nervous system's cellular antioxidant defence systems are not very strong. As a result, they are vulnerable to oxidative stress [67].

The DLE+ paclitaxel-treated rats in the current study showed a considerable increase in GSH and SOD levels and a significant drop in mean MDA values as compared to the paclitaxel-treated group, which have not yet reached the level of the control group, indicating a partial improvement.

The findings of this study were consistent with those of Erdem and Özaslan [68], who discovered that male Wistar Albino rats given 500 mg/kg of DLE intragastrially once a day for five weeks prior to cisplatin administration exhibited a reduction in MDA levels in sciatic nerve tissues, indicating a partial recovery from oxidative stress damage.

The current study's findings are corroborated by Ömür et al. [69], who found that co-administration of dandelion extract at 150 and 200 mg/kg body weight, administered intraperitoneally (IP) for 8 days in male Sprague Dawley rats, improved the effects of gentamicin sulphate oxidative stress and restored antioxidant activity by improving MDA, GSH, and SOD levels in the tissues under study.

Dandelion leaves are rich in hexadecanoic acid, methyl ester, 11-octadecenoic acid, methyl ester, and octadecanoic acid, methyl ester according to the GC-MS study of DLE. These structures have been shown to have potent antioxidant activity that prevents lipid peroxidation and proved to be a strong free radical scavenger [20]. This may show why DLE can raise SOD and GSH levels (antioxidant markers) and lower MDA levels (lipid peroxidation marker).

As regarding histopathological changes, the current study's findings demonstrated that paclitaxel treatment caused hypomyelination and Wallerian

degeneration of the sciatic nerve, which was manifested by uneven axonal thickness, diffuse myelin sheath and axon fragmentation, and the presence of empty spaces.

The current study's findings are consistent with earlier researches. According to Wu et al. [70], myelinic debris, abnormal axonal morphologies, and degenerating swollen axons were the hallmarks of retrograde degeneration of transverse sections of the sciatic nerves, which was evident from day 7 following the initial injection until day 56 in the paclitaxel group.

Kassab and Elkaliny [71] revealed that majority of the myelinated nerve fibers were significantly disrupted by paclitaxel (16 mg/kg once weekly for five weeks). Axon entrapment caused certain fibers to become conspicuous, and other sections showed uneven myelin thickening and noticeable invaginations and evaginations of the myelin sheath. As stated by Pozzi et al. [72], female Wistar rats given paclitaxel intravenously once weekly for four weeks at a dose of 10 mg/Kg developed axonopathy following therapy, exhibiting a significant loss of fibers and general myelinated fiber degeneration.

Administration of dandelion leaf extract with paclitaxel showed a significant improvement of all histopathological changes compared with sciatic nerve tissues from rats treated with paclitaxel alone. The light microscopical examination showed axonal regeneration that represented by proliferated Schwann cells with preserved structures of majority of axons beside mild demyelinated fibers. This improvement in histopathological findings indicate that dandelion leaf extract decreased the oxidative stress, inflammation and apoptosis of sciatic nerve.

Conclusion and Recommendations

Paclitaxel induces painful peripheral neuropathy. The significant increase in Neurotensin levels in the serum of paclitaxel treated group with fragmentation of sciatic nerve axons detected by histopathology are indicators for the neural dysfunction. Inflammation is one of the main mechanisms of Paclitaxel induced peripheral neuropathy which indicated by the significant increase in serum TNFα levels. The histopathological changes caused by Paclitaxel in sciatic nerves are related to the generation of ROS. The significant increase in MDA levels and the decrease in SOD enzymes activity & GSH levels are indicators of Paclitaxel induced oxidative stress and lipid peroxidation. Dandelion leaf extract proved by GC/MS to contain effective compound with vital medical and pharmacological activity that could have a neuroprotective action against paclitaxel-induced peripheral neuropath (PIPN). DLE offer some protection against painful PIPN as it significantly decreases serum Neurotensin levels and reverse all the histopathological changes induced by paclitaxel in sciatic nerves. The anti-inflammatory activity of DLE help to protect peripheral nerves. This is proved by the decrease in the serum TNF-α levels. DLE have antioxidant activity as it significantly decreased MDA level and increased SOD & GSH enzyme activity. So, this study recommends incorporating dandelion as a cost-effective, safe, and widely available plant into the regular diet of cancer patients and advocating its inclusion in hospital meal protocols. Also, Further studies are needed to determine the optimal dose, duration, preparation methods, and potential combinations of dandelion with other herbs as a dietary supplement.

Conflict of interest

The authors declared that they have no conflicts of interest with respect to authorship and/or publication of this article.

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