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Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2019, *18*, 45-54

RESEARCH ARTICLE

Anti-inflammatory and Antioxidant Activities of the Extracts from Leaves and Stems of *Polygonum odoratum* Lour

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ARTICLE HISTORY

Received: May 21, 2018
Revised: October 17, 2018
Accepted: November 06, 2018

DOI:
10.2174/1871523017666181109144548

Abstract: ***Background:*** *Polygonum odoratum* is an indigenous vegetable that has been used as a favoring agent and also used as a Thai traditional medicine to treat flatulence.

Objective: To analyze active ingredients, total phenolic and total flavonoid contents, anti-inflammatory and antioxidant activities from leaf and stem extracts of *P. odoratum*.

Methods: Leaves and stems were dried and extracted by using methanol, dichloromethane and water for obtaining Methanolic Leaf Extract (MLE), Methanolic Stem Extract (MTE), Dichloromethane Leaf Extract (DLE), Dichloromethane Stem Extract (DTE), Water Leaf Extract (WLE) and Water Stem Extract (WTE). The extracts were quantified for total phenolic and total flavonoid contents by spectrophotometry and active compounds were analyzed by using GC-MS. Antioxidant activity was determined by ABTS and DPPH radicals scavenging assays. Anti-inflammatory activity was tested by the inhibition of nitric oxide production in RAW 264.7 macrophage cells induced by lipopolysaccharide.

Results: The DLE exhibited the most potent anti-inflammatory effect by inhibiting nitric oxide production in a concentration-dependent manner (IC_{50} = 53.75±0.72 µg/mL). MLE exhibited strong antioxidant activity and contained the highest concentration of phenolic compounds (52.59±0.58 mg gallic acid equivalent/g extract) and flavonoid (19.97±0.11 mg quercetin equivalent/g extract). E-15-Heptadecenal and 3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol were found predominantly in the methanol extracts.

Conclusion: The leaf extract of *P. odoratum* showed potent anti-inflammatory and antioxidant activities, mediated by DLE and MLE, respectively.

Keywords: Anti-inflammation, antioxidant, macrophage, nitric oxide, *Polygonum odoratum*, phenolic compounds.

1. INTRODUCTION

Inflammation is a crucial self-protective response to tissue injury or infection. During the inflammatory process, many immune cells are involved, including macrophages. These different cells directly trigger immunological events such as the release of cytokines, chemokines and inflammatory mediators [1]. Nitric Oxide ($NO^{\bullet}$) is a potent inflammatory mediator in various organ systems and is also involved in vasodilation and nonspecific host defense [2]. However, prolonged inflammation is associated with many chronic diseases, such as rheumatoid arthritis, diabetes mellitus, cardiovascular diseases and cancers [3-6].

Free radicals including Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) create a highly reactive state that can damage many biomolecules, leading to several chronic diseases such as diabetes mellitus, atherosclerosis, inflammation and cancers [7, 8]. In defense, antioxidants

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1875-614X/19 $58.00+.00

counteract such harmful effects and prevent this pathogenesis. Importantly, there are many natural antioxidant extracts from plants that contain several kinds of powerful bioactive compounds that are known to exhibit antioxidant activity, such as phenolic acids, flavonoids, and tannins [9, 10].

Polygonum odoratum Lour is in the family Polygonaceae, generally known as Pakpaw in Thailand. It is a biennial plant and grows well in wet conditions [11]. The leaves are green and slender, similar to bamboo leaves. The stems are red, straight and about 30 - 35 cm tall. The plant has a strong coriander aroma and a hot spicy taste. It has been used for adding flavor and aroma to food and is also used to treat flatulence and help to relieve constipation in Thai traditional medicine. Many studies have reported on the bioactive compounds in an ethanolic leaf extract of this plant, confirming that it has high levels of phenolic compounds and exhibits strong antioxidant activity [12]. However, the bioactive compounds and biological activities in the different extraction solvents have not been investigated. This study aims to determine total phenolic and flavonoid contents, antioxidant and anti-inflammatory activities, in leaf and stem extracts obtained from three different extraction methods.

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents

Dulbecco's Modified Eagle Medium (DMEM) and fetal bovine serum (FBS) were purchased from Gibco (NY, USA). Penicillin-Streptomycin, Lipopolysaccharide (LPS) from *E. coli*, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT), N-(1-naphthyl) ethylene dihydrochloride, sulfanilamide, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (trolox), 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid (ABTS), quercetin and 1,1-diphenyl-2-picrylhydrazyl (DPPH) were purchased from Sigma-Aldrich Inc. (St Louis, MO, USA). Phosphate Buffered Saline pH 7.0 (PBS), dimethylsulfoxide (DMSO), dichloromethane and methanol are of analytical grade.

2.2. Cell Culture

Murine macrophage cell line (RAW 264.7) was purchased from the American Type Culture Collection (ATCC, TIB-71, VA, USA). It was cultured in DMEM supplemented with 10% (v/v) FBS, 100 U/mL penicillin and 100 µg/mL streptomycin, and maintained at 37°C in 5% CO_2 incubator.

2.3. Plant Collection and Extraction

Leaves and stems of *P. odoratum* were collected fresh from Chiang Rai Province in Thailand during July - August 2016. Authentication of the plant was established by Dr. Jantrararuk Tovaranonte, School of Science, Mae Fah Luang University. The voucher specimen was deposited in the herbarium of the School of Medicine, Mae Fah Luang University (Herbarium number: MD2018080001-1). Each part was lyophilized and crushed to a fine powder. Extraction was performed according to the method established by Legault and colleagues with slight modification [13]. The dried powder of each part (50 g) was extracted by three different solvents; 95% methanol, dichloromethane and water (750 mL each) at 25°C for 72 h with 150 rpm rotation. The extracts were filtered 3 times and concentrated using a rotary evaporator for obtaining Methanolic Leaf Extract (MLE), Methanolic Stem Extract (MTE), Dichloromethane Leaf Extract (DLE) and Dichloromethane Stem Extract (DTE), respectively. The filtrate from water extraction was dried by using lyophilizer for obtaining Water Leaf Extract (WLE) and Water Stem Extract (WTE).

2.4. Determination of Total Phenolic and Total Flavonoid Contents

Total Phenolic Contents (TPCs) of the extracts were measured using a modified Folin-Ciocalteu method [14]. Briefly, extract solution was mixed with Folin-Ciocalteu's reagent, in the presence of 7% sodium bicarbonate, and measured absorbance (A) at 765 nm against reagent. The TPC were calculated from the standard curve constructed by using standard gallic acid (GA) at 10 - 100 µg/mL and expressed as mg of gallic acid equivalent (GAE)/g sample.

Total Flavonoid Content (TFC) was measured using an aluminum chloride colorimetric method [15]. Briefly, the extract solution was mixed with the reagent containing 10% (v/v) aluminum

chloride and 1 M potassium acetate, incubated at room temperature for 40 min, and measured absorbance at 415 nm against reagent blank. The TFC were calculated from the standard curve constructed by using standard quercetin (Q) at 10 - 200 μg/mL and expressed as mg of quercetin equivalent (QE)/g sample.

2.5. Gas Chromatography-Mass Spectrometry (GC-MS)

Volatile organic compounds in the extracts were analyzed by using the GC-MS method previously established by Cai and coworkers [16-18]. Conditions included a capillary column (Model Number 19091S-433, HP-5MS, 30 m x 0.25 mm i.d., film thickness 0.25 μm, Agilent Technologies, Santa Clara, CA, USA), sample volume (0.2 mL), helium gas used as a carrier gas with a flow rate of 1.0 mL/min, and mass spectra obtained by electron ionization at 70 eV and detected in a range of 30 - 300 m/z.

2.6. Determination of Antioxidant Activity

2.6.1. DPPH Radical Scavenging Assay

Stable $DPPH^{\bullet}$ solution (0.1 mM) was incubated with PBS, the extracts (50, 100 and 200 μg/mL), and L-ascorbic acid (AA, 15 mg/mL). The decrease in absorbance at 517 nm after 30 min in the dark was measured [16]. Percentage yields of inhibition was calculated using the following equation (1):

$$\text{Inhibition (\%)} = (A_{517\ nm}\ \text{PBS}) - (A_{517\ nm}\ \text{extracts or AA}) / (A_{517\ nm}\ \text{PBS}) \times 100 \quad (1)$$

2.6.2. ABTS Radical Scavenging Assay

A stock solution of $ABTS^{\bullet+}$, previously prepared by mixing 7 mM ABTS solution and 2.4 mM potassium persulfate solution (1:1, v/v) at room temperature for 12 - 16 h, was diluted with 95% (v/v) ethanol to obtain an absorbance of 0.007±0.050 at 734 nm. In assay, the extracts (50, 100 and 200 μg/mL) were incubated with working $ABTS^{\bullet+}$ solution for 15 min and the absorbance measured at 734 nm. $ABTS^{\bullet}$ scavenging capacity of the extracts was calculated by comparing with a standard curve of trolox (0 - 200 μg/mL) [17, 18]. The percentage of inhibition was calculated using the following equation (2):

$$ABTS^{\bullet}\ \text{scavenging activity (\%)} = (A_{734\ nm}\ \text{PBS}) - (A_{734nm}\ \text{extracts}) / (A_{734\ nm}\ \text{PBS}) \times 100 \quad (2)$$

2.7. Toxic Effect of RAW 264.7 Cells

Cell viability was determined by using MTT assay [19]. Briefly, RAW 264.7 cells ($5x10^3$ cells/well) were seeded in a 96-well plate and treated with various concentrations of the extracts for 24 h. After changing the medium, MTT solution (5 mg/mL in PBS) was added to the treated cells and incubated for another 4 h at 37°C. Next, the medium was removed and DMSO solution was added for dissolving the formazan crystals. Finally, the absorbance was measured at a wavelength of 540/630 nm. The untreated cells were used as a control group (100% of viable cells) for calculating percentage of viable cells after the treatment.

2.8. Nitric Oxide Production in LPS-induced RAW 264.7 Cells

RAW 264.7 cells were seeded in 24-well plates at a density of $5x10^4$ cells/well and incubated at 37°C for 24 h. Firstly, culture medium, aminoguanidine (AG, 100 μg/mL) as a positive control and the extracts (50, 100 and 200 μg/mL) were added to the cell and mixed gently. Next, LPS (2 μg/mL) was added to the wells and incubated for 24 h [20]. After centrifugation, the supernatant media were incubated with Griess reagent composing 0.1% (w/v) naphthyl-ethylene-diamide dihydrochloride, 1% (w/v) sulfanilamide and 5% (v/v) concentrated phosphoric acid and measured absorbance at 650 nm [18]. Produced $NO^{\bullet}$ concentration was calculated from the standard curve of sodium nitrite (0 - 200 nM). Inhibitory effect was determined using the following equation (3):

$$\text{\% Inhibition} = (A - B) / (A - C) \times 100 \quad (3)$$

which A denotes LPS and media well, B denotes LPS and AG or extracts well, and C denotes media well.

2.9. Statistical Analysis

The results are expressed as mean ± SEM of three independent measurements. Statistical analysis was determined by using One-way Analysis of Variance (ANOVA), following this a post-hoc test was applied. Results were indicated as significant at $p < 0.05$.

Table 1. Yield, TPC and TFC of different extracts of *P. odoratum.*

Extract	Yield	TPC	TFC
	(% w/w)	(mg GAE/g Extract)	(mg QE/g Extract)
WLE	4.34	27.97 ± 0.23$^{\#}$	8.30 ± 0.38$^{\#}$
WTE	3.92	6.78 ± 0.16	5.91 ± 0.18
MLE	15.39*	52.59 ± 0.58$^{*\#}$	19.97 ± 0.11$^{*\#}$
MTE	15.38*	40.03 ± 0.37*	5.07 ± 0.07
DLE	2.46	2.35 ± 0.08	0.83 ± 0.48
DTE	1.21	3.24 ± 0.08	0.26 ± 0.64

Data obtained from three independent experiments are expressed as mean ± SEM. $^{*}p$ <0.05 when compared to the water extracts; $^{\#}p$ <0.05 when compare with WTE. TPC: total phenolic content; TFC: total flavonoid content; WLE: water leaf extract; WTE: water stem extract; MLE: methanolic leaf extract; MTE: methanolic stem extract; DLE: dichloromethane leaf extract; DTE: dichloromethane stem extract.

3. RESULTS

3.1. Yield, TPC and TFC of the Extracts

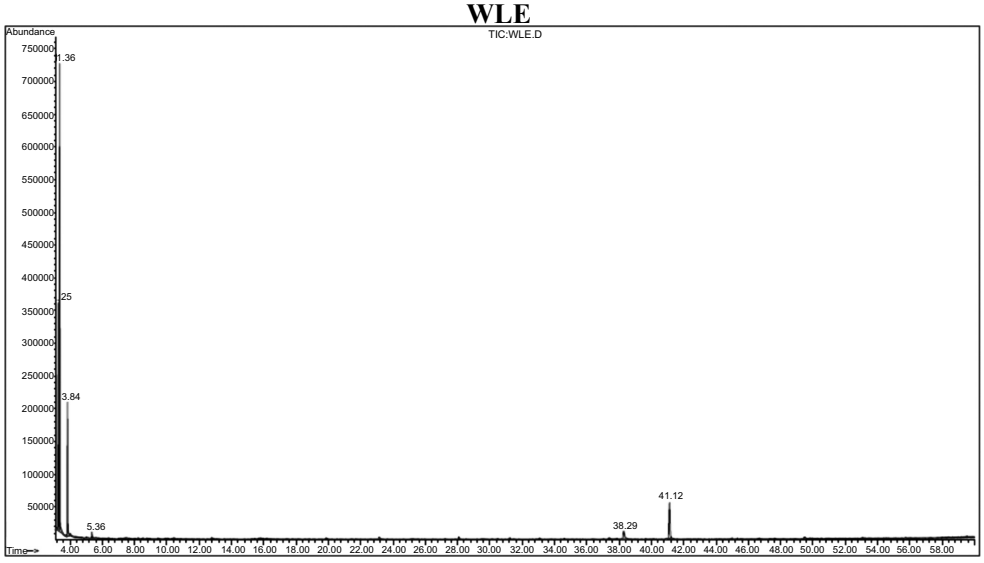
Percentage yields of the extracts from the leaves and stems of *P. odoratum* are shown in Table **1**. The highest yields were obtained from MLE and MTE (~15.39%), the lowest percentage yield was found in DLE and DTE (2.46% and 1.21%, respectively). However, there was not any difference of the yield between leaf extract and stem extract prepared by three different extractions. Obviously, TPC was significantly much higher in the MLE and MTE than the other extract solvents and tended to be higher in the leaf extract than the stem extract. Similarly, TFC was present highest in the MLE and second highest in the WLE when compared with the other extracts (p <0.05), and it was significantly higher in the leaf extract than the stem extract (Table **1**).

3.2. GC-MS Analysis

Result of GC-MS analysis shown in Fig. (**1**), indicated the predominant presence of E-15-heptadecenal (T_R = 55.66 min) as well as 3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol (T_R = 48.62 min) in the two methanol extracts from *P. odoratum*, while none were detected in the two water extracts.

3.3. Free-radicals Scavenging Activities

Result of free-radicals scavenging activity measured in the leaf and stem extracts of *P. odoratum* is presented in Figs. (**2** and **3**). Percentage of



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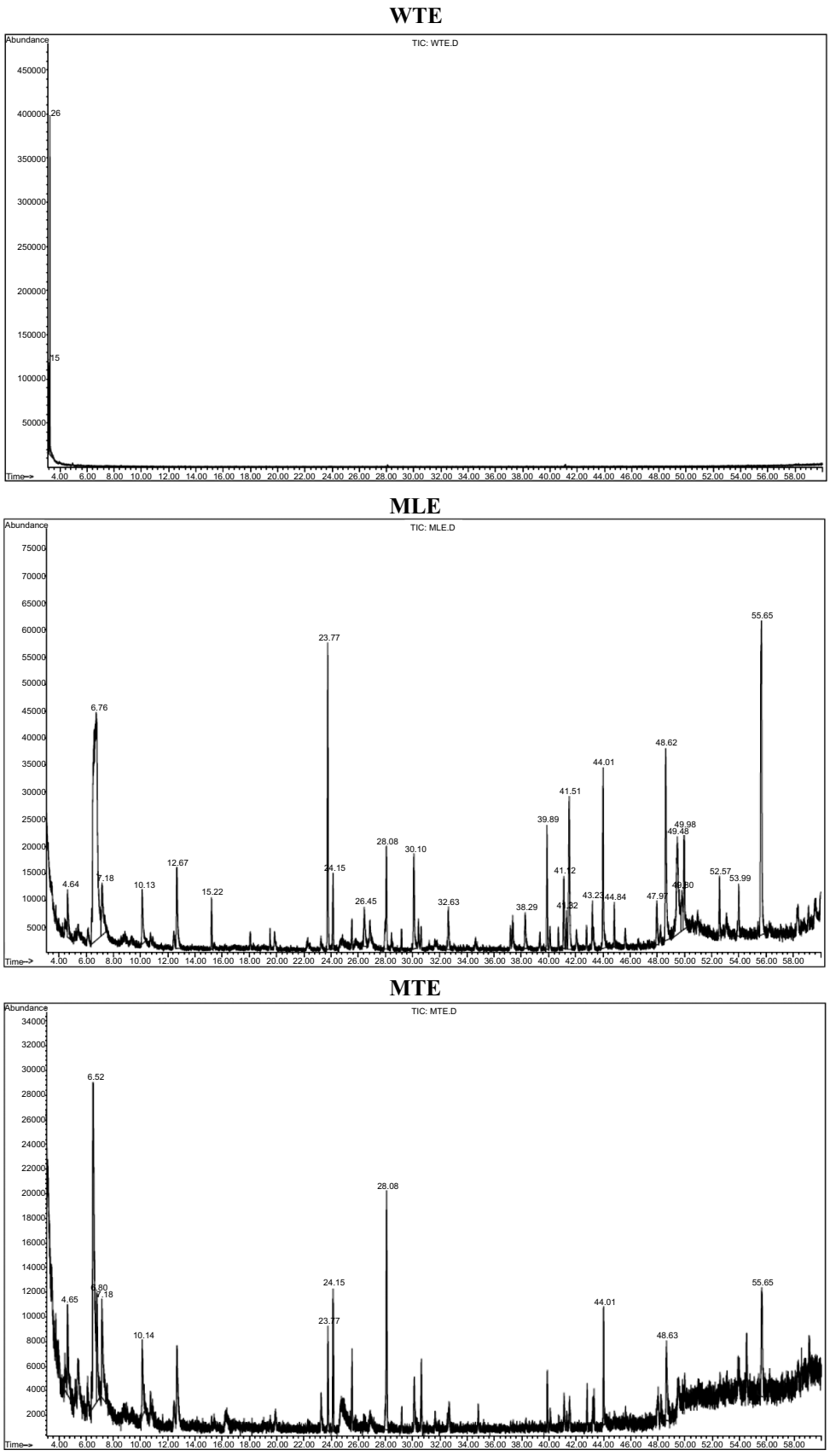

Fig. (1). GC-MS analysis of different extracts from *P. odoratum.* WLE: Water Leaf Extract; WTE: Water Stem Extract; MLE: Methanolic Leaf Extract; MTE: Methanolic Stem Extract.

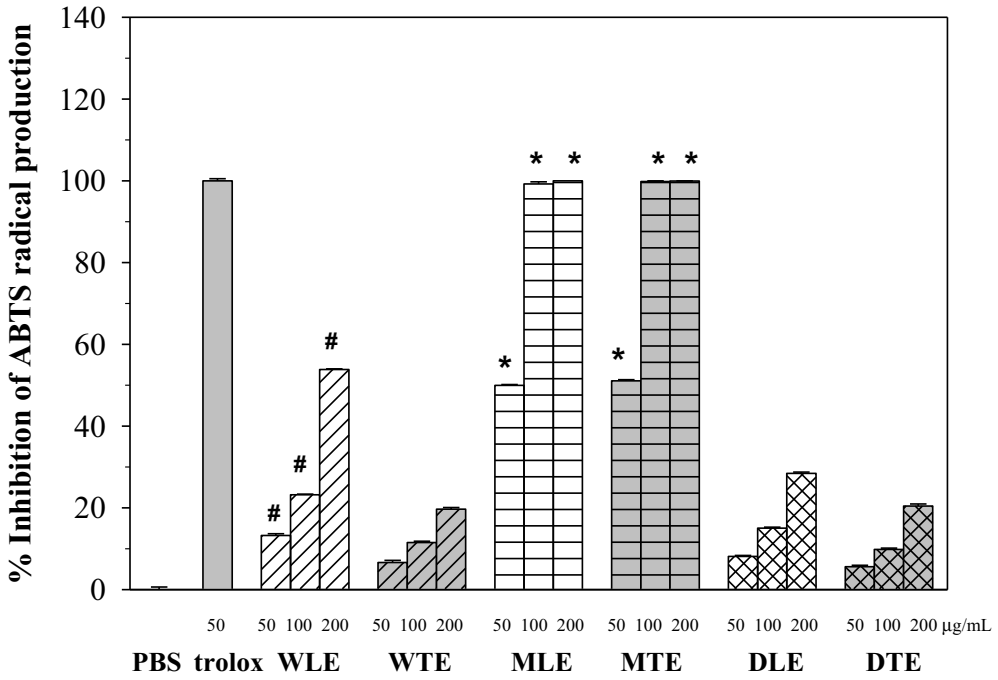

Fig. (2). Antioxidant activity of different extracts of *P. odoratum* as shown by ABTS radical-scavenging activity. Trolox was used as the positive reference. Data obtained from three independent experiments are expressed as mean ± SEM. $^{*}p$ <0.05 when compared with the water extracts; $^{\#}p$ <0.05 when compared with WTE. WLE: Water Leaf Extract; WTE: Water Stem Extract; MLE: Methanolic Leaf Extract; MTE: Methanolic Stem Extract; DLE: Dichloromethane Leaf Extract; DTE: Dichloromethane Stem Extract.

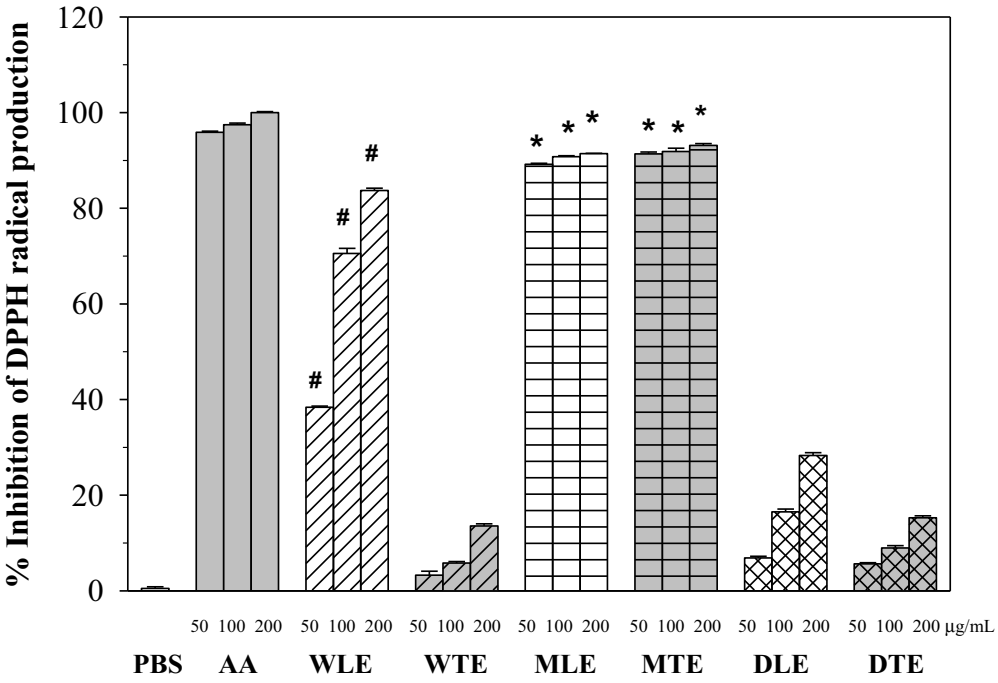

Fig. (3). Antioxidant activity of different extracts of *P. odoratum* as shown by DPPH radical-scavenging activity. Ascorbic Acid (AA) was used as the positive reference. Data obtained from three independent experiments are expressed as mean ± SEM. $^{*}p$ <0.05 when compared with the water extracts; $^{\#}p$ <0.05 when compared with WTE. WLE: Water Leaf Extract; WTE: Water Stem Extract; MLE: Methanolic Leaf Extract; MTE: Methanolic Stem Extract; DLE: Dichloromethane Leaf Extract; DTE: Dichloromethane Stem Extract.

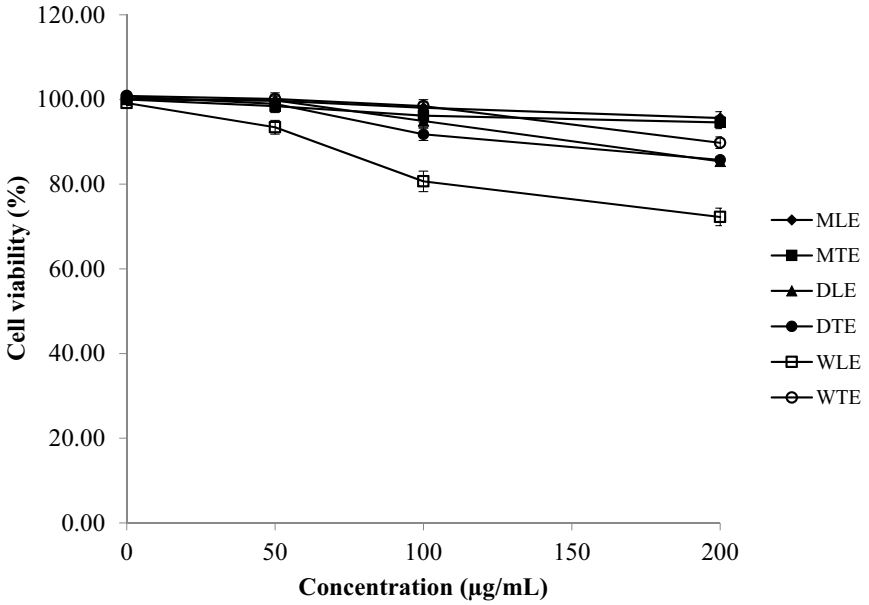

Fig. (4) Viability of RAW 264.7 cells treated by different extracts of *P. odoratum* at various concentrations for 24 h. Data obtained from three independent experiments are expressed as mean ± SEM. $^{*}p$ <0.05 when compared with the water extracts; $^{\#}p$ <0.05 when compared with the stem extracts. WLE: Water Leaf Extract; WTE: Water Stem Extract; MLE: Methanolic Leaf Extract; MTE: Methanolic Stem Extract; DLE: Dichloromethane Leaf Extract; DTE: Dichloromethane Stem Extract.

DPPH and ABTS radical scavenging activities increased in a concentration-dependent manner, which the MLE and MTE clearly showed potent activity. At high concentrations the inhibition was the highest (90%), followed by the WLE (83.69 ± 0.49%) and DLE (28.29 ± 0.60%), respectively. The WTE showed the lowest activity in both radical scavenging assays.

3.4. Viability of RAW 264.7 Cells

As shown in Fig. (**4**), all concentrations of the leaf and stem extracts with the three different solvents showed no cytotoxicity, the cell viability being more than 70%.

3.5. Anti-Inflammatory Activity in LPS-induced RAW 264.7 Cells

Inhibitory effect of the extracts was evaluated by measuring LPS-induced $NO^{\bullet}$ production from RAW 264.7 cells. As shown in Table **2**, the leaf extracts had higher potency than the stem extracts in a concentration-dependent manner. The DLE showed the highest inhibitory effect with IC_{50} = 53.75 ± 0.75 µg/mL, followed by DTE (IC_{50} = 147.50 ± 1.44 µg/mL). On the other hand, the lowest activity was shown in WTE.

4. DISCUSSION

Plant polyphenols have been increasingly investigated because of their potent antioxidant properties and their actions, possibly preventing various oxidative stress associated diseases such as cardiovascular disease, cancer, chronic inflammation, diabetes mellitus, and neurodegenerative disorders [21]. This study suggests that high levels of phenolic compounds and flavonoids can be found in methanolic extracts of *P. odoratum* and that could be related to their antioxidant activity, as shown by the inhibition of free radical production, as was clearly shown in MLE and MTE. However, identification of major active ingredients and further in-depth studies of the biological activities of the extract will have to be performed as a matter of some urgency.

Organic compounds such as (Z)-3-hexenal, (Z)-3-hexenol, decanal, undecanal, dodecanal, sulfanyl-hexanal and 3-sulfanyl-hexan-1-ol were previously identified in *P. odoratum*, some of these compounds have shown anti-*Salmonella* activity [11, 22]. Some studies have reported that phytols, such as 3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol, show interesting pharmacological activities, particularly anti-inflammatory activity. In this

Table 2. Anti-inflammatory activity of different extracts of *P. odoratum*, resulting from the inhibitory effect of NO• production in LPS-induced RAW 264.7 cells.

Extract	% Inhibition of NO• Production			IC_{50} (µg/mL)
	50 µg/mL	100 µg/mL	200 µg/mL	
WLE	2.65 ± 0.16$^{\#}$	5.46 ± 0.12$^{\#}$	10.33 ± 0.21$^{\#}$	> 200
WTE	0.01 ± 1.40	0.01 ± 1.94	0.02 ± 1.61	> 200
MLE	13.5 ± 0.5$^{*\#}$	17.8 ± 0.1$^{*\#}$	25.3 ± 0.1$^{*\#}$	> 200
MTE	2.14 ± 0.93*	1.90 ± 0.08*	8.41 ± 0.15	> 200
DLE	47.7 ± 0.1$^{*\#}$	66.6 ± 0.6$^{*\#}$	90.5 ± 0.4$^{*\#}$	53.8 ± 0.7
DTE	19.6 ± 0.5*	36.9 ± 0.2*	64.8 ± 0.6*	147.5 ± 1.4
AG	-	108 ± 1*	-	NA

Aminoguanidine (AG) was used as the positive reference. Data obtained from three independent experiments are expressed as mean ± SEM. $^{*}p$ <0.05 when compared with the water extracts. $^{\#}p$ <0.05 when compared with WTE. LPS: lipopolysaccharide; WLE: water leaf extract; WTE: water stem extract; MLE: methanolic leaf extract; MTE: methanolic stem extract; DLE: dichloromethane leaf extract; DTE: dichloromethane stem extract. NA = not available.

study we found two major compounds, E-15-heptade-cenal and 3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol, only in the methanol extracts from *P. odoratum* that may be related to their anti-inflammatory effects. These data were supported in previous studies that found 3, 7, 11, 15-tetramethyl-2-hexade-cen-1-ol in other plant extracts, such as a methanol extract of *Alnus nitida* Spach stem bark. This also exhibited anti-inflammatory and analgesic activities in rats [23], as did an acetone extract of *Agave tequilana* which showed anti-inflammatory and immune-modulating properties in Balb/c mice [24].

Although inflammation is a normal self-protective process, prolonged inflammation can cause serious manifestations as part of many chronic diseases. During the inflammatory process, immune cells are activated to release inflammatory mediators that then cause inflammation and damage tissue [25]. Nitric oxide is an important inflammatory mediator that is released by macrophages [26]. Inhibition of nitric oxide production is a way to decrease the levels of inflammation present in many chronic disease processes. In this study, the extracts from dichloromethane showed the greatest potency in reducing nitric oxide production in lipopolysaccharide induced RAW 264.7 macrophage cells. DLE had the highest anti-inflammatory effect and responded in a dose-dependent manner. Although, DLE has low levels of phenolic compounds and flavonoids it could contain other, as yet not identified, anti-inflammatory agents, these should be further investigated. The release of inflammatory cytokines in future animal model studies will help to confirm this.

CONCLUSION

The methanol extracts from both the stem and leaves of *P. odoratum* clearly show a high level of antioxidant activity that might be due to the high levels of polyphenols present. The extracts, using dichloromethane, demonstrated potent anti-inflammatory effects, the leaves being a more potent source, when compared to the stem. This variation should also be further investigated.

ABBREVIATIONS

AA = Ascorbic Acid

ABTS = 2,2’-azinobis (3-ethylbenzothiazoline-6-sulfonic acid

AG = Aminoguanidine

DMEM = Dulbecco’s Modified Eagle Medium

DPPH = 1,1-diphenyl-2-picrylhydrazyl

FBS = Fetal Bovine Serum

GA = Gallic Acid

GAE = Gallic Acid Equivalent

GC-MS = Gas Chromatography-Mass Spectrometry

LPS = Lipopolysaccharide

MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium Bromide

NA = Not Available

NO = Nitric Oxide

Q = Quercetin

QE = Quercetin Equivalent

RNS = Reactive Nitrogen Species

ROS = Reactive Oxygen Species

TFC = Total Flavonoid Content

TPC = Total Phenolic Content

trolox = 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic Acid

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support of Mae Fah Luang University and thank the Department of Biochemistry, Faculty of Medicine, Chiang Mai University and School of Medicine, Mae Fah Luang University for providing facilities.

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