Original Article

Promising pain-relieving activity of an ancient Persian remedy (mixture of white Lily in sesame oil) in patients with chronic low back pain

Saeed Rasoulinezhad[1], Nafiseh Hosseini Yekta[1], Ehsan Fallah[2]

[1]Department of Persian Medicine, Faculty of Medicine, AJA University of Medical Sciences, [2]Department of Orthopedic and Trauma Surgery, AJA University of Medical Sciences, Tehran, Iran

Abstract

Background and Objectives: Chronic low back pain (CLBP) is one the frequent musculoskeletal issues among adults mostly without a specific etiology. In this study, we investigated a traditional Persian remedy for back pain which is based on topical application of a mixture of sesame oil (SO) and white lily (LSM). **Materials and Methods:** The chemical profile, phenol content, and antioxidant activity of the herbal samples were determined using GC-MS, total phenol content (TPC) assay, and DPPH assay, respectively. Clinical efficacy of the herbal samples by a double-blind placebo was examined. **Results:** TPC of SO and LSM was 45 ± 5.7 and 68.3 ± 11.2 mg GAE/g oil mixture, respectively. The SO could inhibit 59.7% of free radicals, whereas LSM showed a radical inhibition rate of 74.7% in DPPH assay. LSM could reduce the pain feeling and obtained the lowest pain scores (Oswestry disability index and numeric rating scale) in weeks 4 and 8 of therapy in comparison to other treatment groups (diclofenac gel and SO) and placebo control (Vaseline). **Conclusions:** The results implicate the LSM as a novel therapeutic alternative for the therapy of the CLBP.

Keywords: Chronic low back pain, *Lilium candidum*, sesame oil, white lily

Introduction

According to a concise definition provided by International Association for the Study of Pain (IASP), low back pain is a discomfort feeling in lumbosacral region. Backache is one of the most occurring musculoskeletal disorders affecting 80% of people at least once during their lifetime. Low back pain was ranked as third leading cause of disease burden in Iranian people aged 15–69 years by a systematic review and meta-analysis.[1] A systematic review determined the life-time prevalence of back pain in Iran. The back pain was estimated 51% (95% CI: 40.1–61.8) by analyzing 20 studies reported from various areas in Iran.[2] Chronic low back pain (CLBP) prevalence was found to be higher (46%–65%) among healthcare workers (physicians, nurses, healthcare personnel).[2,3] Moreover, the economic burden of CLBP is significant considering its direct negative impact on the financial state of patient as a result of high costs of expanded medical services and therapeutics use and indirect effect on national economy by an increased rate of lost workdays following the CLBP-mediated inability of workers.[4] To date, various treatment techniques have been developed for management of CLBP. Monotherapy using medicines such as anti-inflammatory drugs, pain-killers, or muscle relaxants in order to control CLBP may not be sufficient, because of the chronicity and recurrence of pain episodes. As another pharmacological solution, one of the promising candidates to relieve the CLBP is herbal medicine. *Lilium candidum* (LC) also known as white lily (in Persian: Susan-e-Sefid) and Madonna lily is a bulbous flower and grows as a native plant in north of Iran.[5] In the ancient times, it was used as a medical plant for treatment of burn, erythema,

Address for correspondence: Dr. Nafiseh Hosseini Yekta, Department of Persian Medicine, Faculty of Medicine, AJA University of Medical Sciences, Tehran, Iran.
E-mail: nyekta@yahoo.com

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external inflammation, and wound healing.[6,7] LC was indicated by Avicenna, a famous physician in ancient Persia in his book (The Canon of Medicine) for the both analgesic and anti-inflammatory activities.[7] So, in this study, we aimed to evaluate relieving effect of LC as a novel treatment candidate in people with CLBP.

Materials and Methods

Plant material and drug preparation

The flowers of fresh LC in its blossoming stage on late spring were gathered from north of Iran. The sesame oil (SO) was purchased from an Iranian company (Talayetabiat, Iran). Mixture of LC and SO was prepared based on recipes retrieved from ancient Persian medical manuscripts.[6] Briefly, the flowers of LC were mixed with SO in a ratio of 1:18 (w/w) and then kept under the sun for 40 days. Moreover, topical 1% gel of diclofenac was purchased (Behsa Pharmaceutical Co., Tehran, Iran). Vaseline (petroleum jelly) was also purchased (Farabi Ltd., Iran) and used as placebo control.

GC-mass analysis of plant material

The chemical constituents of the SO and LSM were determined using an Agilent 7890N gas chromatograph machine (Agilent Technologies, Santa Clara, CA) equipped with a HP-5MS 5% phenylmethylsiloxane capillary column (30 m × 0.25 mm, 0.25-μm film thickness). The temperature program for column was as the followings: Kept at 60°C for 4 min, then raised at the rate of 3°C/min to 100°C and kept for 2 min, again raised at the rate of 6°C/min to 250°C and kept for 7 min. Injector and detector temperatures were set at 260°C and 270°C, respectively (split ratio: 50.1). Helium was selected as the carrier gas at a flow rate of 1 ml/min. The gas chromatograph machine was also coupled with an Agilent 5975C (Agilent Technologies) mass spectrometry (MS) detector. Same capillary column (HP-5MS) and similar temperature program with GC analysis were also used for MS detector.

Measurement of radical scavenging activity by DPPH method

Briefly, a fresh working methanolic solution (0.004%, w/v) was prepared using a 100× stock solution (400 mg/100 mL) of 2,2-diphenyl-1-picrylhydrazyl (DPPH). About 100 μL of the LSM and SO samples were mixed into 900 μl of DPPH working solution using a vortex machine. The mixtures were kept at room temperature (25°C) for 15 min. Ascorbic acid was used as the reference standard. The absorbance of mixtures was measured at 517 nm.

Measurement of total phenol content

The total phenol content (TPC) of LSM and SO samples were determined using the Folin–Ciocalteu reagent in which gallic acid (0.5 mg/mL) was also incorporated in assay as the reference standard. A reaction mixture was prepared by mixing the 0.5 mL of oil samples (LSM or SO) dissolved in alcohol (EtOH) and 1 mL of water-diluted Folin–Ciocalteu reagent. The mixture was kept for a short time (5 min) at dark then 1 mL of sodium carbonate (Na_2CO_3) solution (7.5%, w/v) was added to the mixture. The final mixture was covered with parafilm and kept at ambient temperature (25°C) for 2 h. At the end of incubation, the mixture was centrifuged at 3,000 rpm for 10 min. The absorbance values were measured at 760 nm gallic acid at various concentrations (0.005–0.025 mg) was used to fit a standard curve ($y = 35.96x + 0.0096$; $r^2 = 0.9986$; y, absorbance; x, gallic acid concentration).

Participants and treatment schedule

Patients (both male and female) attending Imam Reza Hospital, Tehran, Iran, and diagnosed with CLBP were randomly incorporated into the study (March and April, 2018). The study was registered by Iranian Registry of Clinical Trials (IRCT) (registration No.: IRCT20171010036691N2). Moreover, an ethical approve was obtained from local ethics committee (AJA University of Medical Sciences, Tehran, Iran). The volunteers experienced nonspecific and long-term (>3 months) low back pain with an age of 20–55 according to previous epidemiological studies.[2,3] Patients with serious health problem or those receiving corticosteroids were excluded. Patients randomly divided in four groups ($n = 30$): SO-treated, LSM-treated, DG-treated, and placebo-treated (Vaseline) and received treatment for 8 weeks. The pain level was recorded with the help of a standard questionnaire for measuring pain including Oswestry Low Back Pain Questionnaire (score 0–100, Oswestry disability index [ODI]) and a pain scale called numeric rating scale (NRS) for pain (score 0–10).

Statistical analysis

The sample size for *in-vivo* (human RCT) experiments was determined considering the previous studies,[2,3] assuming type I error ($\alpha = 0.05$), statistical power ($\beta = 0.2$, then power = 0.8) and Pocock's formula. The statistical analysis was done using GraphPad software version 6. Dunnett's test was used to compare the mean ODI and NRS values of each time-point with time zero and Tukey's test was used to test the difference between various time-points. Two-tailed Student's *t*-test was used to compare the mean of two measurements.

Results

Chemical profile of SO and LSM

The GC-MS analysis revealed the chemical composition of SO and LSM samples. Various compounds were found in the SO and LSM. The most abundant compound within LSM and the major components of SO have shown in Tables 1 and 2.

TPC and antioxidant activity of SO and LSM

The equation for calibration curve of gallic acid (GAE) concentration was $y = 35.96x + 0.0096$; $r^2 = 0.9986$; y, absorbance; x, gallic acid concentration. According to a comparison to gallic acid as standard, TPC of SO and LSM was 45 ± 5.7 and 68.3 ± 11.2 mg GAE/g oil mixture, respectively. The LSM

Table 1: The table represents the results of GC-MS analysis of mixture of Sesame oil and *Lilium candidum* flowers

Compound name	Retention time (min)	Area under peak (%)
ALPHA.-PINENE	5.776	0.34
DELTA. 3 CARENE	8.535	0.11
Limonene	9.225	0.15
ALPHA.-TERPINOLENE	11.799	0.18
TRANS-ANETHOLE	17.337	0.60
trans, cis-2,4-Decadienal	17.574	0.19
Thymol	17.78	0.38
trans, trans-2,4-Decadienal	18.192	0.26
Eugenol	19.314	0.25
Geranyl acetate	20.024	0.06
trans-Caryophyllene	20.827	0.19
ar-Curcumene	22.485	0.07
beta.-Sesquiphellandrene	23.463	0.06
Hexadecane	25.275	0.15
6-Aza-5,7,12,14-tetrathiapentacene	26.922	0.99
Heptadecane	27.499	0.10
Octadecane	29.609	0.05
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	30.288	0.88
Nonadecane	31.627	0.06
beta.-Farnesene	31.967	0.07
n-Hexadecanoic acid	35.94	0.17
6-Aza-5,7,12,14-tetrathiapentacene	36.074	0.70
Linoleic acid	36.465	4.99
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	38.607	0.88
Cyclopropaneoctanal, 2-octyl-	38.761	0.22
Hexanedioic acid, bis (2-ethylhexyl) ester	40.429	0.06
E, Z-1,3,12-Nonadecatriene	40.789	0.05
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	40.944	1.14
beta.-Monolinolein	41.51	0.45
9-Octadecenal	41.603	0.52
Hexadecyl vinyl ether	42.015	0.13
Bis (2-ethylhexyl) phthalate	42.704	0.60
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	43.147	1.29
1-Benzazirene-1-carboxylic acid, 2,2,5a-trimethyl-1a-[3-oxo-1-butenyl] perhydro-, methyl ester	43.518	0.05
E-2-Methyl-1-phenyl-2-butene	44.31	0.06
3-Methylheneicosane	44.979	0.06
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	45.216	1.42
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	47.162	1.39
gamma.-Tocopherol	49.684	5.19
1,3-Benzodioxole, 5,5'-(tetrahydro-1H,3H-furo[3,4-c] furan-1,4-diyl) bis-, [1S-(1.alpha.,3a.alpha.,4.beta.,6a.alpha.)]-	51.002	27.46
1,4-Anhydro-2-deoxy-3,5-di-O-anisoyl-d-ribitol	51.754	18.99
Stigmasta-5,22-dien-3-ol	52.227	2.21
gamma.-Sitosterol	53.195	16.75
1-aza-1-(methoxyiminomethyl)-5-carbamoyl)-cyclonona[6,7-b] indole	53.401	2.56
Total		92.47

The components names were sorted based on the retention time.

showed a significantly higher amount of phenols (TPC) in comparison to SO ($P < 0.05$, Student's *t*-test).

In DPPH assay, the EC_{50} for radical scavenging activity of SO and LSM was 75.3 ± 4.7 and 60.25 ± 3.1 μg/mL, respectively. The SO could inhibit 59.7% of free radicals whereas LSM showed a radical inhibition rate of 74.7%. LSM was significantly stronger antioxidant in comparison to SO ($P < 0.05$, Student's *t*-test). However, the EC_{50} of both herbal samples (SO and LSM) were lower than the EC_{50} of ascorbic acid (9.35 ± 1.1 μg/mL) as the reference standard.

Pain-relieving activity of SO and LSM

The pain scores (both ODI and NRS values) in all groups of CLPB patients in weeks 4 and 8 after starting the treatment schedule (with one of the SO, LSM, and DG treatments) were significantly reduced in comparison to the pain level in patients

Table 2: The table represents the results of GC-MS analysis of sesame oil

Compound name	Retention time (min)	Area under peak (%)
ALPHA.-PINENE	5.769	0.29
3-Carene	8.517	0.13
Limonene	9.238	0.16
Anethole	17.33	0.38
Thymol	17.773	0.44
Isoeugenol	19.307	0.17
Geranyl acetate	20.038	1.41
trans-Caryophyllene	20.83	0.17
CIS-.ALPHA.-BISABOLENE	23.919	0.20
Geranyl butyrate	24.351	0.12
spathulenol	24.712	0.11
Caryophyllene oxide	24.794	0.08
NERYLACETAT	25.329	0.21
delta.-Cadinene	26.173	0.12
Isopropyl myristate	30.158	0.29
alpha.-methylene-.alpha.-fenchocamphorone	32.134	0.32
Dibutyl phthalate	32.783	0.63
n-Hexadecanoic acid	33.37	0.22
10,13-Octadecadienoic acid, methyl ester	35.264	0.20
8-Octadecenoic acid, methyl ester	35.387	0.22
Linoleic acid	37.199	55.21
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	38.63	0.47
Cycloeicosane	38.836	0.38
LINOLEIC ACID, BUTYL ESTER	39.753	0.14
METHYL 11,13-EICOSADIENOATE	40.864	0.13
4-(3,4-Dimethoxybenzylidene)-1-(4-nitrophenyl)-3-phenyl-2-pyrazolin-5-one	40.957	0.65
LINOLEIC ACID, BUTYL ESTER	41.575	0.31
Elaidic acid, isopropyl ester	41.667	0.34
1-Acetoxytetralin	41.74	0.26
Eicosane	42.069	0.17
Bis (2-ethylhexyl) phthalate	42.748	0.38
2-Oleoylglycerol	44.931	1.20
gamma.-Tocopherol	49.698	1.46
1,3-Benzodioxole, 5,5'-(tetrahydro-1H,3H-furo[3,4-c] furan-1,4-diyl) bis-, [1S-(1.alpha.,3a.alpha.,4.beta.,6a.alpha.)]-	50.995	14.97
2-HYDROXY-2-ETHYL-2-PHENYL-N-FORMYL-ACETAMIDE	51.746	4.36
(24S)-24-Methyl-26,26-dimethyl-27-norcholesta-5,22-dien-3.beta.-ol	52.24	0.76
(23S)-ethylcholest-5-en-3.beta.-ol	53.177	5.92
verecynarmyn E	53.393	0.87
Total		93.86

The components names were sorted based on the retention time

receiving placebo ($P < 0.001$, Dunnett's test) [Figures 1 and 2]. The pain-relief (by considering both ODI and NRS values) in week 8 of therapy with all three treatments (SO, LSM, and DG) was stronger than week 4. The patients who administered with LSM could experience lowest pain scores (ODI and NRS) in weeks 4 and 8 of therapy in comparison to other treatment groups and placebo control ($P < 0.001$, Dunnett's test, $P < 0.001$, Tukey's test) [Figures 1 and 2]. The ODI in patients treated with LSM felled to fewer than 20 in week 8 of the therapy [Figure 1]. The NRS score in patients treated with LSM experienced a substantial fall on week 8 of the therapy and reached to 2.1 [Figure 2]. Also, both of the ODI and NRS scores in LSM-treated patients on week 8 of therapy were significantly lower than that in week 4 ($P < 0.001$, Tukey's test) [Figures 1 and 2]. The ODI values in placebo-receiving patients on day zero, week 4, and week 8 of therapy were 42.4, 46.8, and 55.4 [Figure 1], respectively, whereas the ODI values in patients administered with LSM on day zero, week 4, and week 8 of therapy were 44.2, 30.7, and 13.1 [Figure 1], respectively. Similarly, the NRS values in placebo-receiving patients on day zero, week 4, and week 8 of therapy were 5.5, 6.2, and 7.7 [Figure 2], respectively, whereas the NRS values in patients administered with LSM on day zero, week 4, and week 8 of therapy were 5.7, 3.6, and 2.1 [Figure 2], respectively.

Discussion

In our investigations, we found that not only the SO itself but also the LSM could diminish the pain complaints in CLBP-patients

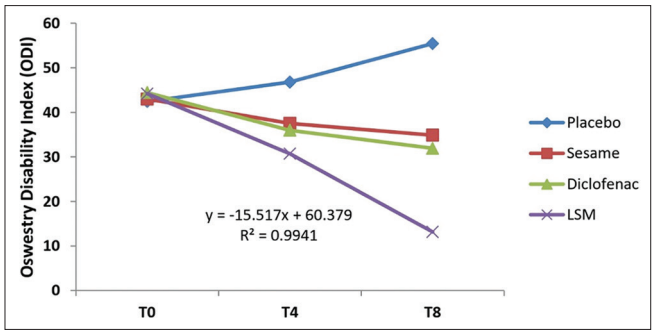

Figure 1: The graph demonstrates the pain level (indicated by ODI values)

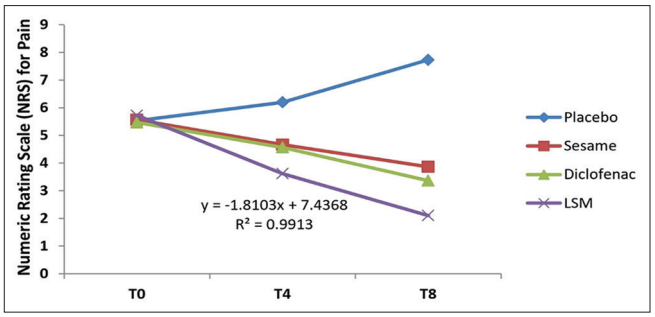

Figure 2: The graph demonstrates the pain level (indicated by NRS values)

on weeks 4 and 8 after receiving the topical treatments. The ODI and NRS values on week 8 of the LSM treatment was reduced ~76% and 73%, respectively, in comparison to the pain values in placebo-receiving patients.

Two phenylpropenoid acylglycerols from *Lilium brownii* var. viridulum showed promising inhibitory effect on production and protein expression of inflammation mediators, including NO, iNOS, COX-2, PGE2, IL-1β, IL-1, IL-6, and TNF-α from macrophages. The components exerted their action via inhibition of two pathways including NF-κB and MAPKs.[8]

The antioxidant activity of *Lilium* spp. has been linked to their phenols, polyphenols (e.g., lignans), flavonoids, polysaccharides, and steroidal saponins.[9,10] In addition, the strong antioxidant activity of different *Lilium* spp. was reported frequently.[9]

In accordance with the studies indicating the high phenol content and antioxidant capacity of the *Lilium* spp., we found a rather high amount of phenols and associated high antioxidant activity in LSM samples (TPC: 68.3 ± 11.2 mg GAE/g oil mixture, DPPH: 60.25 ± 3.1 μg/mL). The TPC in LSM not only was comparable with levels that reported by other studies (TPCs of *Lilium* spp. were reported as following: *L. lancifolium*: 28.27, *L. concolor*: 38.97, *L. leucanthum*: 23.36, *L. davidii*: 20.17, *L. pumilum*: 41.77, *L. regale*: 103.81 mg GAE/g of dry lily bulb),[9] but also, in fact, it seems that the TPC of LSM (68.3 ± 11.2 mg GAE/g oil mixture) was placed among the most phenol-rich *Lilium* spp.

Furthermore, there was a strong relationship between the TPC of the samples (SO and LSM) and the radical scavenging activity. The TPC of different concentrations of LSM showed a strong linear relationship (R^2 = 0.82, linear regression) with the DPPH values. Also, there was a strong linear relationship (R^2 = 0.95, linear regression) between the TPC results and the levels of radical scavenging activity by SO. As the results indicate, we suggest a possible association between the amounts of phenols and the antioxidant power of the herbal samples (LSM and SO).

The most abundant compound within SO was the LC,[11] and in our study, the LSM samples contained app. only 5% LC. Linoleic acid can contribute in either worsening the inflammatory responses or attenuating the inflammation/pain.[12,13]

In our examinations, we found that the SO contains a large amount of sesamin (~15%), which is a type of lignan. Interestingly, the sesamin was also the most abundant chemical constituent (27.46%) of the LSM sample. Our findings might prepare a good reason for the significant pain-relieving and soothing effect of SO and LSM treatments in CLBP patients in comparison to those that received placebo. The sesamin itself possess strong antioxidant, anti-inflammatory, and antinociceptive properties.[14,15] The pain-relieving and anti-inflammatory effects of SO were also repeatedly described in similar studies.[14,15]

We also found that the SO also contains 5.9% (23S)-ethylcholest-5-en-3β-ol (ECH), a compound belongs to phytosterols/phytosteroids. Also, the chemical analysis unrivaled that LSM has a substantial amount of phytosterols, such as γ-sitosterol (16.75%) and stigmasta-5,22-dien-3-ol (β-stigmasterol) (2.2%). Phytosterols can participate in many of the biological functions in the body and have a great potential to get involved in anti-inflammatory, anti-nociceptive, analgesic, and immunomodulatory functions.[16,17]

In addition, we observed a considerable amount of an acetamide derivative (4.36%) in SO samples. The acetamide derivatives with various ethyl, methyl, or phenol substitutions exhibited anti-inflammatory, anti-cancer, and analgesic effects.[18]

Moreover, the chemical profile of both SO and LSM was contained a pyrazoline/pyrazolon derivative. The pyrazoline derivative content in LSM (7%) was higher than that in SO (1.12%). It was known that the compound (pyrazoline derivative) has a strong radical scavenging activity.[19] Edaravone (3-Methyl-1-phenyl-2-pyrazolin-5-one) showed a promising radical scavenging activity.[19] It has also anti-inflammatory and analgesic properties.[19,20]

In our evaluations, we also observed that high quantity of γ-tocopherol (5.2%), the major form of the vitamin E, is present within the LSM constituents. The SO samples also contained app. 1.5% γ-tocopherol. γ-Tocopherol (Vit E) is a known natural antioxidant.[21]

Other major compound in LSM was a ribose derivative (ribitol also called adonitol, ~19%). The high amount of ribitol present in LSM composition, which is a monosaccharide in nature may also be a result of catalyzing or degradation of initial polysaccharides. The polysaccharides of *Lilium* spp. are known for their anti-inflammatory and anti-oxidant properties.[10]

Moreover, we found an indole derivative (~2.5%) in LSM by chemical analysis. The compound has been found to be a potential cannabinoid receptor type 2 (CB_2) agonist (×100) and therefore can play a role in reduction of special types of pain irresponsive to conventional treatments such as neuropathic pain.[22] In addition, the indole derivatives can influence the intracellular levels of cyclic adenosine monophosphate in immune cells, such as T lymphocytes and ultimately cause the alleviation of immune system.[23] Therefore, indole derivatives can exert the inhibitory effects on immune cells and subsequently induce the anti-inflammatory effects on immune system.[22]

Conclusion

The result of this study shows the LSM as a novel therapeutic alternative could reduce the pain feeling and obtained the lowest pain scores.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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