AMDHS ADVANCES IN MEDICAL, DENTAL AND HEALTH SCIENCES
e-ISSN: 2581-8538

RESEARCH ARTICLE OPEN ACCESS

Pain Relieving Properties of Ginger (*Z. officinale*) and Echinacea (*E. angustifolia*) Extracts Supplementation among Female Patients with Osteoarthritis. A Randomized Study

Louay Labban[1,*], Maysoun Kudsi[2,4], Zeina Malek[3], Nasser Thallaj[4]

[1]*Faculty of Pharmacy, Al Jazeera Private University, Damascus, SYRIA.*
[2]*Faculty of Medicine, Damascus University, Damascus, SYRIA.*
[3]*Faculty of Pharmacy, Syrian Private University, Damascus, SYRIA.*
[4]*Faculty of Pharmacy, Al Rasheed Private University, SYRIA.*

Received: 21 August 2020;
Accepted: 27 September 2020

***Correspondence to:**

Prof. Louay Labban,
Faculty of Pharmacy, Al Jazeera Private University, Deir ez Zor, Aleppo, SYRIA.
Email: drlouay@msn.com

Published by : OZZIE PUBLISHERS

Abstract

Objectives: To evaluate the efficacy and safety of the Echinacea and ginger species extracts supplementation among patients with knee osteoarthritis (OA). Methods: Three hundred female patients with knee OA participated in this randomized study. They had OA of the knee and moderate-to-severe pain and they were divided into two groups. Study group (n=150) and control group (n=150). The study which lasted for 6-week. The study group received Ginger and Echinacea extract supplementations twice daily, with/without acetaminophen. The study examined the reduction in "knee pain on standing for the study group (Ginger and Echinacea group)" defined by a reduction in pain of > or = 15 mm on a visual analog scale. The study measured other biological values such as BP, ESR, Creatinine and liver enzymes. Results: The supplementation of ginger and Echinacea extracts resulted in improvements in many values. Systolic blood pressure dropped from 120.5 ± 10.4 to 119.7 ± 8.9 mmHg, pain intensity VAS decreased from 6.9 ± 2.1 to 6.6 ± 1.5, ESR17.3 ± 11.9 and 21.0 ± 9.8mm/h, creatinine 0.87 ± 0.19mg/dl and 0.85 ± 0.16 mg/dl and liver enzymes 21.6 ± 8.5 IU/L and 20.9 ± 4.5 IU/L for ALT and 20.9 ± 4.5 IU/L and 20.3 ± 7.4 IU/L for AST. Conclusion: The use of ginger extract in knee osteoarthritis patients had a moderately statistically significant effect on reducing pain with safe profile and mild GI adverse events.

Key words: Ginger, Echinacea, Knee OA, Osteoarthritis, visual analogue scale (VAS), tumor necrosis factor (TNF)-α.

INTRODUCTION

Osteoarthritis (OA) is the most common rheumatologic degenerative disease in the elderly,[1] which by time affects the function and the quality of life.[2,3] Non-pharmacologic, pharmacologic and modalities are used to improve pain and disability.[4] Pharmacological management of OA includes nonsteroidal and anti-inflammatory drugs, analgesics and intra-articular injections as a pain reliever.[5] Patients may use alternative therapy such as herbal medicine, although its efficacy and safety have not been established by controlled trials.[6]

The beneficial effects of medicinal plants have been reported in so many studies.[7-9] Among these herbs is ginger which have had analgesic and anti-inflammatory. Ginger (*Zingiber officinale* Rosc.) belongs to the family *Zingiberaceae*, in the order *Zingiberales* of monocotyledons, which is composed of 50 genera and around 1500 species of perennial tropical herbs. Taxonomically, the two main groups can be named: *Z. officinale* which is cultivated throughout the tropics and *Z. officinale* which is grown on a small scale in South-East Asia for medicinal use and as a culinary spice. Ginger consists of a biologically active combination of constituents such as gingerols, shogoals and paradols which have for the majority of its anti-inflammatory properties.[10] With regard to the medicinal properties, ginger exhibits antispasmodic and anti-inflammatory activity, helps reduce cholesterol, lower blood pressure and shrink liver tumor in test animals. In humans, rhizome powder is effective against nausea, for example, post-operative nausea, motion sickness and morning sickness. The principles compound which is responsible for this anti-emetic activity might be shogaols and gingerols.[11] Ethanolic rhizome extracts have shown inhibition of skin tumour promotion in mice. Zingiberene, beta-sesquiphellandrene, ar-curcumene and shogaol show anti-ulcer principles. Furthermore, gingerol has been shown to be a cholagogue after intraperitoneal administration in rats and gingerol to have hepatoprotective activity,[11] as it prevents the toxic effects of carbon tetrachloride in rat hepatocytes. Ginger oil has considerable antifungal and

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DOI : 10.5530/amdhs.2020.3.11

antibacterial activity and is used as a seed dressing in India. Meat cooked with fresh rhizomes becomes more tender due to the action of the proteolytic enzyme zingibain.[12]

Ginger products, mainly the oleoresin, are official in several European pharmacopoeias and are used as ingredients in digestive, laxative, antitussive, carminative, antacid and anti-emetic preparations.

Preclinical research has shown that ginger inhibits cyclooxygenase, lipo-oxygenase, resulting in suppression in the synthesis of the inflammatory leukotrienes.[10] Furthermore, Ginger extracts found to inhibit the expression of tumor necrosis factor (TNF)-α in synoviocytes activated by either TNF-α or interleukin (IL)-1β,[11,12] and in one study a ginger extracts showed an anti-inflammatory effect of betamethasone.[13]

On the other hand, Echinacea is a plant which is native to North America where they grow in prairies and open, wooded areas. This group has nine species, but only three are used in herbal supplements. *Echinacea purpurea, Echinacea angustifolia* and *Echinacea pallida.*[14] Both the plant's upper parts and roots are used in tablets, tinctures, extracts and teas. Echinacea plants contain an impressive variety of active compounds, such as caffeic acid, alkamides, phenolic acids, rosmarinic acid, polyacetylenes and many more.[15] In addition, studies have linked echinacea and their compounds to many health benefits, such as reduced inflammation, improved immunity and lower blood sugar levels. Echinacea is loaded with antioxidants, such as flavonoids, cichoric acid and rosmarinic acid, which may help defend your body against oxidative stress. Echinacea appears to be safe and well tolerated in the short term.[16] Studies have found that Echinacea powdered supplements to be effective in aiding immunity if given in 300–500 mg dose, three times daily. However, a combination of Ginger and Echinacea extracts is more effective in decreasing inflammatory mediators than an individual compound,[17] and the length of the side chains determines the level of effectiveness.[18] The aim of this study was to assess the clinical efficacy and safety of oral ginger and Echinacea extracts supplementation in the symptomatic treatment of OA as the growing interest in use of these herbal products in the treatment of OA.

Patients and Methods

The study recruited 380 female patients who had been diagnosed with osteoarthritis. 80 patients were excluded from this study according to the exclusion criteria which included: Patients who had a secondary cause of osteoarthritis, pregnancy or lactation, uncontrolled hypertension (blood pressure > 140/90), heart failure (class 3 or 4 on NYHA), history of myocardial infarction, cerebral vascular accident, peptic disease or bronchospasm in the past year, serum creatinine (> 1.5), liver enzyme > 1.5 times more than normal and raised ESR (according age and sex).

This randomized clinical trial study was carried out on 300 outpatients who provided a written consent to participate in this study. Their ages were between 45 - 65 years old (the mean age was 54.6 ± 3.6 years), with knee OA diagnosed according to ACR criteria[15] and they were suffering from clinical dysfunction and pain on movement of more than 4 cm on a 10 cm VAS (16) (mean 7.1 ± 0.9) at first visit, selected from the rheumatologic clinic at Al-Moussat University Hospital in Damascus after obtaining signed informed consent. The study was approved by the Ethics Committee of Faculty of medicine at Damascus University.

Patients were selected randomly and they were divided into two groups:

Group 1(control group): consisted of 150 patients to receive nothing (placebo) and group 2(150 patients) who received the mixture of 200 mg powder of Echinacea and Ginger. Supplementation with Echinacea and Ginger extracts was administered 2 times per day for 6 weeks for duration of the study.

Prior to the commencement of the study, blood pressure, body mass index (BMI), ESR, serum Creatinine, liver enzymes and simple X ray of the knees of all participants were done. Only Acetaminophen use was allowed during the study and their consumption in the past week was recorded.

The used visual analogue scale (VAS) and physician global assessment (according to a 4-scale scoring system: 0 for inadequate, 1 for moderate, 2 for good and 3 for excellent) and the amount of analgesic use in the past week to assess the efficacy. A responder was defined by a reduction in pain of ≥ 2 cm on a visual analog scale.[19]Any adverse effects such as dyspepsia and headache were recorded; the blood samples to measure the serum Creatinine and liver enzymes were obtained at the beginning and at the end of the study.

Statistical analysis

Statistical analysis was done by the SPSS-23 using χ^2 test, Independent *t*-test for comparisons of mean values of patients at baseline and after the intervention. The level of significant *P* value was assumed 0.05.

RESULTS

Three hundred female patients with osteoarthritis of the knee participated in this study, 150 patients in the study group (Ginger and Echinacea extract supplements) and 150 patients in the control group. None of the patients in the both groups dropped from the study due to the inefficacy or for the side effect of the treatment.

The mean BMI of the patients was (29.7± 3.9 kg/m^2) and (91.6%). The demographic and baseline characteristics of the patients were shown in Table 1.

All patients in the study had grade 1or 2 in knee X ray according to Lawrence and Kellgren criteria (19), which is shown in Table 2.

All patients were previously treated with simple analgesic such as acetaminophen and various groups NSAIDs and at the beginning of the study. 168 patients (56%) (88 patients in the study group and 80 patients in control group) were receiving analgesics.

The results of this study have shown noticeable improvements in many

Table 1: Mean age and BMI of patients in both groups.

Parameter	Study Group	Control Group	*P* Value
Age (Years)	55.2 ± 3.1	53.9 ± 2.9	non-significant
BMI (kg/m^2)	29.1 ± 4.3	28.6 ± 4.6	0.12

Table 2: Patient's number according to Lawerence and Kellgren classification.

Number of patients	Grade 1	Grade 2
Study group	98	52
Control group	91	59

Table 3: The changes of physical and chemical values of control and study groups at the beginning and the end of the study.

Physical and chemical values	Control group		Study group	
	Beginning	End	Beginning	End
Systolic blood pressure (mmHg)	120.5±10.4	121.8±11.2[b]	120.7±8.9_	114.8±6.6[a]
Pain intensity (VAS)	6.9 ± 2.1	5.4 ± 1.9[b]	6.6 ± 1.5	4.1 ± 0.[a]
ESR (mm/h)	20.3 ± 11.9	20.6±11.9[b]	21.0 ± 9.8	20.10±11.6[b]
Creatinine (mg/dL)	0.87 ± 0.19	0.84 ± 1.0[b]	0.85±0.16	0.82±0.11[a]
ALT (IU/L)	21.6 ± 8.5	19.6 ± 7.9[a]	20.9 ± 4.5	20.6 ± 6.7[b]
AST (IU/L)	20.9 ± 4.5	21.0 ± 11.7[b]	20.3 ± 7.4	19.36±7.8[a]

*Different letters designate significant difference $P<0.05$

vital values after supplementation. Systolic blood pressure decreased from 120.7±8.9 to 114.8±6.6 in the study group and the difference was significant ($P<0.05$) whereas the difference in the control group was not significant as the systolic pressure did not change that much. The pain intensity in study group was decreased significantly according to VAS ($P = 0.03$) and to the physician evaluation according to a 4- scale scoring ($P = 0.02$) as shown in the Table 3.

After Six weeks both groups were re-evaluated and the results of this study demonstrated that analgesic use in the study group changed from 5.1 ± 3.4 to 3.7 ± 3.9 and in control group from 4.1 ± 5.0 to 3.4 ± 4.9. The differences were statistically significant as shown in Table 4.

Totally 8 complications in drug users and 9 in placebo group were recorded (21.1% vs. 24.3%). In drug group, 3 patients experienced dyspepsia, 2 headache, 1 raised blood pressure, 1 diarrhea and 1 fatigue. In placebo group, 4 participants had dyspepsia, 1 headache, 1 oral ulcer, 1 rash, 1 raised blood pressure and 1 constipation.

DISCUSSION

Our study showed a significant change on pain intensity and physician evaluation of the knee OA patients after 6 weeks of using 200 mg combined *E. angustifolia* and ginger extract comparing with placebo, with little safe side effect as shown in the results.

The ginger herb is used thousand years ago for different purposes in Asia and Europe.[20] *E. angustifolia* was suggested to have had anti-inflammatory and analgesic effects and anti-oxidant affecting NO synthesis.[21-23] Ginger constituents include oleoresin (gingerol), linoleic acid, volatile oils and trace elements such as potassium magnesium and phosphorus,[7] which are effective in inhibiting the production of COX2,PGE2 and TNFα, expression in human cnidocytes by regulating the activation of NF-κB and the degradation of its inhibitor IkB-α.[24,25]

E. angustifolia extract e an effect as a muscle relaxant, anti-nociceptive by interacting with prostaglandins and arachidonic acid metabolites.[26,27]

There are many trials that studied the efficacy of ginger extract or

Table 4: Pain Intensity Changes and Safety Profile after 6 Weeks Intervention.

Evaluation	Study Group	Control group
Patient self-evaluation	Improvement shown	No improvement has been shown
Not enough	4 (12.5)***	8 (27.6)
Moderate	12 (37.5)***	9 (31.0)
Good	8 (25)	12 (41.4)***
Excellent	8 (25)***	2 (6.9)
Physician evaluation	Significant pain reduction	Slight reduction in pain
Not enough	3 (9.4)	9 (31.0)
Moderate	12 (37.5)	9 (31.0)
Good	11 (34.4)	11 (37.9)
Excellent	6 (18.8)***	0
Analgesic consumption (count/week)	4.1 ± 3.98	3.8 ± 4.96

E. angustifolia in OA., some found that it is efficacy in reducing pain using VAS scale / Lequesne index?[28]WOMAC score,[29] such as the study of Bliddal *et al.* showed significant difference between ginger and placebo.[20] Haghighi M. *et al*. Showed that Ibuprofen > ginger extract > placebo was found for visual analogue scale of pain and the Lequesne-index.[30] Alishiri G, *et al.* study demonstrated that decreased pain and function more than acetaminophen and placebo. Zahra Zakeri, *et al*. Study showed that the pain reduction according to VAS was more significant in ginger group than placebo ($p<0.05$). Although pain reduction according to WOMAC was greater in ginger than placebo group, the difference was not statistically significant,[31] the results of a study by Zeinab Alipour *et al.* showed that ginger is effective in relieving pain in patients with knee osteoarthritis and it can be used as a safe method.[32] Altman RD *et al.* showed that improvement in knee pain on standing and after walking 50 feet and reduction in the Western Ontario and McMaster Universities osteoarthritis composite index, statistically significant with a good safety profile, with mostly mild GI adverse events in the ginger extract group.[18] In a systematic review and meta-analysis showed that there is insufficient evidence to support the use of oral ginger compared with placebo in the pain relief and function improvement in patients with knee osteoarthritis. For other comparisons, no statistically significant differences were found.[33]

CONCLUSION

Ginger and Echinacea can be used as pain relievers because of their anti-inflammatory, antioxidant properties. This would reduce the dependence of medications especially analgesics

Recommendations

There are some limitations in this study mainly the short time of intervention period which was not enough for the evaluation of long-term efficacy or safety and analgesic consumption. Further, more studies are needed to study the effect of ginger and Echinacea separately. Therefore, it's suggested further studies with different doses and durations of intervention of Echinacea and Ginger extract.

ACKNOWLEDGEMENT

The authors would like to thank all colleagues who contributed totally or partially to this study. Special thanks are extended to the lab technicians who performed all analysis and for the medical residents who assisted in data collection

CONFLICT OF INTEREST

The authors declared that there was no conflict of interest.

ABBREVIATIONS

OA: Osteoarthritis; **Bp:** Blood pressure; **ESR:** Erythrocytes Sedimentation Rate; **(TNF)-α:** tumor necrosis factor; **NYHA:** New York Heart Association; **(ACR):** American College of Rheumatology.

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Cite this article as: Labban L, Kudsi M, Thallaj N. Pain Relieving Properties of Ginger (*Z. officinale*) and Echinacea (*E. angustifolia*) Extracts Supplementation among Female Patients with Osteoarthritis. A Randomized Study. Adv. Med. Dental Health Sci. 2020;3(3):45-8.