Improving of Knee Osteoarthritic Symptom by the Local Application of Ginger Extract Nanoparticles: A Preliminary Report with Short Term Follow-Up

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Objective: *An evaluation of the efficacy and safety of Ginger (Zingiber officinale Roscoe) extract nanoparticle for treatment of osteoarthritis (OA) of the knee.*
Material and Method: *Sixty patients at the age range of 50 to 75 years old who were diagnosed with OA knee based on the American College of Rheumatology (ACR) diagnosis criteria were included in the present study. Participants received ginger extract in Nanostructure Lipid Carrier (NLC) rubbed three times a day for 12 weeks. Efficacy was assessed by Knee Injury and Osteoarthritis Outcome Score (KOOS), Index of Severity for Osteoarthritis (ISOA), and patient's global assessment (PGA). A series of biochemical tests in serum and hematological parameters were established the safety of ginger extract in NLC. The paired t-test was used to compare the score before and after treatment. The comparisons of baseline and the 4-, 8-, and 12-week used repeated ANOVA.*
Results: *Ginger extract nanoparticles improved, with statistical significance, the patient's global assessment, knee joint pain, symptoms, daily activities, sports activities, and quality of life measured by KOOS, ISOA, and PGA, following 12 weeks of treatment ($p<0.05$). There were no safety issues, adverse events, or laboratory values.*
Conclusion: *Ginger extract nanoparticles relieves joint pain and improves problematic symptoms and improves the quality of life in osteoarthritis knees during a 12-week treatment.*

Keywords: *Osteoarthritis, Ginger, Zingiber officinale Roscoe, Nanoparticle, Clinical trial*

J Med Assoc Thai 2015; 98 (9): 871-7
Full text. e-Journal: *http://www.jmatonline.com*

Osteoarthritis (OA) of the knee is a common degenerative disease characterized by pain, stiffness and decreased range of motion[1]. It is a major cause of morbidity, physical limitation, and increased health care utilization, including total joint arthroplasty, especially in elderly[2]. The pathophysiology of OA associates degeneration of articular cartilage is mediated by distinct factor like inflammatory mediators, biochemical factors, changes with aging, and metabolic factor[3]. The treatment of OA involves multiple intervention, both pharmacological and non-pharmacological. The result of treatment is to relive pain, improve mobility of joint, and minimize disability. Non-steroidal anti-inflammatory drugs (NSAIDs), non-narcotic, and narcotic drugs constitute the mainstay of pain-relieving therapy in OA. However, the efficacy of these drugs and their adverse reactions vary considerably[4,5]. As a result, herbal medicines are needed to provide alternative therapies with reduced incidence of adverse effect. Ginger (*Zingiber officinale*) is one of the most commonly used natural products and a promising agent for treatment of OA[6,7]. Phytochemical studies have shown that the ginger rhizome contains a wide variety of biologically active compound. Active components present in the volatile oil (1-3%) are the mono and sesquiterpens[8,9]. The non-volatile oil pungent of ginger consists of gingerol, shogaol, paradols, and zingerone (4.0-7.5%). The pungent of ginger has demonstrated anti-inflammatory actions in vitro, inhibiting leukotriene synthesis and activating cyclooxygenase enzymes (COX-1 and COX-2)[10]. In addition, [6]-gingerol was attributed to inhibition of prostaglandin release and other mediator. Evidence shows that ginger modulates the biochemical pathway activated in chronic inflammation[11]. However, the major adverse event of oral ginger is heartburn and gastrointestinal disturbances, similar to the side effects

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of oral NSIADs[12,13]. Furthermore, because of the poor absorption, rapid metabolism, and elimination of the active compound, the bioavailability of polyphenolic compound is poor. In an effort to solve these issues, the topical Ginger extract in Nanostructure Lipid Carrier (NLC) forms is preferable to the oral forms[14].

The formulation of ginger extract in NLC is based on an extract of the *Zingiber officinale* rhizome. Five percent ginger extract's preparation (equivalent to [6]-gingerol content 11.18%), conducted to form a NLC that is prepared by weight, with the composition of solid lipid, liquid lipid, surfactant, and water mix. The quality and stability is controlled by physical and chemical stability. NLC have emerged as novel systems composed of physiological lipid materials suitable for topical, dermal, and transdermal administration. Furthermore, it is non-toxic and inexpensive. However, there are few studies about the therapeutic efficacy of the topical ginger extract nanoparticles in patients with knee osteoarthritis. Therefore, the researchers conducted a clinical study to assess the efficacy and safety of ginger extract in NLC, which has [6]-gingerol for pain relief, in knee with OA.

Material and Method

Patient selection

The present study was approved by the Ethical Committee of Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health (Thai Clinical Trial Registry No. TCTR20140306001). Informed consent was signed by all participants prior to the start of any study-related procedure. Subject recruitment and data collection occurred between May and August 2014. Inclusion criteria were: (a) both men and female 50 to 75 years of age, and (b) physician-diagnosed primary OA, diagnosis criteria were based on American College of Rheumatology[15,16] classification knee pain, and radiographic osteoarthritis that was grade 2-3 of Kellgren and Lawrence criteria (Grade 0 = Normal; Grade 1 = Possible osteophytes, Doubtful narrowing of joint space; Grade 2 = Definite osteophytes, Absent or questionable narrowing of joint space; Grade 3 = Moderate osteophytes, Marked narrowing of joint space, Severe sclerosis, Possible deformity; Grade 4 = Large osteophytes, Marked narrowing of joint space, Severe sclerosis, Definite deformity)[17]. Exclusion criteria were (a) secondary causes of knee OA, (b) history of allergy herbs used medicinally during investigation, and (c) severe joint instability or severe deformity (grade 4 Kellgren and Lawrence).

Study protocol

Before study entry, patients entered a 1-week washout for anti-inflammatory and analgesic medication, during which they were allowed to take acetaminophen for pain-500 mg three times a day (or every four to six hours) but not any other topical analgesics, NSAID, or COX-2 inhibitors. If subjects took acetaminophen for OA pain during the 7-day wash-out, they have to record. At baseline visit, patients underwent physical examination, vital sign, laboratory studies included complete blood count (CBC), renal function test (blood urea nitrogen (BUN) and creatinine), and liver function test (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP)). If patients were determined to be eligible for the study, they were taken the Ginger extract in NLC with application of a 1 g three times a day for four weeks.

Treatment

The Ginger extract in NLC contained extract of ginger by ratio of about 5% by weight ([6]-gingerol content 11.18%). The potency of extraction and preparation were followed by analysis with high-performance liquid chromatography (HPLC) on the active molecule 6-gingerol. In addition, in vitro release study of preparation was done by modified Franz diffusion cell. The release of [6]-gingerol from NLC were exhibited approximately 92% within 24 hours. Subjects had to apply two inches of extruded gel topically around the index knee and gently massage until the gel was dry, three times a day. The returned gel was weighed at each followed-up. Treatment compliance was measured by assigning the subjects to report in treatment diary.

Assessments

Efficacy was assessed using the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire and patient's global assessment (PGA). The KOOS is a validated questionnaire consisting of 42-items in five subscale (9 on pain, 7 on symptoms, 17 on Function in Daily living (ADLs), 5 on function in sport and recreation (Sport/Rec), and 4 on quality of life (QOL). In addition, the KOOS is an extension of the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) and can be converted to WOMAC scores. Scores are interpreted on 5-point Likert scale (4 = very poor, 3 = poor, 2 = average, 1 = good, 0 = very good)[18,19]. Index of Severity for

Osteoarthritis Index (ISOA) of the knee by Lequesne et al[20] is consisted of three dimension, including pain or discomfort (five items), the maximum walking distance (two items), and activities of daily living (ADL; four items). Each dimension has a maximum total score of 8; consequently, the total score range from 0 to 24(20). The PGA is evaluated on a 5-point Likert scale (5 = very poor, 4 = poor, 3 = average, 2 = good, 1 = very good)[21].

The responder criteria defined by the Outcome Measures in Rheumatology (OMERACT) Committee and the Osteoarthritis Research Society International (OARSI) Committee[22]. The responder criteria covered three domains (pain, function and PGA) that defined as a participant with: 1) 50% reduction in pain or 50% improvement function, 2) 20% reduction in pain or 20% improvement function, adding 10% of the PGA from the baseline. Efficacy assessments were performed at baseline and after 4-, 8-, and 12-week of treatment.

Safety was evaluated via laboratory test and all adverse event, the onset, duration, and intensity (mild, moderate, or severe) of event, as well as the action taken and outcome, were reported. The relationship between an adverse event and study medication was assessed by the investigator, as unlikely, possible, probable and certain. Adverse event was corded according to Naranjo's alogorithm[23]. Laboratory studies were recorded at baseline and after 12-week of treatment including hematology (CBC) and blood chemistries; renal function test (BUN and Creatinine) and liver function test (SGOT, SGPT and ALP).

Data analysis

Baseline examined for their characteristic and demographic data were described as descriptive statistics; mean, SD, 95% CI, percentage, and frequencies. The efficacy of the phase II study was determined the score of change from the baseline, corroborated by any change in KOOS score, ISOA score, and PGA, which performed by the student pair t-test and repeated ANOVA assessed the mean difference of KOOS parameter, ISOA index, and PGA. The responder rate was described as descriptive statistics.

Results

Baseline demographic and clinical characteristics

Between May and August 2014, 80 patients with OA knee were screened. Sixty patients were completed the wash out and eligible for assessment of response. Twenty patients were excluded from the present study (eight excluded by radiographic osteoarthritis criteria, three secondary OA, five BMI >30 kg/cm^2, and four refused to participate). No patients were on any concomitant medication during the study period. The mean of the topical ginger extract in NLC received per patient was 28.8±8.7 g for four weeks. Baseline demographic and clinical characteristics were summarized in Table 1.

Clinical efficacy

Sixty patients initially enrolled and 59 patients were completed and reported for testing at baseline, 4-, 8-, and 12-week of evaluation period. One patient discontinued the trial before completing evaluation of safety and efficacy due to adverse event. The data regarding the normalized distribution of KOOS score, ISOA, and PGA, which were confirmed by Kolmogorov-Simimov, at baseline and treatment period were summarized in Table 2. The paired t-test result demonstrated significant improvement of all parameters (KOOS subscale, ISOA, and PGA) when compared at the initiation of treatments and following 12 weeks of treatment (p<0.000) and the magnitude of mean different are 49% in pain subscale (Table 2). The mean of five subscale of KOOS, ISOA, and PGA at baseline, 4-, 8-, and 12-week follow-up periods after treatment showed statistical difference (p<0.05) in the repeated ANOVA (Fig. 1, Table 3).

The responder criteria defined by OMERACT and OARSI committee can be converted KOOS score to WOMAC scores and covered three domains (pain, function (ADL), and PGA) that defined as a participant with: 1) 50% reduction in pain or 50% improvement function, 2) 20% reduction in pain or 20% improvement function, adding 10% of the PGA from the baseline. The results of OMERACT-OARSI responder criteria were shown a responding rate more than 50% in three domain and OMERACT-OARSI responder are 66.1% (Table 4).

Adverse events

The adverse effect reported was skin reaction at the application site and adverse event led to discontinuation of only one participant (1.69%). However, the skin reaction resolved promptly upon withdrawal of treatment.

As a part of the safety evaluation, laboratory test were performed for assessment of different biochemical (BUN, SGOT, SGPT, and ALP), and hematological (CBC) parameters. The paired t-test was

Table 1. Demographic characteristics of patients with knee OA

Characteristic	Value			
	Mean (SD)	Median	Range (min-max)	%
Sex (n = 59), %				
Male (n = 8)				13.5
Female (n = 51)				86.4
Age (years), mean (SD)	61.8±6.7	63	53-73	
Duration of disease	2.7±2.4	2	2-7	
Body mass index (kg/m^2), mean (SD)	25.9±3.0	26	18.5-30.0	
Heart rate (bpm), mean (SD)	76.5±3.0	76	61-99	
Systolic blood pressure (mmHg), mean (SD)	136.2±17.1	136	98-150	
Diastolic blood pressure (mmHg), mean (SD)	72.6±7.8	73	53-93	
Screening index of severity for OA (ISOA score 0-24), mean (SD)	10.0±3.9	11	1-19	
Radiographic classification of knee OA (Kellgren and Lawrence X-ray), %				6.7
Grade II	8			93.3
Grade III	51			
Baseline laboratory values (normal range)				
Biochemical parameters				
ALP (30-120 U/L), mean (SD)	74.6±20.6	71.0	30-121	
SGOT (0-50 U/L), mean (SD)	25.0±13.0	22.0	14-64	
SGPT (0-45 U/L), mean (SD)	27.1±16.8	22.0	7-54	
BUN (5-23 mg/dl), mean (SD)	15.8±5.8	15.3	7-25	
Creatinine (0.7-1.3 mg/dl), mean (SD)	1.0±0.2	1.0	0.8-1.9	
Hematology				
White blood cell count (4.00-10.00x10^3/µL), mean (SD)	7.7±1.7	7.2	4.5-12.0	
Total RBC count (3.5-5.5x10^6/µL), mean (SD)	4.3±0.4	4.3	3.2-5.6	
Platelet count (150-400x10^3/µL), mean (SD)	286.0±72.3	275.0	171-460	
Hematocrit (35-40%), mean (SD)	37.9±3.7	37.0	24.1-46.4	

OA = osteoarthritis; ISOA = index of severity for OA; ALP = alkaline phosphatase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; BUN = blood urea nitrogen; RBC = red blood cell

Table 2. Efficacy evaluation of the mean of KOOS, ISOA, and PGA at baseline and 12-week

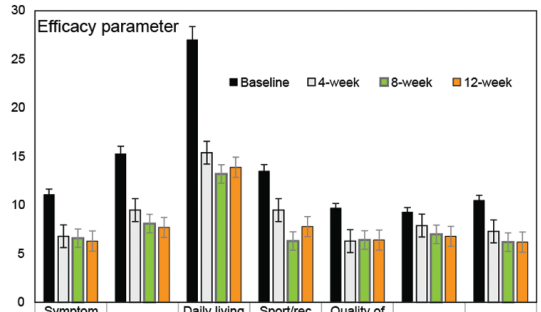
Efficacy variable	Baseline mean (SD)	At 12-week mean (SD)	Mean different (SD)	95% CI (lower-upper)	*p*-value*
KOOS score	(n = 59)	(n = 59)	(n = 59)	(n = 59)	(n = 59)
Symptom (0-28)	11.1 (4.3)	6.3 (3.8)	4.8 (5.3)	3.4-6.2	0.000
Pain (0-36)	15.3 (5.6)	7.7 (5.8)	7.5 (7.2)	5.6-9.5	0.000
Daily living (0-68)	27.0 (10.9)	13.9 (12.0)	10.3 (12.3)	9.7-16.4	0.000
Sport/recreation (0-20)	13.5 (4.3)	7.8 (5.4)	5.7 (5.1)	4.3-7.0	0.000
Quality of life (0-16)	9.7 (2.8)	6.4 (3.3)	3.2 (3.7)	2.3-4.2	0.000
PGA (0-10)	9.3 (2.0)	6.8 (4.0)	4.3 (4.6)	3.0-5.5	0.000
ISOA (0-24)	10.5 (3.7)	6.2 (3.3)	3.2 (3.7)	2.3-4.2	0.000

KOOS = knee injury and osteoarthritis outcome score; PGA = patient's global assessment, ISOA = index of severity for OA
* Paired t-test

used to compare the values at different evaluation over the 12 weeks period with those of baseline. Statistical analyses of these parameters did not indicate any significant change. Although minor changes were observed in some of the parameters, they remained within the normal laboratory range.

Discussion

Osteoarthritis (OA) is the most degenerative join disorder of synovial joints. Physical disability arising from pain and loss of functional capacity reduce quality of like. The European League Against Rheumatism (EULAR) guidelines recommend oral



	Symptom (0-28)	Pain (0-36)	Daily living (0-68)	Sport/rec (0-20)	Quality of life (0-16)	PGA (0-10)	ISOA (0-24)
Baseline	11.1	15.3	27	13.5	9.7	9.3	10.5
4-week	6.8	9.5	15.4	9.5	6.3	7.9	7.3
8-week	6.6	8.1	13.2	6.3	6.4	7.0	6.2
12-week	6.3	7.7	13.9	7.8	6.4	6.8	6.2

Fig. 1 The mean of outcome measured by KOOS parameter, PGA, and ISOA at baseline, W4, W8, and W12.

Table 3. The comparison of the mean of KOOS, ISOA, and PGA between baseline and at 4-, 8-, 12-weeks by repeated ANOVA

Efficacy variable	F-test	*p*-value*
KOOS score		
Symptom (0-28)	26.2	0.00
Pain (0-36)	36.2	0.00
Daily living (0-68)	42.1	0.00
Sport/recreation (0-20)	41.2	0.00
Quality of life (0-16)	36.3	0.00
PGA (0-10)	54.7	0.00
ISOA (0-24)	52.8	0.00

* *p*-value for the difference between baseline and at 4-, 8-, and 12-week by repeated ANOVA

Table 4. Efficacy evaluation of the OMERACT-OARSI responder criteria

Efficacy variables	n	Number (%) of responder
50% reduction in pain	59	30 (50.8)
50% improvement in function	59	33 (55.9)
10% improvement in PGA	59	40 (67.7)
OMERACT-OARSI responder*	59	39 (66.1)

Responder is defined as a participant with 1) 50% reduction in pain or 50% improvement function, 2) 20% reduction in pain or 20% improvement function, adding 10% of the PGA from the baseline.

and topical NSAID as first-line treatment for OA pain, while a recent study suggested that daily use of acetaminophen for symptom of OA of the knee did not improve overall levels of pain, stiffness, or physical functional. The present study is the first recorded clinical trial of the topical use of ginger (*Zingiber officinale* Roscoe) extract in NLC for the treatment of OA. The active components of ginger are [6]-gingerol and [6]-shagaol, which can inhibit arachidonic acid metabolism, leading to its anti-inflammatory properties. In animal model, ginger has been shown to act as a dual inhibitor of both cyclooxygenase (COX) and lipooxygenase (LOX) to inhibit leukotriene synthesis, and to reduce carregenan-induced rat-paw edema[11-13]. However, due to poor absorption, rapid metabolism, and elimination of active compound, the bioavailbility of polyphenolic compound is poor[8,9]. Because gingerol and shogaol are insoluble in water limits their application in aqueous base systems. The present study was based on an extract of the *Zingiber officinale* rhizome, done with by acetone, having a [6]-gingerol content of 11.18%. The ginger extract's preparation was conducted to formed a NLC. NLC had been intensively investigated for dermal application because of its reported positive features. The lipid matrix, the small particle size, and the adhesive properties increase the residence time of NLC on the skin. We could only find one study using Plygersic gel with extract component from ginger and plai (*Zingiber cassumunar* Roxb), at a ratio of about 4% by weight, that was done for the treatment of OA. The use of Plygersic gel have the ability to improve pain and other symptoms when measured by KOOS between two and six weeks of treatment[24]. In addition, Plygersic gel decreased the pain as studied by Altman and Marcussen. The effect of ginger extract (capsule of ginger extract contained 225 mg, extracted from dried ginger rhizome and galangal rhizome) on knee pain in patient with OA during six weeks of treatment[25] was studied. The present study demonstrates the potential of Ginger extract in NLC to relieve pain, joint stiffness, and improve physical function in OA patients, measured by KOOS, ISOA, and Patient Global Assessment parameters (Fig. 1, Table 3).

The OMERACT-OARSI initiative used a consensus approach to derive dichotomous responder criteria. Through their meta-analysis of suitable trial, the authors found that for trial of topical NSAIDs versus oral NSAIDs, the responder rate were 55% and 54% respectively[26]. In the present study, OMERACT-OARSI responder rate had shown 72.8%, and at least 50% reduction in pain shown 67.7% (Table 4). Safety analysis revealed no serious adverse event in any clinical observation or laboratory test. However, some minor application-site skin reaction had contact

dermatitis. This finding was similar to result from previous studies.

Conclusion

Ginger extract nanoparticle relieved joint pain and improved problematic symptoms and quality of life in osteoarthritis knees during a 12-week treatment.

What is already known on this topic?

In their study, Altman and Marcussen (2001)[25] evaluated the efficacy of ginger extract and combination of ginger and galanga (plai) in patient with OA knee. The patients received 225 mg extract per capsule, twice daily, for six weeks. Result shown a better reduction in knee pain in treatment group compared with placebo. In 2012, Niempoog et al[24] studied the efficacy of the combination of ginger and galanga (Plysersic) gel for treatment of OA of the knee. The result showed that the Plygersic gel provided for the treatment of osteoarthritis of the knee similar to the 1% Diclofenac gel group. The combination of ginger and galanga (plai) is good because ginger has strong anti-inflammatory activity but a rapid metabolism and elimination of active compound, whereas galanga has extended anti-inflammatory activity[24].

What this study adds?

The present study had demonstrated ginger extract in new formulation (NLC). There is a requirement for a formulation of a topical drug delivery system of ginger extract that could increase the presence of drug locally for a long period and reduce the risk of systemic toxicity. A 12-week treatment with ginger extract in NLC could relieve joint pain and improve problematic symptoms and the quality of life in OA knee patients. The topical ginger extract in NLC should be studied in Phase III in the future.

Acknowledgements

The present research received funding from the Thai Traditional Medical knowledge Fund, The 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund), and CU-57-065-AS.

Potential conflicts of interest

None.

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ประสิทธิผลและความปลอดภัยของสารสกัดขิงนาโนในการรักษาผู้ป่วยข้อเข่าเสื่อม

ปุณยนุช อมรดลใจ, สุรศักดิ์ ฐานีพานิชสกุล, สัญญาณ เนียมปุก, อุบลทิพย์ นิมมานนิตย์

วัตถุประสงค์: *เพื่อประเมินประสิทธิผลและความปลอดภัยของสารสกัดขิงนาโนในการรักษาผู้ป่วยข้อเข่าเสื่อม*
วัสดุและวิธีการ: *ผู้ป่วยข้อเข่าเสื่อม จำนวน 60 ราย อายุระหว่างอายุ 55-75 ปี วินิจฉัยตามหลักเกณฑ์ของวิทยาลัยแพทย์โรคข้อและรูมาติซั่มสหรัฐอเมริกา ผู้ป่วยได้รับสารสกัดขิงนาโนทาเช่า วันละ 3 ครั้ง เป็นเวลา 12 สัปดาห์ การประเมินประสิทธิภาพการรักษาโดยใช้ตัววัด Knee Injury and Osteoarthritis Outcome Score (KOOS), Index of Severity for Osteoarthritis Index (ISOA) และ Patient's global assessment (PGA) การประเมินความปลอดภัยโลหิตวิทยาและชีวเคมีในเลือด ใช้สถิติ paired t-test เปรียบเทียบก่อนและหลังรักษา*
ผลการศึกษา: *สารสกัดขิงนาโนลดอาการข้อเข่าเสื่อม ลดปวดข้อเข่า เพิ่มสภาพทั่วไป กิจวัตรประจำวัน และคุณภาพชีวิตของผู้ป่วยแตกต่างจากก่อนรักษาอย่างมีนัยสำคัญที่ $p<0.05$ ประเมินจากตัววัด KOOS, ISOA และ PGA และไม่พบความแตกต่างของอาการไม่พึงประสงค์ทางคลินิกและทางห้องปฏิบัติการโลหิตวิทยาหลังการรักษา*
สรุป: *สารสกัดขิงนาโนสามารถลดกลุ่มอาการข้อเข่าเสื่อม คุณภาพชีวิตดีขึ้น ในการรักษา 12 สัปดาห์*
