Received 27 September 2019
Revised 8 January 2020
16 April 2020
15 May 2020
11 June 2020
1 August 2020
Accepted 17 August 2020

Efficacy of rtsa-byugs vs diclofenac gel in relieving knee pain of patients with osteoarthritis of the knee

Dorji Nidup and Somboon Kietinun
Chulabhorn International College of Medicine, Thammasat University–Rangsit Campus, Patumthani, Thailand
Sunyarn Niempoog
Department of Orthopaedic, Faculty of Medicine, Thammasat University, Patumthani, Thailand, and
Kusuma Sriyakul
Chulabhorn International College of Medicine, Thammasat University–Rangsit Campus, Patumthani, Thailand

Abstract

Purpose – Rtsa-byugs, a massage oil from Bhutan, is a traditional herbal formula known for its anti-inflammatory properties and used in osteoarthritis treatment. This study investigates the efficacy of rtsa-byugs vs diclofenacgel in relieving knee pain in osteoarthritis patients.

Design/methodology/approach – A single-blind, randomized controlled trial was conducted amongst osteoarthritis knee patients at an orthopedic outpatient department of Thammasat University Hospital. Participants were randomly allocated to the rtsa-byugs ($N = 31$) or the Diclofenac gel ($N = 31$) group. Primary outcomes were assessed by the knee injury and osteoarthritis outcome scores (KOOS), visual analog scale (VAS) and goniometer at day 0, 1, 3, 7.

Findings – 62 participants completed the study. The result of the KOOS scores demonstrated a significant improvement of symptoms at the end of the study in both treatment groups. Improvement of symptoms, pain, daily life living, sport and recreational score and quality of life assessment showed a significant difference from baseline ($p < 0.001$) within both groups. The quality of life score for the rtsa-byugs group increased significantly on day 3 and 7. The VAS score in both groups decreased with a significant difference from baseline to day 7. The mean value of extension of angle measurement was decreased in day 7, and the mean of flexion score increased in both groups when compared with the baseline.

Research limitations/implications – The duration of the study was very limited and included a small sample consisting of men and women.

The authors would like to thank Thammasat University for the provision of research funding and also acknowledge with deep appreciation and gratitude the Integrative Medicine under Chulabhorn International College of Medicine, Thammasat University for the generous scholarship. All Integrative Medicine staff members and seniors are also acknowledged for their supported and inspirational motivation in achieving the study goals.

Conflicts of interest: The researchers declare no conflict of interest. Rtsa-byugs production has been fully subsidized by the Royal Government of Bhutan, and the product is provided free of charge to healthcare services and research. Research found from Chulabhorn International College of Medicine at Thammasat University No.MD1/2562 (1/11/2019).

Journal of Health Research
Vol. 35 No. 5, 2021
pp. 424-433
Emerald Publishing Limited
e-ISSN: 2586-940X
p-ISSN: 0857-4421
DOI 10.1108/JHR-09-2019-0223

Originality/value – Rtsa-byugs is safe and effective in relieving pain from osteoarthritis of the knee and can be used as an alternative treatment for knee osteoarthritis.

Keywords Rtsa-byugs, Diclofenac gel, Osteoarthritis

Paper type Research paper

Introduction

Osteoarthritis of the knee (OAK) is a chronic disease caused by cartilage degradation after a long progression of friction between the two knees bones, combined with a reduction of synovial fluid resulting in aggravated inflammation in the knee joint. It is associated with various factors such as aging, bone density and obesity. Although pharmaceutical managements of osteoarthritis are available, such as administration of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), the result of the treatment sometimes appears to cause side effects and are not effective enough to reduce patients' pain to improve their quality of life [1]. Osteoarthritis of the knee is a leading global health problem affecting the quality of life, especially amongst the elderly population. In the United States, more than 30 million people have been affected by osteoarthritis which costs approximately 185bn US dollars of the total healthcare spend in the US per year [2].

Heidari reports that more than 10% of elderly aged 60 years and older are experiencing functional impact caused by OAK which could lead to chronic disability. The incidence of OAK tends to rapidly increase due to the increasing prevalence of risk factors such as aging and the rise in obesity [3]. In Asia, a high prevalence of both OAK and knee pain in the elderly was reported, with prevalence ranging from approximately 38–50%. [4, 5]. Thailand is one of the countries that was reported to have a high prevalence of OAK. According to a survey study of Thai elderly in the community conducted by Kuptniratsaikul *et al.*, the prevalence of OAK was up to 40% [6]. Current diagnosis of OAK includes physical examination with x-ray, MRI scan and arthroscopy, if necessary. The European League against Rheumatism (EULAR) states that there are three symptoms for the diagnosis of OAK, i.e. persistent knee pain, limited morning stiffness and reduced function [7]. The main treatment of OAK mainly focuses on pain management using, for example, physical activity, painkillers and joint replacement [8]. However, some OAK patients still seek other ways to reduce their suffering.

The World Health Organization (WHO) stated that traditional and complementary medicine (T&CM) played an important role in the management of lifestyle-related chronic disease such as osteoarthritis, especially among the aging population, and has urged several countries to attempt to integrate T&CM into the healthcare service [9]. Bhutan, also called the valley of medicinal herbs, possesses a long history of traditional medicine embedded in society. More than a thousand herbal recipes appear in the traditional Bhutanese medicine (TBM). The TBM is based on ancient Tibetan traditions incorporated with ancient medical practices connected with Buddhism. [10, 11]. The great principles of Buddhism provide a comprehensive way of understanding the universe, man and illness. There are many traditional ways of pain management in Bhutanese traditional medicine, and rtsa-byugs, a common massage oil in Bhutan is one of them.

The rtsa-byugs massage oil combines six herbal extracts from different species, namely crude extract from C*urcuma longa, Carumcarvi, Myristicafragrans, Delphinium brunoniaum, Cautleya spicata,* and *Sesamum indicum* [12]. The word "rtsa" means nerves, and "byugs" means application/massage. This indigenous medicinal product has been traditionally used as a basic remedy in massage therapy. Rtsa-byugs is usually utilized among patients suffering from musculoskel *et al.* diseases such as arthritis, joint pain, muscle stiffness, paralysis and facial palsy. Nevertheless, the scientific evidence of its safety and efficacyare still limited.

Based on relevant literature, the medicinal plants that make up the rtsa-byugs oil is reported to possess an anti-inflammatory effect. *Curcuma longa,* or turmeric, is a well-known

spice belonging to the ginger family. The main chemical component of turmeric is curcumin. Many studies on the anti-inflammatory properties of curcumin included *in vitro*, *in vivo,* and human studies. The anti-inflammatory activity of curcumin extract from the root C*urcuma longa* has been demonstrated in the laboratory, and the result showed that curcumin can inhibit different molecules playing a major role in inflammation, namely phospholipase, lipooxygenase, cyclooxygenase 2 (COX-2), leukotrienes, thromboxane, prostaglandins, nitric-oxide, collagenase, elastase, hyaluronidase, monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein, tumor necrosis factor (TNF) and interleukin-12 (IL-12) [13]. This is in line with the *in vitro* study conducted by Lev-Ari *et al.* [14] which revealed that the anti-inflammatory activity of curcumin involves inhibition of COX-2 activity.

Another admixture is *Carum carvi* or caraway that is also known for its anti-inflammatory activity. Some studies revealed that carvone, the active component of caraway, can inhibit cyclooxygenase and 5-lipoxygenase activity by reducing biosynthesis of leukotriene and prostaglandin [15], In addition, *Myristicafragrans, Cautleya spicata, and Sesamum indicum,* also revealed the potential to reduce inflammation. Dewi *et al.* [16] state that quercetin from *Myristicafragrans* extracts can inhibit inflammatory cytokines and nitric oxide production since quercetin tends to be the active compound. A study of the biological activity screening of an Indian plants found that *Cautleya spicata* rhizomes extract detected anti-inflammatory, antibacterial, antifungal, antiprotozoal and antifertility effects [17]. Similarly, *Sesamum indicum* also reported the presence of potent anti-inflammatory and antioxidant compounds [18, 19].

Apart from its anti-inflammation capacity, a study by Tripathee [20] reported that the *Delphinium brunoniaum* extract, which is mixed in rtsa-byugs, exhibits antibacterial properties. For example, the ability to inhibit bacillus subtilis, salmonella flexinarie, pseudomonas aureginous and staphylococcus aureus.

This illustrates the potential of rtsa-byugs in reducing pain from inflammation. However, its efficacy, complications and adverse effects have not yet been reported. This study aimed to investigate the efficacy of rtsa-byugs vs 1% diclofenac gel in relieving osteoarthritis knee pain for short-term effects.

Materials and method

Study area and population

This study was a prospective, randomized, evaluator-blind, controlled trial. Participants were enrolled from the orthopedic outpatient department of Thammasat University Hospital, Pathumthani Province of Thailand, between April to June 2019. Osteoarthritis of the knee was diagnosed by an orthopedic physician. The Kellgren Lawrence grading scale (from X-ray image) and visual analog scale (VAS) were used to assess the severity of OAK to recruit participants. Tools of assessment during the experiment included the knee injury and osteoarthritis outcome scores (KOOS), visual analog scale (VAS) and goniometer for measurement of the joint angle (extension and flexion positions).The experimental period was seven days, and all participants were assessed four times (baseline, Day 1, 3 and 7). The inclusion and exclusion criteria are explained below:

Inclusion criteria

(1) Ability to give informed consent

(2) Age 45–75 years old

(3) OAK patients with minimum visual analog scale (VAS) score of 4–6 (mild to moderate)

(4) OAK patients with grade 1–2 of Kellgren Lawrence grading systems

(5) Participants oriented to the risks and benefits of the research and willing to sign the consent form.

Exclusion criteria

(1) Patients who had herbal sensitivity to Curcuma *longa*, *Myristicafragrans*, *Carumcurvi*, *Delphinium brunoniaum*, *Cautleya spicata* and *Sesamum indicum.*

(2) Patients who had undergone lower extremity surgery in the past six months.

(3) Pregnant or breastfeeding women.

(4) Patients who planned to be admitted for surgery or move to another place during the study.

(5) Those already using other topical medicine on the knee.

(6) Patients with inflammatory arthropathy, gout, pseudogout and recent knee injury on the side affected by OA.

Sample size

The sample size was calculated by the G * Power program with a type I error rate of alpha of 0.05, a power of 90%, and an effect size of 0.8. As a result, the appropriated number of samples was 56 plus a 10% drop out. Hence, the total sample size was 62 people [21]. A simple random technique using a computer-generated method was applied to allocate participants into two groups: (1) the rtsa-byugs group ($N = 31$) and (2) the diclofenac group ($N = 31$).

Preparation and analysis of rtsa-byugs

Rtsa-byugs was obtained by the water extraction method using the following plants: Curcuma longa rhizome (3.4 g), Carumcarvi seed (3.4 g), Myristicafragrans seed (1.7 g), Cautleya spicata rhizome (1 g) and the whole plant of Delphinium brunoniaum (0.3 g) which were mainly collected in India and Bhutan. Crude drugs were soaked in a sufficient volume of water for eight hours in a steam jacket kettle and then filtered and evaporated. The 6.86 g. of the extract was yielded (70% yield) and then mixed with sesame oil (Sesamum indicum) (20 g) in a steam-jacket kettle. In this study, rtsa-byugs oil was produced in Bhutan by Menjong Sorig Pharmaceutical Corporation limited under the subsidization of the Ministry of Finance, and the finished product was qualified by the Drug Regulatory Authority of the Royal Government of Bhutan. The finished product of rtsa-byugs oil was analyzed by Gas Chromatograph Mass Spectrometer (GC-MS) as part of the quality control process.

Treatment procedure

The study was carried out for seven days on each participant. After informed consent was given, the researcher performed a physical examination and assessment of OAK by using the assessment tools mentioned above. A total of 31 patients in group 1 were given rtsa-byugs as a treatment of OAK, while participants in group 2 received 1% diclofenac gel. Both remedies were put in an identical tube to avoid bias, and all participants were given demonstrations and practice of how to use the rtsa-byugs oil or diclofenac gel correctly. Importantly, all participants were prohibited from taking any medicine during the study period.

The procedure for applying treatment was as follows:

(1) Participants sat comfortably on a chair

(2) Participants applied the intervention on the knee area (three drops of rtsa-byugs in group 1 and 3 mm. of 1% diclofenac gel in group 2)

(3) Participants massaged the intervention into the knee for 10 minutes twice a day (morning and before bedtime) every day for one week.

(4) Participants remained seated for five minutes to allow the intervention to absorb

(5) Participants did not take any medicine during the study period.

Statistical analysis

Analysis of data was performed by SPSS (version 10) statistical software. Results were expressed as mean ± standard error of the mean (SEM). Characteristic differences were calculated by an independent-sample-*t*-test and χ^2 *test*. Statistical differences of KOOS, VAS, and goniometer tests within the group were calculated by repeated measure ANOVA test for within-group comparison and calculated by independent-sample-*t*-test for between-group comparison. The minimal level of significance was identified at $p < 0.05$.

Ethical considerations

This study received ethical approval from the Human Research Ethics Committee of Thammasat University, Faculty of Medicine Approval number MTU-EC-OO-0-029/62. This research project was registered in the Thai Clinical Trial Registry (Trial registration identification number: TCTR2019062300). All participants were asked to sign an informed consent before conducting the study and the risks and benefits of the research were acknowledged beforehand.

Results

A total of 62 participants were recruited to participate in this study. 31 patients received rtsabyugs, and 31 patients received 1% diclofenacgel as a treatment. All participants stayed for the duration of the 7-day experiment. Demographic characteristics of the initial two allocation groups were compared at baseline for sex, age, body mass index (BMI) and severity of OAK using the Kellgren–Lawrence (K&L) grading system, as shown in Table 1.

This experimental study utilized three measurements for the investigation of OAK treatment outcome, namely KOOS,VAS and angle of joint using goniometer. As shown in Table 2, KOOS indicated an improvement of symptoms, pain, dairy life living score, sport and recreational score and quality of life during seven days of treatment in both groups. The KOOS increased significantly from baseline to day 7 in almost every aspect of the two treatment groups, except for the quality of life in the diclofenac group that did not show a significant difference at the end of the study. Comparison of KOOS between the rtsa-byugs and diclofenac group at the end of the treatments was made, and the results revealed that patients receiving rtsa-byugs showed higher scores at day 7 of the treatment in all subscales with a statistical significance in terms of difference as the score at baseline was comparable.

The mean visual analog scale (VAS) scores of the rtsa byugs group and the diclofenac gel group at baseline, day 1, 3 and 7 of the treatment showed thatVAS scores in both groups decreased with a significant difference at the end of the experiment. The VAS scores of the rtsa-byugs group were less than the diclofenac group at day 3 ($p = 0.002$) and day 7 ($p < 0.001$) with a significant difference, as shown in Table 3.

For the measurement of the angle of joints by a goniometer, the average score of extension decreased significantly after receiving treatment in both groups. Furthermore, the mean flexion score of the two groups increased with statistically significant differences between

Demographic characteristics	Groups		*p*-value
	Rtsa-byugs ($N = 31$)	Diclofenac gel ($N = 31$)	
Female No (%)	27 (87.10%)	27 (87.10%)	0.65 [b]
Male No (%)	4 (12.90%)	4 (12.90%)	
Age (year)Mean (SD)	62.77 ± 7.22	62.61 ± 8.38	0.93 [a]
Body Mass index (kg/m^2) mean (SD)	25.11 ± 3.92	25.73 ± 4.16	0.55 [a]
Kellgren–Lawrence grade			
Grade 1 (Frequency %)	11 (35.50%)	5 (16.10%)	0.73 [b]
Grade 2 (Frequency %)	20 (64.50%)	26 (83.90%)	

Note(s): Values are expressed in mean ± standard deviation
[a]*p* value is calculated by independent-sample-*t*-test for between-group comparison
[b]*p* value is calculated by χ^2 test for between-group comparison
Abbreviations: *N* number of patients in each group
*=*p*-value < 0.05 is considered a statistically significant difference

Table 1.
Baseline characteristics of patients in rtsa-byugs and diclofenac group

	Group	Baseline	Day 1	Day 3	Day 7	[a]*p*-value
Symptoms	Rtsa-byugs	64.86 ± 8.90	75.23 ± 9.62	82.95 ± 9.83	89.29 ± 7.77	0.001*
	Diclofenac	64.52 ± 13.55	71.20 ± 12.68	79.95 ± 11.43	80.99 ± 11.79	0.001*
	[b]*p*-value	0.91	0.16	0.27	0.002*	
Pain	Rtsa-byugs	60.22 ± 10.10	68.82 ± 11.45	78.76 ± 12.56	88.71 ± 10.17	0.001*
	Diclofenac	65.05 ± 14.94	73.75 ± 15.61	81.36 ± 14.60	77.60 ± 14.02	0.001*
	[b]*p*-value	0.14	0.16	0.46	0.001*	
Daily living score	Rtsa-byugs	65.13 ± 9.62	75.62 ± 8.60	87.43 ± 10.56	91.75 ± 8.37	0.001*
	Diclofenac	71.44 ± 15.51	79.65 ± 11.69	87.14 ± 10.05	84.44 ± 9.98	0.001*
	[b]*p*-value	0.06	0.12	0.91	0.003*	
Sports and recreational score	Rtsa-byugs	49.03 ± 14.05	53.71 ± 11.97	62.41 ± 15.38	67.26 ± 15.21	0.001*
	Diclofenac	47.58 ± 16.43	53.39 ± 10.36	58.55 ± 10.74	58.71 ± 8.36	0.001*
	[b]*p*-value	0.71	0.910	0.255	0.008*	
Quality of life score	Rtsa-byugs	45.57 ± 9.01	48.19 ± 8.26	52.42 ± 13.95	52.62 ± 9.92	0.004*
	Diclofenac	44.15 ± 11.29	45.16 ± 6.19	45.36 ± 4.83	47.58 ± 6.78	0.296
	[b]*p*-value	0.59	0.11	0.010*	0.023*	

Note(s): Values are expressed in mean ± standard deviation
[a]*p* value is calculated by repeated measure ANOVA test for within-group comparison
[b]*p* value is calculated by independent-sample-*t*-test for between-group comparison
Knee injury and osteoarthritis outcome score (KOOS) is 0–100, which higher score indicated better Improvement
$N = 31$ in each group
*=*p*-value < 0.05 is considered a statistically significant difference

Table 2.
The comparison of the mean score of KOOS in rtsa-byugs and diclofenac gel during the treatment

pretreatment and posttreatment. There is no significant difference when comparing the score between the two groups. The results of extension and flexion scores are shown in Table 4.

Discussion

To the researcher's knowledge, this is the first recorded clinical trial of rtsa-byugs massage oil which, according to the result, appears to be safe and effective in relieving the pain of osteoarthritis of the knee.

This effectiveness is probably due to the principal components of rtsa-byugs that is composed of the crude extract of anti-inflammatory herbs such as *Curcuma longa*,

Carum carvi, *Myristica fragrans* and *Sesamum indicum*. Several studies claimed that the active compound obtained fromturmeric (*Curcuma longa*) is curcumin which is capable of inhibiting the translocation of NF-κB into the nucleus. The study conducted by Shep *et al.* [22] also reported that the oral administration of curcumin exhibits a similar efficacy in OAK patients as diclofenac with better tolerance. Similar results were found in studies by Sahebkar and Henrotin [23] and Haroyan *et al.* [24] whose research reported curcumin's ability to reduce pain via clinical trials, and therefore it can prevent the inflammation response of the cell [25]. Hence, the positive results in this study are probably due to the combination of curcumin and other herbs.

Furthermore, the results have shown that rtsa-byugs helps improve OAK complications significantly as it reduces symptoms and pain, improves daily activity, sport and recreational, as well as the quality of life scores when measured by the KOOS. The improvement in patients' pain and other symptoms in the diclofenac gel group appears to conform to the previous studies [26, 27]. When comparisons were made between the rtsa-byugs and diclofenac gel groups, the improvement of the KOOS scores at the end of the study showed significant differences suggesting that that rtsa-byugs is more effective. Moreover, a visual analog scale in both groups decreased significantly. When comparing VAS of the rtsa-byug to diclofenac groups, the result showed that rtsa-byug tends to reduce pain better than the diclofenac group.

The mean score of extension measured by goniometer decreased in day 7 and the mean score of flexion increased in both groups when compared with the baseline. This suggests that the movement of the knee is better after the treatment. This result is similar to the clinical study conducted on the efficacy of topical administration of sesame oil in OAK patients. Askari *et al.* demonstrated that sesame oil can improve knee pain when compared to diclofenac and that it also reduced stiffness of the knee [28].

	Group	Baseline	Day 1	Day 3	Day 7	*p*-value[a]
VAS	rTsa-byugs	4.74 ± 0.68	3.39 ± 1.15	2.29 ± 1.35	1.42 ± 1.20	0.001*
	Diclofenac gel	4.90 ± 0.75	3.94 ± 1.21	3.29 ± 1.10	2.74 ± 1.34	0.001*
	[b]*p*-value	0.378	0.72	0.002*	0.001*	

Note(s): Values are expressed in mean ± standard deviation
[a]*p* value is calculated by repeated measure ANOVA test for within-group comparison
[b]*p* value is calculated by independent-sample-*t*-test for between-group comparison
visual analog scale (VAS) is 0–10, which higher scale indicated worse pain
$N = 31$ in each group
*=*p*-value < 0.05 is considered a statistically significant difference

Table 3.
The mean VAS in the rtsa-byugs group at baseline, day 1, 3, 7 of treatment

Group	ROM	Baseline	Day 1	Day 3	Day 7	*p*-value[a]
Extension	Rtsa-byugs	4.19 ± 2.89	4.06 ± 0.96	3.35 ± 0.61	2.10 ± 0.91	0.001*
	Diclofenac	5.29 ± 1.40	4.29 ± 1.51	3.65 ± 1.28	2.26 ± 1.34	0.001*
	[b]*p*-value	0.06	0.49	0.26	0.58	
Flexion	Rtsa-byugs	125.90 ± 8.62	129.71 ± 8.39	134.48 ± 8.03	141.10 ± 7.65	0.001*
	Diclofenac	126.16 ± 6.76	131.68 ± 7.21	135.48 ± 4.19	140.68 ± 4.17	0.001*
	[b]*p*-value	0.38	0.31	0.54	0.79	

Note(s): Values are expressed in mean ± standard deviation
[a]*p* value is calculated by repeated measure ANOVA test for within-group comparison
[b]*p* value is calculated by independent-sample-*t*-test for between-group comparison
$N = 31$ in each group
*=*p*-value < 0.05 is considered a statistically significant difference

Table 4.
The mean score of extension and flexion measured by goniometer

When considering baseline variables of the present study which included sex, age, body mass index and grading of OAK, it tends to reveal an interesting point. According to the result, the average value of the body mass index of the patients was 25.11–25.73 which was classified as a level 1 of obesity. This provides supporting evidence of the correlation between body weight and incidence of OAK [29].

In conclusion, this study demonstrated that rtsa-byugs is effective as an OAK treatment when compared with the standard treatment of diclofenac gel. In addition, there are no other serious side effects that were observed during clinical observation, thus, rtsa-byugs appears to be safe to use.

Conclusion

The short-term study on the efficacy of rtsa-byugs showed that the massage oil is as effective as 1%of diclofenac gel. When comparing the efficacy of the two treatments, rtsa-byugs exhibited the capacity to reduce VAS more than diclofenac gel on the last day of the OAK treatment. Therefore, rtsa-byugs could be considered as a potential alternative treatment for osteoarthritis of the knee.

Limitations

This study included a small sample consisting of men and predominantly women in Thailand. The duration of the study was very limited. Future research could involve sample sizes that include a larger population in Bhutan to evaluate the long-term effects of the drug.

Future plan

Short-term efficacy of rtsa-byugs is compatible and found significant in reducing knee pain in osteoarthritis patients during one week of treatment. Further research into rtsa-byugs should explore the long-term efficacy in clinical trials and preclinical studies.

References

1. World Health Organization. Chronic rheumatic conditions. [cited 2019 May 16]. Available at: https://www.who.int/chp/topics/rheumatic/en.
2. Healthday. Senior-citizen-information. [cited 2019 May 16]. Available at: https://consumer.healthday.com/senior-citizen-information-31/misc-arthritis-news-41/osteoarthritis-costs-u-s-over-185-billion-a-year-633410.html.
3. Heidari B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: part I. Caspian J Intern Med. 2011; 2(2): 205-12.
4. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brook P. The epidemiology of osteoarthritis in Asia. Int J Rheum Dis. 2011; 14: 113-121.
5. Cho HJ, Chang CB, Kim KW, Park JH, Yoo JH, Koh IJ, Kim TK. Gender and prevalence of knee osteoarthritis types in elderly Koreans. J Arthroplasty. 2011; 26(7): 994-9.
6. Kuptniratsaikul V, Tosayanonda O, Nilganuwong S, Thamalikitkul V. The epidemiology of osteoarthritis of the knee in elderly patients living an urban area of Bangkok. J Med Assoc Thai. 2002; 85(2): 154-61.
7. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS, Mazières B, Pavelka K, Punzi L, So AK, Tuncer T, Watt I, Bijlsma JW. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2010; 69(3): 483-9.

8. Versus Arthritis. State of Musculoskeletal Health [Internet]. Chesterfield: versus arthritis; 2019. [Cited 10 May 2020]. Available at: https://www.versusarthritis.org/about-arthritis/data-and-statistics/state-of-musculoskeletal-health-2019/.
9. World Health Organization. WHO global report on traditional and complementary medicine 2019. Geneva: World Health Organization; 2019. [Cited 10 May 2020]. Available at: https://apps.who.int/iris/handle/10665/312342.
10. Sonam D. Introduction, development and present status of traditional medicine in Bhutan. Health Syst. Policy Res. 2017; 4: 2.
11. Wangchuk P, Wangchuk D, Aagaard-Hansen J. Traditional Bhutanese medicine (gSo-BA Rig-PA): an integrated part of the formal health care services. Southeast Asian J Trop Med Public Health. 2007; 38(1): 161-7.
12. Pharmaceutical and Research Unit. Traditional medicine formulary of Bhutan. Thimphu: Institute of Traditional Medicine Services, Department of Medical Services, Ministry of Health; 2016.
13. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of tumeric(Curcuma longa). J Altern Complement Med. 2003; 9(1): 161-8.
14. Lev-Ari S, Strier L, Kazanov D, Elkayam O, Lictenberg D, Caspi D, Arber N. Curcumin synergistically potentiates the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis synovial adherent cells. Rheumatology (Oxford). 2006; 45(2): 171-7.
15. Keshavarz A, Minaiyan M, Ghannadi A, Mahzouni P. Effects of Carumcarvil (Caraway) extract and essential oil on TNBS-induced colitis in rats. Res Pharm Sci. 2013 Jan; 8(1): 1.
16. Dewi K, Widyarto B, Pande Putu E, Widowati W. In vitro study of Myristicafragrans seed (Nutmeg) ethanolic extract and quercetin compound as anti-inflammatory agent. Int J Res Med Sci. 2015; 3(9): 2303-10.
17. Goel AK, Kulshreshtha DK, Dubey MP, Rajendran SM. Screening of Indian plants for biological activity: part XVI. Indian J Exp Biol. 2002; 40: 812-827.
18. Monteiro EM, Chibli LA, Yamamoto CH, Pereira MC, Vilela FM, Rodarte MP, *et al.* Antinociceptive and anti-inflammatory activities of the sesame oil and sesamin. Nutrients. 2014; 6(5): 1931-44.
19. Selvarajan K, Narasimhulu CA, Bapputty R, Parthasarathy S. Anti-inflammatory and antioxidant activities of the nonlipid (aqueous) components of sesame oil: potential use in atherosclerosis. J Med Food. 2015; 18(4): 393-402.
20. Tripathee HP, Sharma RP, Timilsina YP, Pathak R, Devkota KP. An assessment of ethnomedicinal use, chemical constituents analysis and bioactivity evaluation on high altitude medicinal plant Delphinium brunonianum of manang district. Nepal. J Sci Technol. 2012; 12: 111-8.
21. Sansila P, Eungpinichpong W, Buakate L, Ruangrungsi N. The efficacy of court-type Thai traditional massage on knee pain relief in osteoarthritis patients. J Health Res. 2014; 28(2): 121-6.
22. Shep D, Khanwelkar C, Gade P, Karad S. Safety and efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open-label parallel-arm study. Trials. 2019 Dec; 20(1): 214.
23. Sahebkar A, Henrotin Y. Analgesic efficacy and safety of curcuminoids in clinical practice: a systematic review and meta-analysis of randomized controlled trials. Pain Med. 2016. 17(6): 1192-1202.
24. Haroyan A, Mukuchyan V, Mkrtchyan N, Minasyan N, Gasparyan S, Sargsyan A, Narimanyan M, Hovhannisyan A. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. BMC Complement Altern Med. 2018; 18(1): 7.
25. Chin KY. The spice for joint inflammation: anti-inflammatory role of curcumin in treating osteoarthritis. Drug Des DevelTher. 2016; 10: 3029-42.
26. Baraf HS, Gold MS, Clark MB, Altman RD. Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial. Phys Sportsmed. 2010; 38(2): 19-28.
27. Niempoog S, Siriarchavatana P, Kajsongkram T. The efficacy of Plygersic gel for use in the treatment of osteoarthritis of the knee. J Med Assoc Thai. 2012; 95(Suppl 10): S113-9.

28. Askari A, Ravansalar SA, Naghizadeh MM, Mosavat SH, Khodadoost M, Jazani AM, Hashempur MH. The efficacy of topical sesame oil in patients with knee osteoarthritis: a randomized double-blinded active-controlled non-inferiority clinical trial. Compl. Ther. Med. 2019; 47: 102183.

29. Messier SP, Beavers DP, Mihalko SL, Miller GD, Lyles MF, Hunter DJ, Carr JJ, Eckstein F, Guermazi A, Loeser RF, DeVita P. The effects of intensive dietary weight loss and exercise on gait in overweight and obese adults with knee osteoarthritis. The Intensive Diet and Exercise for Arthritis (IDEA) trial. J. Biomech. 2020; 98: 109477.

Corresponding author
Kusuma Sriyakul can be contacted at: kusuma_cat@yahoo.com