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Original Article

Efficacy and Safety of Traditional Transdermal Patch (Ya-Pok-Dud-Pid) in Primary Knee Osteoarthritis Patients: A Randomized Controlled Trial

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ABSTRACT

Background: Patients with Knee Osteoarthritis (KOA) have a progressive decline in their social and physical abilities, which affects their quality of life. The Thai Traditional Transdermal Patch (Ya-Pok-Dud-Pid; YP) has been widely used for the treatment of KOA. **Objective**: To determine the clinical efficacy and safety of YP in comparison with diclofenac gel (DG) for the treatment of KOA. **Methods:** 74 primary KOA Patients were enrolled and randomly assigned to YP groups or DG groups. The outcomes were assessed the Visual Analog Scale (VAS), Time Up and Go (TUG), Active Knee Flexion (AKF) and Passive Knee Flexion, chair sit and reach, and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). **Results**: YP and DG significantly improved VAS, TUG, AKF, PKF, chair sit and reach, and WOMAC ($p < 0.05$). Remarkably, YP experienced the same immediate pain relief after day 1 treatment as DG. The VAS scores of the YP group exhibited a significant reduction from 60±11.06 to 38.92±17.76, while DG decreased VAS score from 61.24±17.84 to 39.19±20.05 ($p < 0.001$). However, there was no significant difference between the two treatment groups. For adverse event, skin reaction (rash, itchy, and dry skin) was noted in the YP group because of the participant receiving YP for an extended period. Altogether, YP has a similar effect to diclofenac gel on pain severity and physical function in patients with knee osteoarthritis. **Conclusion**: YP is recommended as a natural therapeutic agent with efficacy and safety treatment for knee osteoarthritis.

Keywords: Traditional, Transdermal Patch, Diclofenac, Osteoarthritis of knee.

INTRODUCTION

Osteoarthritis (OA) is a painful condition caused by physiological changes. It is characterized by the deterioration of a joint and usually affects the cartilage as well as the ligaments, tendons, and bone.[1,2] It typically occurs at the knee and hip joints. Approximately 80% of individuals over 75 are diagnosed with OA.[3,4] Interestingly, KOA is more problematic than other OA, especially among the elderly, due to its greater incidence rate, painful and disabling condition.[5] KOA is categorized into primary and secondary groups based on etiologic. Primary OA is defined as articular deterioration with no evident cause whereas secondary OA is commonly caused by trauma or mechanical misalignment. The pathophysiology of KOA involves multiple factors, including inflammation within the knee joint, mechanical wear and tear, and articular cartilage deterioration, all of which cause pain and other symptoms in most individuals. Moreover, it may have a significant impact on quality of life as well as both physical function and psychological aspects.[6,7] Because this disease is a progressive condition, current treatment focuses on symptom control and pain relief before requiring joint replacement. Diclofenac is a well-known non-steroidal anti-inflammatory medicine (NSAIDs), that is frequently recommended for alleviating inflammation and pain in KOA. Diclofenac has been shown to suppress the activity of the cyclooxygenase 2 (COX-2) and cyclooxygenase 1 (COX-1).[8] COX-2 is mostly overexpressed during tissue damage, resulting in pain. The suppression of COX-2 enzyme can reduce pain and inflammation at the site of target tissues such as synovial fluid and joint capsules. However, the inhibition of COX-1 enzymes in other tissues such as stomach mucosa and kidneys may cause side effects including gastrointestinal erosions, and renal insufficiency.[9] Due to the risks and limitations that come with using NSAIDs, there is a necessity for more effective[10] and safe alternative treatment for KOA.[11] Traditional and complementary medicine (TCM) includes dietary supplement and herbal remedies, which have been used for many centuries to reduce pain and inflammation. In Thailand, a traditional Thai transdermal patch (Ya-Pok-Dud-Pid;YP) has long been utilized by Thai people with KOA. YP have 20 Ingredients. It comprises *Zingiber cassumunar,* camphor, *Citrus hystrix, Piper nigrum, Curcuma aromatica, Globba malaccensis, Alpinia galanga, Plumbago indica, Piper retrofractum, Putranjiva roxburghii, Tamarindus indica, Acacia concinna, Zingiber zerumbet, Zingiber officinale, Cleome viscosa, Acorus calamus, Gloriosa superba, Crinum asiaticum, Tradescantia zebrina,* and salt as ingredients.[12] Previous research has indicated that the medicinal plants used to make YP have anti-inflammatory and analgesic properties.[13] For instance, *Zingiber cassumunar.* and *Piper nigrum.* demonstrated anti-inflammatory and analgesic[14,15] effect by lowering COX-2 and proinflammatory cytokines including IL-6 and Tumor necrosis factor-

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α (TNF-α). Therefore, YP has the potential to relieve pain while also reducing inflammation. However, scientific evidence supporting the safety and efficacy of YP is still inadequate. Therefore, the aim of this study was to determine the efficacy and safety of the YP versus diclofenac gel (DG) for knee pain alleviation in primary KOA patients.

MATERIALS AND METHODS

Research design

This study was a randomized single-blinded controlled trial which the evaluator was blinded conduct at Sukhothai Thammathirat Thai Traditional Medicine Clinic, School of Health Science Sukhothai Thammathirat Open University, Nonthaburi province, Thailand, Between June to November 2023.The study was approved by The Human Research Ethics Committee of Thammasat University (medicine) Number of Approval 072/2023. It was also registered at Thai Clinical Trails Registry (TCTR20230829005).

Drug preparation

All plants were cleaned immediately of extraneous material, dried at 50°C, weighed according to YP recipe, mix together, and ground into powder. The YP powder was macerated at room temperature with 40% ethanol for 14 day. Filter out of 40 % ethanol YP onto a cotton pad (30 ml. per cotton pad). They were produced at Herbal Medicines and Products Manufacturing Unit, manufactured under GMP by U-thong Hospital, Supunburee province. Chemical fingerprinting and HPLC were used to control the quality of YP powder at the Drug Discovery and Development Center, Thammasat University.

Sample size and patient's characteristic

The sample size was calculated by G *power program with a type I error rate of alpha of 0.05, a power of 90%, and effect size = 0.80. As a result, the appropriate number of samples was 68 plus a 10 % dropout. Therefore, the total sample size was 74 participants. A block of 4 random techniques using a computer-generated method was applied to allocate participants into two groups (37 participants each). The inclusion criteria included both sex, age between 50 –80 years old, diagnosed by an orthopedic physician with primary knee osteoarthritis according to the American College of Rheumatology's clinical and grade 1 to 3 of the Kellgren-Lawrence grading from X-ray and measured pain intensity by VAS at least 40 mn of 100 mn over 7 days preceding enrollment. The exclusion criteria were patients with open wound knee, plan for knee arthroplasty in three months, who had herbal and alcohol allergies, pregnant or breastfeeding women, gout, pseudogout, rheumatoid arthritis, recent knee injury, paralysis, parkinson, using other topical medicine on the knee, using NSAIDs or other treatment for relieve KOA such as physiotherapy, knee massage, acupuncture in 7 days, Intra-articular (corticosteroid or hyaluronate) injection in three months, using Symptomatic Slow-Acting Drug of Osteoarthritis (SYSADOA) for example glucosamine, diacerein, chondroitin in 4 months and using a walker.

The participants who met the inclusion criteria were informed, signed a consent form, a divided randomly into two groups of treatment, using a computer-generated program. The researcher demonstrated to the participant how to use YP. The affected knee should first be cleaned. Next, the patch should be placed on the knee, and leave it there for 15 minutes twice a day (morning and evening). Following the time limit, clean the knee region. The control group received approximately 2-3 grams of 1 % diclofenac gel which was administered three times a day (morning, noon, and evening). Both groups took the medicine for 28 consecutive days.

Outcome measurement

The primary efficacy of the YP was assessed by pain score using VAS consisting of a score 0 - 100 with the endpoints defining extreme limits such as no pain (number 0) and extreme pain (number 100), TUG, goniometer for measurement of the knee joints angle (flexion positions) and chair sit and reach at the first visit for baseline data and on day 1 (after the first receiving treatment 15 minutes), day 14, day 28 and day 42 (follow-up after treatment 14 days). Another assessment of efficacy was evaluated by the Western Ontario and Mcmaster Universities (WOMAC) contains 3 indicators (pain index, stiff index, and physical function index) at baseline, day 14, 28, and day 42 (follow-up after treatment 14 days).

Statistical analysis

Data were analysis using SPSS version 25. Results were reported as descriptive, frequency, percentage, mean and standard deviation. Demographic characteristic differences and knee osteoarthritis symptoms were calculated by an independent t-test and Chi-square test. Statistic differences of VAS, TUG, AKF, PKF, and chair sit and reach test within the group were calculated by Pair-t-test at baseline to day 1 and calculated by independent t-test for between-group comparison. Statistic differences of VAS, TUG, AKF, PKF, chair sit and reach, and WOMAC within the group were calculated by Repeated measure ANOVA test for within-group comparison and calculated by independent t-test for between-group comparison. The mean change variable from baseline outcome measurement on both treatments after each trial visit (day 1, 14, 28, and 42) was normally distributed. The minimal level of significance was identified at $p < 0.05$.

RESULTS

In this study, 262 patients were enrolled and randomized into two groups. A total number of 74 completed the study as Figure 1.

Demographic characteristic data, the groups were not statistically different in terms of gender, age, weight, height, BMI, occupational (Table 1).

In addition, the groups were not statistically different in terms of Kellgren-Lawrence grade, disease duration, and VAS (Table 2).

After 15 minutes of treatment day1, both YP and DG significantly reduced VAS pain scores and TUG ($p < 0.05$). Both groups had significantly increased active knee flexion, passive knee flexion, and chair sit and reach ($p < 0.05$). However, there was no statistical difference between the two groups (Table 3).

When comparing the mean change in score at day 1, 14, 28, and day 42 to the baseline, the effectiveness of the treatment was shown to be significantly improved ($p < 0.05$) in all variables. Both the YP and DG had significantly reduced the VAS pain scores and TUG ($p < 0.05$). Both groups had significantly increased the passive knee flexion and chair sit and reach ($p < 0.05$). However, YP significantly increased the mean AKF on days 1, 14, 28, and 42 while diclofenac no significant differences in mean AKF. Nevertheless, there was no statistical difference between the two groups (Table 4).

The mean of the WOMAC parameters of pain index, stiffness index, and physical function index according to the treatment group and different visits on days 14, 28, and 42 of the trial were significantly reduced from baseline in both groups ($p < 0.05$) (Table 5).

The most common adverse event recorded in the YP group was a skin reaction at the application site including rash and itchy 3(8.11%), dry skin 2(5.41%), and redness 2 (5.41%). The adverse event appeared after the participant received overuse time YP (more than 15 minutes). However, the skin reaction was quickly alleviated by washing the knee and using moisturizer or vaseline.

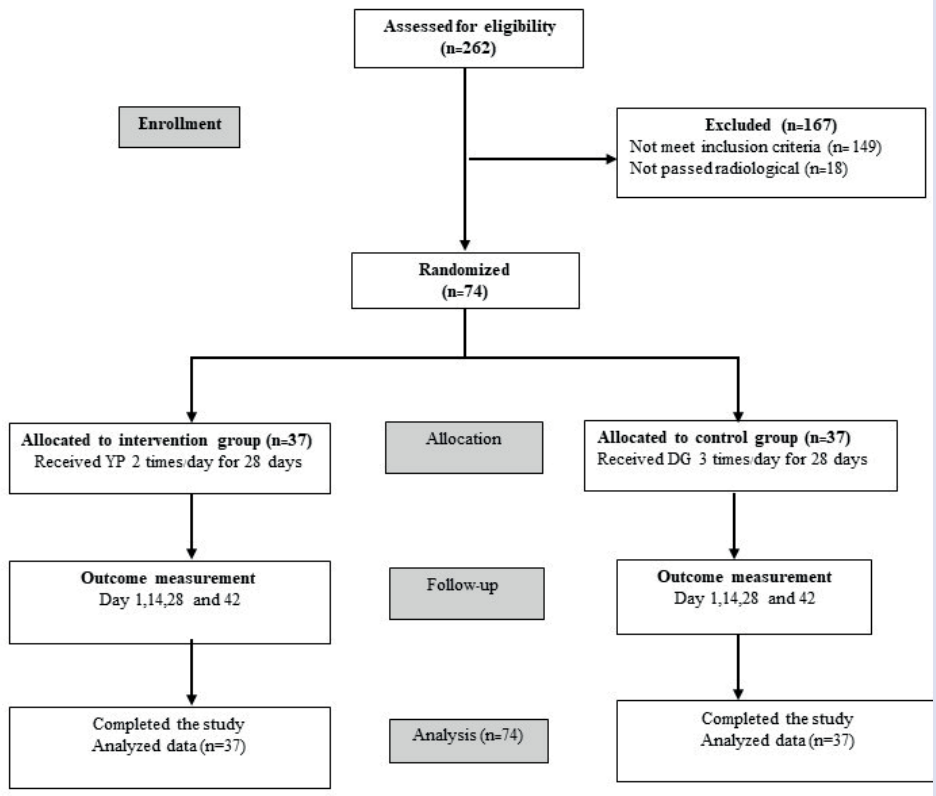

Figure 1: Flow chart of participants.

Table 1: Demographic characteristics of participants.

Characteristic	Group		p-value
	YP (n=37)	DG (n=37)	
Gender, n(%)			
Female	32(86.5)	33(89.2)	0.72
Male	5(13.5)	4(10.8)	
Age (years) mean ± SD	63.32±5.38	62.27±5.81	0.42
Weight (kg) mean ± SD	60.42±9.98	63.30±12.47	0.28
Height (cm) mean ± SD	157.35±7.12	155.97±8.43	0.45
BMI (kg/m2) mean ± SD	24.36±3.27	25.87±4.30	0.09
Occupation, n(%)			
Housekeeper	17(21.5)	22(59.5)	
Entrepreneur	11(14)	10(27)	0.82
Retire	1(1.3)	1(2.7)	
None	8(10.1)	4(10.8)	

Note: YP; Ya Pok Dud Pid, DG = Diclofenac gel, Data were represented as mean±SD n%, p-value data were analyzed by independent t-test between groups, and and p-value are significant difference ($p \leq 0.05$)

Table 2: Knee osteoarthritis symptoms of participants.

Knee osteoarthritis symptoms	Group		p-value
	YP (n=37)	DG (n=37)	
Kellgren-Lawrence grade, n(%)			
Grade 1 (Doubtful OA)	2(5.41)	3(8.11)	
Grade 2 (Mild OA)	19(51.35)	14(37.84)	0.50
Grade 3 (Moderate OA)	16(43.24)	20 (54.05)	
Disease duration, n(%)			
Less than 1 year	9(24.32)	12(32.43)	
1 - 3 year	19(51.35)	17(45.95)	0.42
More than 3 years	9(24.32)	8(21.62)	
VAS (Moderate pain) mean ± SD	60±11.06	61.24±17.84	0.72

Note: YP; Ya Pok Dud Pid, DG; Diclofenac gel. Data were expressed as n% and mean±SD, Independent t-test between groups, and p-value are significant difference ($p \leq 0.05$)

Table 3: Comparison mean±SD of VAS, TUG, AKF, PKF, and chair sit and reach at baseline and day 1 in both groups.

Variables	Group	Baseline	Day1	p-value[a]
VAS (mm)	YP	60±11.06	38.92±17.76	<0.001*
	DG	61.24±17.84	39.19±20.05	<0.001*
	p-value[b]	0.72	0.95	
TUG (sec)	YP	10.09±1.79	9.40±1.24	<0.001*
	DG	10.27±2.03	9.23±1.62	<0.001 *
	p-value[b]	0.68	0.61	
AKF (degree)	YP	119.16±10.64	123.68±8.20	<0.001*
	DG	117.22±15.95	120.11±12.93	0.030*
	p-value[b]	0.60	0.16	
PKF (degree)	YP	132.81±10.91	136.05±9.25	0.004*
	DG	127.84±15.28	131.38±13.59	0.003*
	p-value[b]	0.11	0.09	
Chair sit and reach (cm)	YP	6.18±9.89	9.50±9.83	<0.001*
	DG	7.68±8.64	11.46±8.96	<0.001*
	p-value [b]	0.49	0.37	

Note: YP; Ya Pok Dud Pid, DG; Diclofenac gel, VAS; visual analog scales , TUG; time up and go test, AKF; active knee flexion, PKF; passive knee flexion. Data were represented as mean±SD, p-value[a] data were analyzed by Pair t-test within the group between baseline and day 1, p-value[b] data were analyzed by independent t-test between groups, and *; p < 0.05.

Table 4: Comparison Mean±SD of VAS, TUG, AKF, PKF, and chair sit and reach at baseline, treatment period, and follow-up in both groups.

Variables	Group	Baseline	Treatment period		Follow-up	p-value [a]
			Day 1	Day 14	Day 28	Day 42	
VAS (mm)	YP	60±11.06	38.92±17.76	28.92±14.30	12.97±14.31	17.84±15.30	<0.001*
	DG	61.24±17.84	39.19±20.05	26.22±19.91	12.97±14.88	17.03±17.14	<0.001*
	p-value[b]	0.72	0.95	0.51	1.00	0.83	
TUG (sec)	YP	10.09±1.79	9.40±1.24	8.82±1.39	8.29±1.19	8.20±1.22	<0.001*
	DG	10.27±2.03	9.23±1.62	8.29±1.15	7.82±1.20	8.20±1.53	<0.001*
	p-value[b]	0.68	0.61	0.08	0.10	0.99	
AKF (degree)	YP	119.16±10.64	123.68±8.20	121.62±8.72	122.14±9.11	121.32±9.82	0.018*
	DG	117.22±15.95	120.11±12.93	117.57±11.97	117.97±12.29	117.86±10.98	0.335
	p-value[b]	0.54	0.16	0.10	0.10	0.16	
PKF (degree)	YP	132.81±10.91	136.05±9.25	132.73±7.67	136.46±8.72	136.81±9.48	0.033*
	DG	127.84±15.28	131.38±13.59	127.92±13.86	133.11±12.67	132.35±12.15	0.015*
	p-value[b]	0.11	0.09	0.07	0.19	0.08	
Chair sit and reach (cm)	YP	6.18±9.89	9.50±9.83	7.41±11.72	11.55±9.91	8.01±7.69	0.026*
	DG	7.68±8.64	11.46±8.96	9.84±8.40	13.24±9.48	11.72±10.03	0.016*
	p-value[b]	0.49	0.37	0.31	0.46	0.08	

Note: YP; Ya Pok Dud Pid, DG; Diclofenac gel, VAS; visual analog scales , TUG; time up and go test, AKF; active knee flexion, PKF; passive knee flexion. Data were represented as mean±SD, *p*-value[a] data were analyzed by Repeated ANOVA measurement within group between baseline and day 1,14,28 and 42, *p*-value [b] data were analyzed by independent t-test between groups, and *; p < 0.05.

Table 5: Comparison mean±SD of the WOMAC parameters at baseline, treatment period and follow-up in both groups.

Variables	Group	Baseline	Treatment period		Follow-up	p-value[a]
			Day 14	Day 28	Day 42	
Pain index	YP	9.24±4.74	4.11±2.37	2.89±2.37	3.11±2.68	<0.001*
	DG	9.38±4.74	4.24±2.89	2.59±2.09	3.41±2.901	<0.001*
	p-value[b]	0.90	0.83	0.57	0.65	
Stiff index	YP	3.54±2.26	1.86±1.52	1.11±1.31	1.19±1.39	<0.001*
	DG	3.57±2.27	1.38±1.09	0.76±1.04	1.19±1.38	<0.001*
	p-value[b]	0.96	0.12	0.21	1.00	
Physical function index	YP	30.05±17.51	13.35±10.51	10.22±10.57	9.54±9.97	<0.001*
	DG	30.54±16.14	13.11±9.40	7.97±7.544	10.03±9.31	<0.001*
	p-value[b]	0.90	0.92	0.30	0.83	
Total WOMAC score	YP	42.84±23.25	19.30±12.91	14.27±13.40	13.84±13.50	<0.001*
	DG	43.49±22.11	18.73±12.23	11.32±9.52	14.62±12.71	<0.001*
	p-value[b]	0.90	0.85	0.28	0.80	

Note: YP; Ya Pok Dud Pid, DG; Diclofenac gel. Data were represented as mean±SD, *p*-value[a] data were analyzed by Repeated ANOVA measurement within group between baseline and day 1, 14, 28 and 42, *p*-value[b] data were analyzed by independent t-test between groups, and *; p < 0.05.

DISCUSSION

Traditional and complementary medicine (TCM) had been used clinically to treat various disease, particularly KOA, to alleviate pain and inflammation. It had several advantages, including multitarget therapeutic effects and low side effects. To the best of our knowledge, this was the first study of Ya-Pok-Dud-Pid (YP), a traditional Thai transdermal patch versus diclofenac gel in relieving pain in KOA patients. The findings indicated that YP provided comparable pain relief as diclofenac in patients with KOA. Considering that no adverse reaction was reported, YP could be used as a safe alternative treatment to relieve OA pain.

The results of this study showed that there was a significant decrease in the VAS, TUG, chair sit and reach, AKF and PKF in both groups. Notably, YP had the same rapid pain suppression after day 1 treatment as diclofenac. At day 1, the VAS scores of the YP group exhibited a significant reduction from 60±11.06 to 38.92±17.76, while diclofenac group decreased VAS score from 61.24±17.84 to 39.19±20.05 ($p < 0.001$) (Table 3). There was no significant difference between the two treatment groups. We hypothesized that because YP was derived from Thai herbal poultices to enhance medicine absorption and skin penetration, it would reduce acute pain similarly to diclofenac gel. In addition, this patch was easier to apply than the traditional Thai herbal poultice. To support our idea, previous research found that topical NSAIDs were applied directly to the painful area, the precise formulation of a topical drug might enhance the speed of drug absorption. [8] Furthermore, we hypothesized that the effectiveness of YP in reducing pain was probably due to the anti-inflammatory effect of each extract. For instance, *Piper nigrum*. and *Piper longum*. could suppressed the expression of proinflammatory cytokine such as Interleukin-6 (IL-6) and IL-1β in a dose dependent manner.[15,16] Besides, *Zingiber cassumunar* had a significant benefit in pain reduction for muscle pain and anti-inflammatory effect. [17,18] As a result, the advantageous results of this study were essentially probably due to the combination of Thai herbs.

According to WOMAC score, continued usage of YP could reduce pain, stiffness, and physical index, similar to diclofenac gel. At baseline, the YP group had a total WOMAC score of 42.84±23.25. After 14 and 28 days of consecutive use, the total Womac scores were 19.30±12.91 and 14.27±13.40, respectively. In addition, the overall WOMAC score for the diclofenac group was 43.486±22.11 at baseline and 18.73±12.23 and 11.32±9.52 after using the gel for 14 and 28 days, respectively. In addition, we subsequently followed all the individuals at day 42 (after discontinuing treatment for 14 days), and their overall WOMAC scores were approximately the same as those of the patients on day 28. Along with the WOMAC scores, the VAS and TUG were nearly equivalent to the patients on day 28. In line with the results of this study, prior study demonstrated that the combination of *Garcinia mangostana*, *Sesamum indicum*, *Glycine max*. and *Centella asiatica* could decrease VAS knee pain noninferior to diclofenac gel.[19] In addition, after 21 days of treatment, *Nigella sativa* oil could alleviate pain better than diclofenac group.[20] Furthermore, the topical 1% *Hedera. helix* extract gel has a relatively similar effect to diclofenac gel on pain severity, stiffness, and physical function in patients with KOA patients.[21]

CONCLUSION

YP might be an effective alternative therapy for alleviating KOAdiscomfort. YP was as effective as the diclofenac and caused no side effects. Altogether, It was a safe and cost-effective treatment for KOA patients. Because this was the first randomized controlled trial on the effects of YP on KOA patients, there were some limitations to this study. These limitations could be named in this regard. To begin, it was unethical to prevent elderly people from taking their medications, therefore, polypharmacy was one of limitation in this study. Small sample size might have affected the power of the study. Another limitation of the current study was the lack of a third control group using placebo to ensure that the analgesic effects were related to the treatment.

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CONFLICTS OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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DECLARATIONS OF ANY CONFLICTS OF INTEREST

No conflicts of interest.

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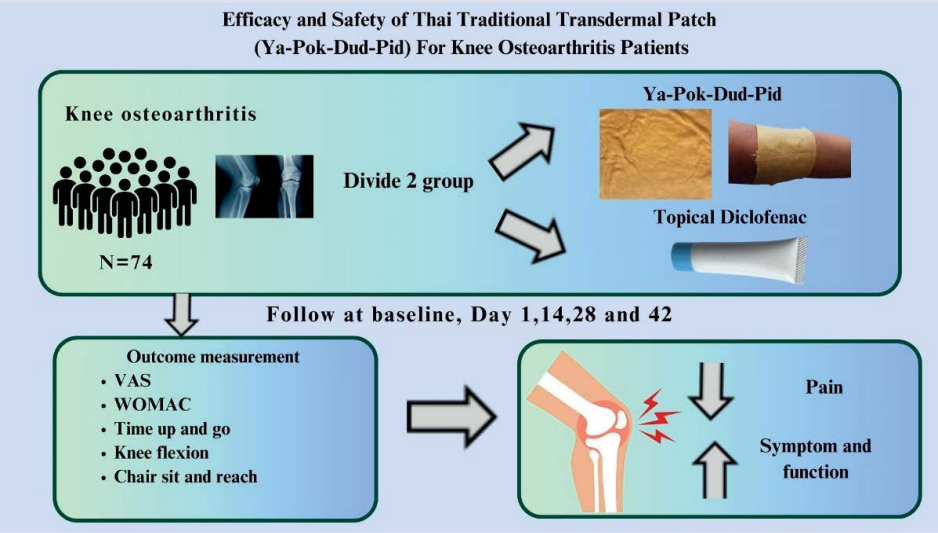
GRAPHICAL ABSTRACT



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