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Clinical Effects of Krachaidum (*Kaempferia parviflora*): A Systematic Review

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Abstract

Kaempferia parviflora (Krachaidum) is a medicinal plant in the family Zingiberaceae. Its rhizome has been used as folk medicine for many centuries. A number of pharmacological studies of Krachaidum had claimed benefits for various ailments. Therefore, this study aimed to systematically search and summarize the clinical evidences of Krachaidum in all identified indications. Of 683 records identified, 7 studies were included. From current clinical trials, Krachaidum showed positive benefits but remained inconclusive since small studies were included. Even though results found that Krachaidum significantly increased hand grip strength and enhanced sexual erotic stimuli, these were based on only 2 studies and 1 study, respectively. With regard to harmful effects, we found no adverse events reported even when Krachaidum 1.35 g/day was used. Therefore, future studies of Krachaidum are needed with regards to both safety and efficacy outcomes.

Keywords

Kaempferia parviflora, systematic review, complementary and alternative medicine

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Kaempferia parviflora or Krachaidum (in Thai), also known as ''Thai ginseng,'' is a medicinal plant in the family Zingiberaceae. It is found in tropical areas such as Malaysia, Sumatra, Borneo Island, and Thailand. Its rhizome has been long used as folk medicine for many centuries.[1] Among the Hmong hill tribe, Krachaidum is widely believed to reduce perceived effort, improve physical work capacity, and prolong hill trekking. A number of pharmacological studies of Krachaidum have shown the following properties: antiallergenic,[2,3] anti-inflammatory,[4] antimutagenic,[5] antidepressive,[6] anticholinesterase,[7] antimicrobial,[8,9] anticancer,[10-12] anti–-peptic ulcer,[13] cardioprotective,[14,15] antiobesity activity,[16] and aphrodisiac.[17-20]

Phytochemicals of Krachaidum contain 2 major constituents: 5,7-dimethoxyflavone and 5,7,4′-trimethoxyflavone.[21] In an in vitro study, methoxyflavone was examined for its inhibitory activities against nitric oxide production. Compound 5 (5-hydroxy-3,7,30,40-tetramethoxyflavone) exhibited the highest activity, followed by compounds 4 (5-hydroxy-7,40-dimethoxyflavone) and 3 (5-hydroxy-3,7,40-trimethoxyflavone), whereas other compounds possessed moderate or weak activity.[4] In addition, more than 20 chemically identifiable constituents have been reported to have potent pharmacological effects.[22] For example, flavonoids contained in Krachaidum rhizome extract was reported to possess antioxidant activity, neuroprotective effects, and cognition-enhancing effects.[21] Methoxyflavone substances in Krachaidum showed an inhibitory effect of phosphodiesterase types 5 and 6, which enhanced sexual performance.[20] For antimicrobial activity, 5,7,4′-trimethoxyflavone and 5,7,3′,4′-tetramethoxyflavone exhibited antiplasmodial activity

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against *Plasmodium falciparum*, and 3,5,7,4′-tetramethoxyflavone showed antifungal activity against *Candida albicans*.[8] For cholinesterase inhibitory effect, Krachaidum showed the potential inhibitors toward acetylcholinesterase and butyrylcholinesterase, which may be of great interest to be considered as a treatment agent for Alzheimer's disease.[7] Considering adverse events of Krachaidum used, an animal histopathological study of visceral organs revealed no remarkable lesions related to the toxicity of Krachaidum extract.[23]

According to the anecdotal evidence of safety and efficacy, Krachaidum has been selected in Thailand as 1 of the 5 champion herbal products that have been widely used and have generated income to the country.[22,24] However, even though widely used for a long time and having shown benefits, clinical studies in human are still limited. Therefore, this study aims to systematically search and summarize the evidence in favor Krachaidum from existing clinical trials in all identified indications.

Methods

This systematic review was conducted in line with the Cochrane Collaboration framework guidelines,[25] and the study follows the PRISMA Statement.[26]

Search Strategies

The following databases were used to search for original research articles from inception to January 2016: PubMed, EMBASE, Cochrane Central Register of Clinical Trials, CINAHL, AMED, WHO Registry, www.clinicaltrial.gov, Health Science Journals in Thailand, Thai Library Integrated System, Thai Thesis Database, Thai Index Medicus, and Thai Medical Index. Strategic search terms included "*Kaempferia parviflora*," "Black ginger," "Krachaidum" (a Thai word for *Kaempferia parviflora*), or other synonym names. References of articles derived for full-text review were scanned to identify potential studies not indexed in the above databases.

Study Selection

Studies were included if they met the following inclusion criteria: (1) conducted in humans, (2) evaluated clinical effects of Krachaidum, and (3) had a control group. Two authors (SS and PW) independently scanned all the titles and abstracts to determine whether the studies assessed the clinical effects of Krachaidum. Full-text articles of the potential studies were subsequently assessed by SS and PW. When disagreements and uncertainties regarding eligibility occurred, they were resolved by consensus discussions.

Data Extraction

Two authors (PW and PR) independently extracted data using a data extraction form and confirmed by a third author (SS) in line with the CONSORT statement for reporting herbal medicinal interventions.[27] The data extracted and reported included the following: study design, number of participants, age of participants, herbal compress ingredients, characteristics of the intervention, and outcome measurement. Outcomes of interest depended on indication of Krachaidum, for example, physical or exercise performance, erectile response.

Quality Assessment

Studies included in this review were assessed for methodological quality by SS and PW using the Cochrane risk of bias tool[25] and Jadad score.[28] The Cochrane risk of bias evaluates bias in intervention studies based on a number of criteria, including the following: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. Studies in which baseline characteristics were different among study groups or not tested for their difference were considered as high risk for the domain of "other risk of bias." Each study was classified as having low risk (low risk of bias for all key domains), high risk (high risk of bias for one or more key domains), or unclear risk (unclear risk of bias for one or more key domains). Disagreements between the reviewers were settled through discussion and consensus.

Statistical Analysis

Data from all studies were pooled in a meta-analysis to determine the overall effect size with 95% confidence interval. Pooled effects were calculated and stratified according to indications of Krachaidum and its comparators. The outcome variables were compared between intervention and comparator arms by calculating the overall mean differences, which could be (1) standardized mean difference for outcomes that were measured by different scales across studies; or (2) weighted mean difference for outcomes that were measured on the same scale.[25]

Statistical heterogeneity between studies was assessed using the χ^2 test and I^2. Thresholds of I^2 were interpreted in accordance with the magnitude and direction of effects and strength of evidence of heterogeneity (ie, P value) as follows: might not be important (0% to 40%), moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%), and considerable heterogeneity (75% to 100%).[25] The DerSimonian and Laird random-effects model[29] was employed for all analyses. Meta-analyses were conducted using STATA version 14 (STATA Corp, College Station, TX).

Results

Study Selection

A total of 683 records were identified through database searching (n = 680) and other sources (n = 3). A total of 462 records remained after duplicates were removed. Of the remaining 462 records, 378 were deemed ineligible based on title and abstract. Of the 84 articles qualified for a full-text review, 77 full-text articles were excluded because they did not meet the study eligibility criteria. The flow chart in Figure 1 presents the results describing exclusions at different stages during the review process. Seven studies were included in this systematic review.[30-36]

Characteristics of the Included Studies

The general characteristics of included studies are presented in Table 1. Of the 7 included randomized controlled trials, 6 studies were from Thailand,[30-35] and 1 study was done in Japan.[36] Five studies were conducted in healthy volunteers,[30-32,34,36] and one each studied in male soccer players[33] and patients with diagnosed osteoarthritis.[35] Among the included studies that reported patients' age and gender, the average age

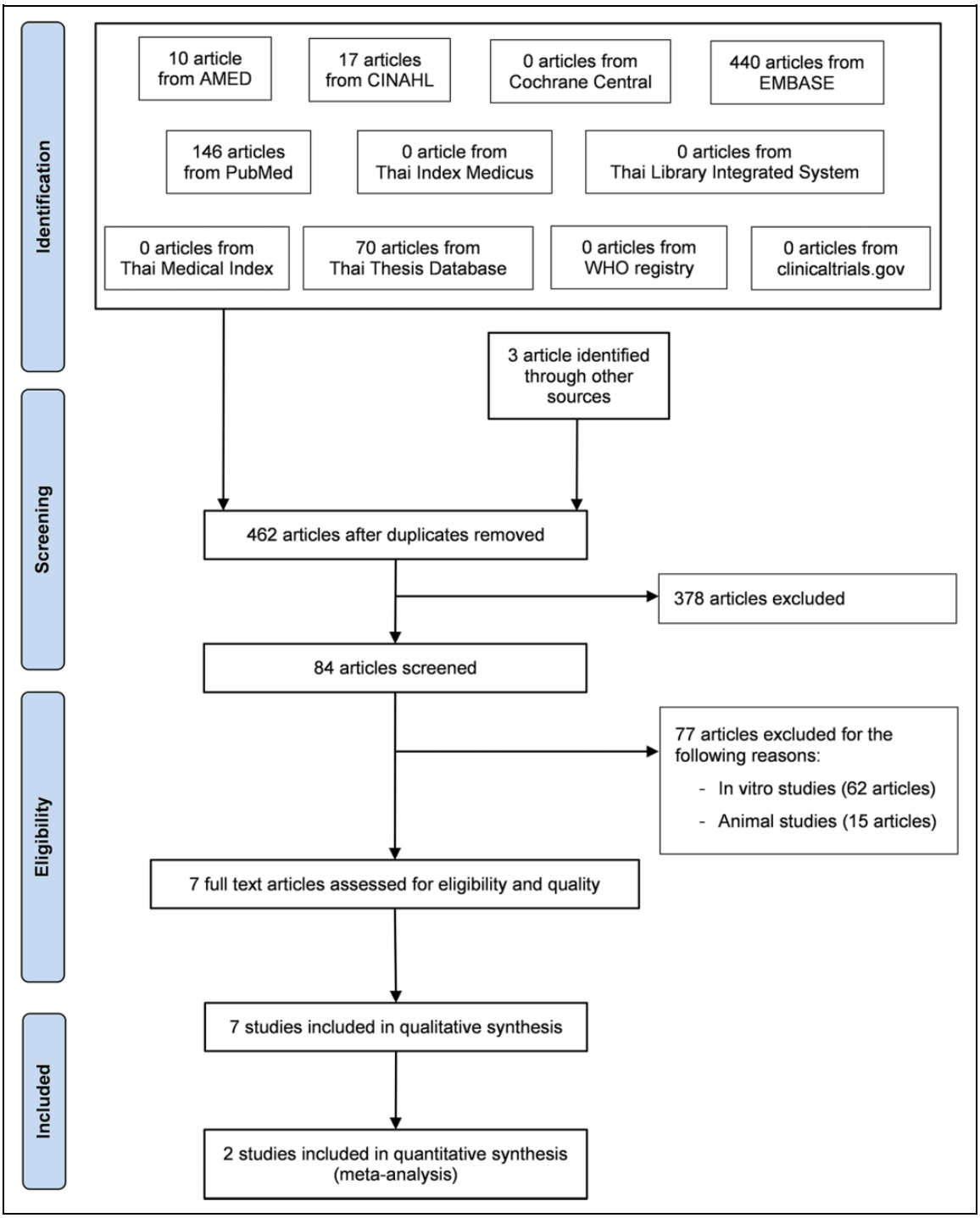

Figure 1. Flow diagram of selected articles.

ranged from 16 to 66 years, and all patients were men in 5 studies,[30,31,33,34,36] except the study of Chalee,[35] which consisted of 26.5% of men, while one study did not report gender of participants.[32] Most studies used Krachaidum as powder in capsule and compared with placebo, except the study of Chalee,[35] which used Krachaidum as cream and compared with analgesic creams. Duration of study varied from 90 minutes[31,36] to 4 weeks,[35] 8 weeks,[30,32,34] and 12 weeks.[33] Considering outcomes of interest, 4 studies focused on physical or exercise performance,[30-33] while one each focused on erectile response,[34] pain indicators,[35] and energy expenditure.[36] All studies reported that they used standardized extract of Krachaidum. Three studies reported that they used thin-layer chromatography fingerprint[30] or high-performance liquid chromatography,[31,36] while 4 studies reported that a standardized extract of Krachaidum was prepared by the Center for Research and Development of Herbal Health Product, Faculty of Pharmaceutical Sciences, Khon Kaen University.[32-35]

Table 1. Characteristics of the Included Studies.

Study, Country	Design (Jadad Scale)	Participants' Characteristics	N	Mean Age (in Years)	Men (%)	Intervention Group With Dose	Comparison Group	Standardization of Krachaidum		Extraction Method	Outcomes	Duration of Study
								Description	Method			
Physical or exercise performance												
Deema (2007),[30] Thailand	RCT (Jadad = 3)	Healthy males age 18-35 years	30	22.0	100	KP 1.35 g in capsules with endurance training (n = 11) or without endurance training (n = 5)	Placebo capsules with endurance training (n = 10) or without endurance training (n = 4)	Quantifying its content according the standard procedure	TLC fingerprint	Ethanol extract	Maximum power output (watt), Time to finish work max test (min), Heart rate (BPM), Lactate threshold (watt)	8 weeks
Wasuntarawat (2010),[31] Thailand	RCT (Jadad = 4)	Healthy males	19	20.0	100	KP 1.35 g in capsules	Placebo	Validated by quantifying its content of 5,7-dimethoxyflavone and 5,7,40-trimethoxyflavone	HPLC	NR	Maximum power output (watt), Mean power output (watt), Time to exhaustion (min), Rating of perceived exertion, Percentage fatigue (%), Heart rate (BPM)	90 minutes
Wattanathorn (2012),[32] Thailand	RCT (Jadad = 4)	Healthy elderly were older than 60 years	45	62.8	NR	KP 25 mg in capsules (n = 15) and 90 mg (n = 15)	Placebo (n = 15)	Assured by strict in-process controls during manufacturing and complete analytical control of the resulting dry extract	KKU	95% ethanol extract	Hand grip strength test (kg), 30-Second chair stand test (seconds), 6-Minute walk test (meter), Tandem test (seconds)	8 weeks
Promthep (2015),[33] Thailand	RCT (Jadad = 4)	Males soccer players age 15-18 years	60	16.0	100	KP 180 mg in capsules (n = 30)	Placebo (n = 30)	Assured by strict in-process controls during manufacturing and complete analytical control of the resulting dry extract	KKU	95% ethanol extract	Grip strength test (kg/wt), Back-and-leg test (kg/wt), Sit-and-reach test (cm), 40-Yard technical test (seconds), 50-Metre sprint test (seconds), Cardiorespiratory fitness (VO_2 max) test (mL/kg/min)	12 weeks

(continued)

Table 1. (continued)

Study, Country	Design (Jadad Scale)	Participants' Characteristics	N	Mean Age (in Years)	Men (%)	Intervention Group With Dose	Comparison Group	Standardization of Krachaidum		Extraction Method	Outcomes	Duration of Study
								Description	Method			
Erectile response												
Wannanon (2012),[34] Thailand	RCT (Jadad = 5)	Healthy elderly volunteers	45	66.0	100	KP 25 mg in capsules (n = 15) and 90 mg (n = 15)	Placebo (n = 15)	Assured by strict in-process controls during manufacturing and complete analytical control of the resulting dry extract	KKU	95% ethanol extract	Latency time (min), Penile circumference and length (cm), Serum hormones concentrations (testosterone (ng/mL), FSH (IU/L), LH (IU/L)	8 weeks
Pain indicators												
Chalee (2010),[35] Thailand	RCT (Jadad = 5)	Patients were older than 50 years with diagnosed OA	70	61.0	26.5	KP 7%w/w creams applied 1 sachet (2 g) 3 time a day (n = 35)	Analgesic creams (n = 35)	KP 7%w/w	KKU	95% ethanol extract	Pain score, Circumference of knee joint (cm), Range of motion of knee joint (ROM), Modified WOMAC score	4 weeks
Energy expenditure												
Matsushita (2015),[36] Japan	RCT, crossover trial (Jadad = 1)	Healthy males aged 21-29 years	20	24.1	100	KP 100 mg/day in capsules	Placebo	Revealed that the KP extract contained 3,5,7,4′-tetramethoxyflavone (2.16%), 5,7-dimethoxyflavone (4.07%), and 3,5,7,3′,4′-pentamethoxyflavone (4.25%)	HPLC	60% ethanol extract	Energy expenditure change (kJ/day)	90 minutes

Abbreviations: RCT, randomized controlled trial; KP, *Kaempferia parviflora*; N, number of participants; TLC, thin layer chromatography; BPM, beats per minute; HPLC, high-performance liquid chromatography; NR, not reported; KKU, a standardized extract of *Kaempferia parviflora* prepared by the Center for Research and Development of Herbal Health Product, Faculty of Pharmaceutical Sciences, Khon Kaen University; FSH, follicle-stimulating hormone; LH, luteinizing hormone; WOMAC, Western Ontario and McMaster Universities Arthritis Index; OA, osteoarthritis.

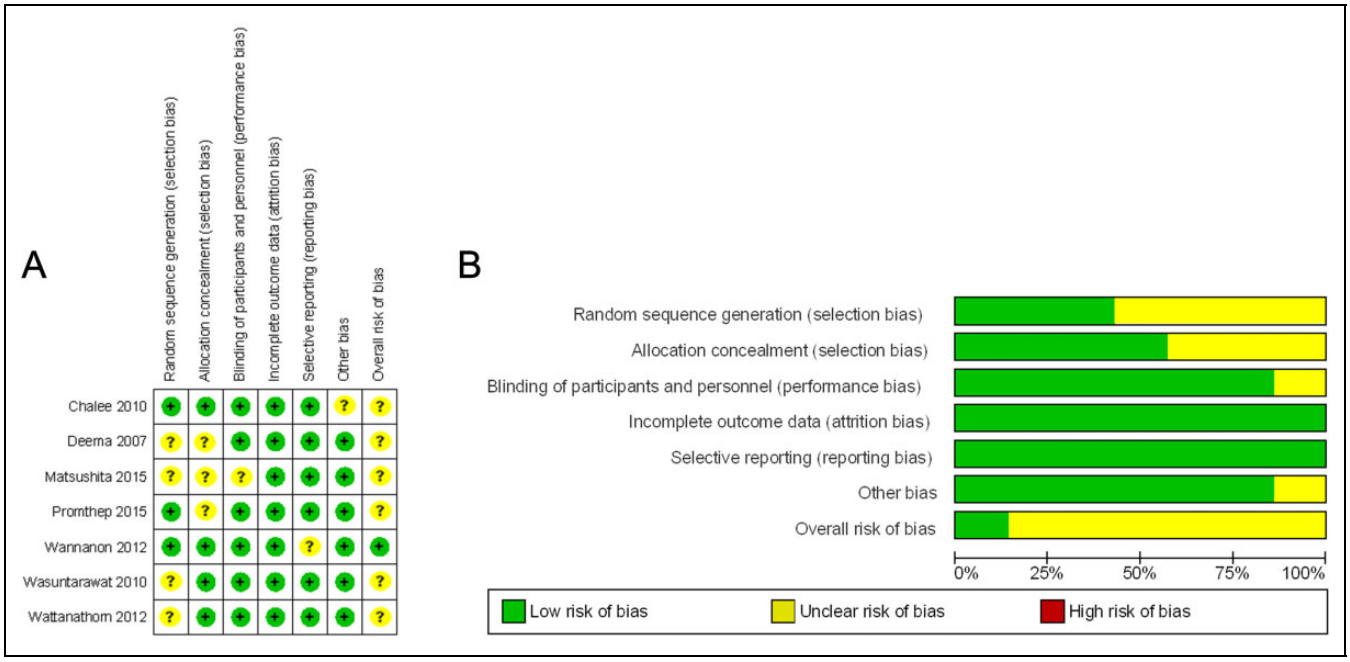

Figure 2. Risk of bias: (A) Risk of bias in each study; (B) Summary risk of bias of included studies.

Quality Assessment

The methodological quality of the 7 randomized controlled trials included in the systematic review was high as shown by Jadad scale score of 3 (scale score range of 0-5), except the study of Matsushita et al,[36] which had a Jadad scale score of 1 (Table 1). In addition, based on the risk of bias of key domains, overall risk of bias within the studies in most studies yielded unclear risk of bias (Figure 2).

Clinical Effects of Krachaidum on Physical or Exercise Performance

To determine the effects of Krachaidum on physical or exercise performance, many tests were used, including maximum power output, mean power output, time to exhaustion, rating of perceived exertion, percentage fatigue, heart rate, lactate threshold, hand grip strength, 6-minute walk test, and so on (Table 2). The main findings from 2 studies[30,31] indicated that Krachaidum showed no acute improvement in either repeated sprint performance or endurance exercise. However, 2 studies[32,33] provided data of hand grip strength test, which determined the upper-body muscle strength by using a digital dynamometer. We pooled such data based on this outcome and found that they were combinable without heterogeneity ($I^2 = 0\%$, $P > .05$). We found that the Krachaidum group significantly increased hand grip strength of both right-hand (standardized mean difference = 0.44, 95% confidence interval = 0.02-0.86, $P = .038$) and left-hand sides (standardized mean difference = 0.49, 95% confidence interval = 0.07-0.91, $P = .048$) at 2 months compared with the placebo group (Figure 3).

Clinical Effects of Krachaidum on Erectile Response

Only one randomized controlled trial compared Krachaidum with placebo in human subjects on erectile response.[34] Subjects receiving Krachaidum 25 mg/day (n = 15), or 90 mg/day (n = 15), were compared with those receiving placebo (n = 15) for 8 weeks of study period. They found that Krachaidum at a dose of 90 mg/day significantly decreased the response latency time to sexual erotic stimulation and still showed significant changes during the delay period. In addition, after 1 month and 2 months, the Krachaidum group at a dose of 90 mg/day experienced a statistically significant increase in length and width of penis both in resting state and erection state compared with the placebo group. Krachaidum showed no effects on serum hormones (ie, follicle-stimulating hormone, luteinizing hormone; Table 2).

Clinical Effects of Krachaidum on Pain Indicators

A study by Chalee[35] compared Krachaidum cream with analgesic cream on pain reduction indicators. Pain severity, circumference of knee joint, range of motion of knee joint, and modified Western Ontario and McMaster Universities Arthritis Index score were assessed and compared within the group from baseline, or between the groups with analgesic cream. Comparing with baseline, the results in both groups showed significantly reduce pain in all indicators at 4 weeks. On the contrary, comparing with analgesic cream, Krachaidum cream showed nonsignificant different (Table 2).

Clinical Effects of Krachaidum on Energy Expenditure

A study by Matsushita et al[36] evaluated the effect of 2 doses of Krachaidum 100 mg/day or 180 mg/day on energy expenditure

Table 2. Clinical Effects of Krachaidum Classified by Outcomes.

Outcomes, Study	Sample Subgroup	Interventions	Time or Methods of Measurement	*Kaempferia parviflora* Mean	*Kaempferia parviflora* SD	Control Mean	Control SD	Summary
Physical or exercise performance								
Maximum power output (watt)								
Deema, 2007	Endurance training groups	KP 1.35 g/day vs placebo	Baseline	203.50	3.30	214.20	2.40	Significantly increased at weeks 4 and 8 in the KP group and week 8 in the placebo group (difference from baseline)
			4 weeks	233.70	2.90	232.10	1.60	
			8 weeks	245.00	3.20	247.00	2.90	
	No endurance training groups		Baseline	184.10	2.80	200.80	4.90	No significant effects
			4 weeks	190.50	2.10	197.40	5.30	
			8 weeks	192.00	2.00	198.20	5.30	
Wasuntarawat, 2010	Anaerobic exercise (exhaustive sprint)	KP 1.35 g/day vs placebo	Wingate 1	545.00	95.00	554.00	114.00	Maximum power output declined ($P < .05$) across Wingate tests 1, 2, and 3 but there were no differences ($P > .05$) between KP and placebo
			Wingate 2	499.00	99.00	495.00	109.00	
			Wingate 3	454.00	116.00	473.00	96.00	
Mean power output (watt)								
Wasuntarawat, 2010	Anaerobic exercise (exhaustive sprint)	KP 1.35 g/day vs placebo	Wingate 1	417.00	65.00	416.00	65.00	Mean power output declined ($P < .05$) across Wingate tests 1, 2, and 3 but there were no differences ($P > .05$) between KP and placebo
			Wingate 2	369.00	59.00	369.00	58.00	
			Wingate 3	323.00	61.00	334.00	57.00	
Time to finish work max test (minutes)								
Deema, 2007	Endurance training groups	KP 1.35 g/day vs placebo	Baseline	8.20	0.10	8.50	0.10	Significantly increased at weeks 4 and 8 in the KP group and week 8 in the placebo group (difference from baseline)
			4 weeks	9.20	0.10	9.40	0.10	
			8 weeks	9.70	0.10	9.90	0.1 0	
	No endurance training groups		Baseline	7.20	0.10	7.90	0.20	No significant effects
			4 weeks	7.50	0.10	7.80	0.20	
			8 weeks	7.50	0.10	7.80	0.10	
Time to exhaustion (minutes)								
Wasuntarawat, 2010	Anaerobic exercise (exhaustive sprint)	KP 1.35 g/day vs placebo		28.30	12.50	27.60	11.50	Acute ingestion of KP did not improve time to exhaustion
Rating of perceived exertion								
Wasuntarawat, 2010	Anaerobic exercise (exhaustive sprint)	KP 1.35 g/day vs placebo	10 min	14.00	2.00	14.00	2.00	Ratings of perceived exertion at 10 and 20 minutes and immediately after exhaustion were also not different between placebo and KP. Time to exhaustion was rated between 17 ("very hard") and 19 ("extremely hard")
			20 min	17.00	2.00	17.00	2.00	
			Post[a]	19.00	1.00	18.00	1.00	
Percentage fatigue (%)								
Wasuntarawat, 2010	Anaerobic exercise (exhaustive sprint)	KP 1.35 g/day vs placebo	Wingate 1	43.00	13.00	40.00	15.00	No differences in percent fatigue during each 30-second sprint were observed between placebo and KP. Percent fatigue during the third Wingate test was significantly ($P < .05$) greater than during the first Wingate test in both placebo and KP trials
			Wingate 2	48.00	12.00	44.00	15.00	
			Wingate 3	51.00	13.00	53.00	10.00	
Heart rate (BPM)								
Deema, 2007	Maximum heart rate Endurance training groups	KP 1.35 g/day vs placebo	Baseline	181.00	0.80	179.60	0.50	Significantly increased at week 8 in the placebo group (difference from baseline)
			4 weeks	184.70	0.70	181.30	0.60	
			8 weeks	184.60	0.80	186.60	0.80	
	No endurance training groups		Baseline	185.00	2.00	180.00	2.40	No significant effects
			4 weeks	199.60	0.60	176.20	2.60	
			8 weeks	186.40	1.60	181.20	1.80	
Wasuntarawat, 2010	Aerobic exercise (endurance)	KP 1.35 g/day vs placebo	10 min	165.00	13.00	164.00	11.00	Heart rate at 10 and 20 minutes and immediately after exhaustion were also not different between placebo and KP
			20 min	174.00	10.00	172.00	9.00	
			Post[a]	177.00	8.00	174.00	10.00	

(continued)

Table 2. (continued)

Outcomes, Study	Sample Subgroup	Interventions	Time or Methods of Measurement	*Kaempferia parviflora*		Control		Summary
				Mean	SD	Mean	SD	
Lactate threshold (watt)								
Deema, 2007	Endurance training groups	KP 1.35 g/day vs placebo	Baseline	129.60	1.70	142.50	1.70	Significantly increased lactate threshold at weeks 4 and 8 in the KP group (difference from baseline)
			4 weeks	156.80	2.70	155.00	2.30	
			8 weeks	165.90	3.3 0	160.00	1.80	
	No endurance training groups		Baseline	120.00	4.20	120.00	4.20	No significant effects from baseline
			4 weeks	118.80	5.40	118.80	6.00	
			8 weeks	118.80	2.80	106.30	3.10	
Hand grip strength test								
Wattanathorn, 2012	Right hand (kg)	KP 25 mg/day vs placebo	Baseline	25.06	3.01	24.53	2.55	No significant effects
			4 weeks	25.00	2.97	24.33	2.28	
			8 weeks	24.86	3.18	24.33	2.46	
		KP 90 mg/day vs placebo	Baseline	23.93	3.30	—	—	No significant effects
			4 weeks	24.60	3.13	—	—	
			8 weeks	24.80	3.14	—	—	
	Left hand (kg)	KP 25 mg/day vs placebo	Baseline	22.06	1.86	21.06	1.83	No significant effects
			4 weeks	21.66	1.50	21.33	1.58	
			8 weeks	21.26	1.48	21.20	1.56	
		KP 90 mg/day vs placebo	Baseline	20.86	2.72	—	—	No significant effects
			4 weeks	21.60	2.02	—	—	
			8 weeks	21.60	1.84	—	—	
Promthep, 2015	Right hand (kg/wt)	KP 180 mg/day vs placebo	Baseline	0.65	0.09	0.63	0.07	Significantly enhanced at weeks 4, 8, and 12 (difference from the placebo group in the same week) and significant difference compared with the baseline score at week 4
			4 weeks	0.70	0.09	0.66	0.07	
			8 weeks	0.68	0.10	0.63	0.07	
			12 weeks	0.65	0.08	0.62	0.07	
	Left hand (kg/wt)	KP 180 mg/day vs placebo	Baseline	0.62	0.08	0.60	0.08	Significantly enhanced at week 8 (difference from the placebo group in the same week)
			4 weeks	0.65	0.10	0.62	0.07	
			8 weeks	0.64	0.08	0.59	0.08	
			12 weeks	0.61	0.08	0.57	0.07	
30-Second chair stand test (seconds)								
Wattanathorn, 2012		KP 25 mg/day vs placebo	Baseline	18.33	2.58	19.13	2.79	No significant effects
			4 weeks	19.00	2.77	19.26	1.43	
			8 weeks	20.00	3.11	18.93	1.70	
		KP 90 mg/day vs placebo	Baseline	18.60	2.52	—	—	Significantly increased at week 8 compared with baseline
			4 weeks	19.60	2.13	—	—	
			8 weeks	20.66	2.28	—	—	
6-Minute Walk Test (m)								
Wattanathorn, 2012		KP 25 mg/day vs placebo	Baseline	571.26	33.68	567.33	33.52	No significant effects
			4 weeks	570.33	38.32	598.73	31.57	
			8 weeks	575.53	36.04	571.26	32.05	
		KP 90 mg/day vs placebo	Baseline	572.80	32.65	—	—	Significantly increased at week 8 compared with either baseline or placebo
			4 weeks	575.46	34.29	—	—	
			8 weeks	601.26	33.70	—	—	

(continued)

Table 2. (continued)

Outcomes, Study	Sample Subgroup	Interventions	Time or Methods of Measurement	*Kaempferia parviflora* Mean	*Kaempferia parviflora* SD	Control Mean	Control SD	Summary
Tandem stance test (seconds)								
Wattanathorn, 2012	Opened eye							
	Right leg is in front	KP 25 mg/day vs Placebo	Baseline	161.8	11.16	164.80	12.34	No significant effects
			4 weeks	164.06	9.63	163.06	10.35	
			8 weeks	162.26	8.93	165.06	9.80	
		KP 90 mg/day vs placebo	Baseline	164.00	10.50	—	—	No significant effects
			4 weeks	166.60	6.81	—	—	
			8 weeks	168.46	6.90	—	—	
	Left leg is in front	KP 25 mg/day vs placebo	Baseline	111.93	7.77	112.33	11.00	No significant effects
			4 weeks	112.33	11.39	110.66	10.01	
			8 weeks	111.80	10.16	109.00	10.20	
		KP 90 mg/day vs placebo	Baseline	108.20	11.32	—	—	No significant effects
			4 weeks	109.33	13.62	—	—	
			8 weeks	111.80	13.31	—	—	
	Closed eye							
	Right leg is in front	KP 25 mg/day vs placebo	Baseline	31.86	10.12	33.80	9.22	No significant effects
			4 weeks	32.60	7.44	30.80	10.74	
			8 weeks	32.73	7.67	31.66	10.41	
		KP 90 mg/day vs placebo	Baseline	31.26	11.09	—	—	No significant effects
			4 weeks	31.86	9.33	—	—	
			8 weeks	33.40	8.94	—	—	
	Left leg is in front	KP 25 mg/day vs placebo	Baseline	20.93	3.41	18.80	3.60	No significant effects
			4 weeks	21.33	3.79	19.86	5.01	
			8 weeks	21.26	3.19	21.20	4.57	
		KP 90 mg/day vs placebo	Baseline	20.46	4.24	—	—	No significant effects
			4 weeks	21.26	4.58	—	—	
			8 weeks	22.06	3.93	—	—	
A sit-and-reach test (cm)								
Promthep, 2015		KP 180 mg/day vs placebo	Baseline	17.98	4.60	16.14	4.93	Significant difference compared with the baseline score at week 4 (both the treatment and placebo groups)
			4 weeks	16.43	5.15	14.64	4.92	
			8 weeks	16.88	5.19	14.61	5.24	
			12 weeks	18.28	5.10	17.01	4.55	
A back-and-leg strength test (kg/wt)								
Promthep, 2015		KP 180 mg/day vs placebo	Baseline	2.77	0.54	2.45	0.39	No significant effects
			4 weeks	2.68	0.55	2.45	0.51	
			8 weeks	2.77	0.55	2.44	0.40	
			12 weeks	2.79	0.59	2.53	0.52	
A 40-yard technical test (seconds)								
Promthep, 2015		KP 180 mg/day vs placebo	Baseline	11.61	0.07	11.99	0.86	Significantly decreased at week 12 compared with the baseline
			4 weeks	12.06	1.16	12.34	1.33	
			8 weeks	11.50	0.74	11.46	0.75	
			12 weeks	10.08	0.47	10.47	0.90	
A 50-metre sprint test (seconds)								
Promthep, 2015		KP 180 mg/day vs placebo	Baseline	6.24	0.31	6.29	0.37	No significant effects in both groups. No significant differences between the groups
			4 weeks	6.26	0.31	6.33	0.49	
			8 weeks	6.37	0.26	6.50	0.50	
			12 weeks	6.33	0.24	6.47	0.52	

(continued)

Table 2. (continued)

Outcomes, Study	Sample Subgroup	Interventions	Time or Methods of Measurement	*Kaempferia parviflora* Mean	*Kaempferia parviflora* SD	Control Mean	Control SD	Summary
A cardiorespiratory fitness test VO_2 max (mL/kg/min)								
Promthep, 2015		KP 180 mg/day vs placebo	Baseline	45.09	9.88	45.09	9.96	Significantly increased cardiorespiratory fitness, as indicated by VO_2 max values at week 12. No significant difference between the groups
			4 weeks	46.95	7.61	47.85	10.08	
			8 weeks	49.40	8.40	48.34	7.17	
			12 weeks	51.05	8.40	47.10	8.45	
Pain indicators								
Chalee, 2010	Pain severity	KP 7% w/w vs analgesic cream	Baseline	8.11	0.99	8.15	1.09	Significantly decreased at week 4 compared with the baseline (both the treatment and placebo groups). No significant difference between the groups
			4 weeks	6.80	0.76	6.87	0.65	
	Circumference of knee joint (cm)		Baseline	37.91	2.75	37.15	3.00	
			4 weeks	37.03	2.56	36.30	2.64	
	Range of motion of knee joint (ROM)		Baseline	110.57	9.45	109.39	10.66	
			4 weeks	117.43	5.86	116.21	6.62	
	Modified WOMAC score		Baseline	40.31	6.63	39.97	6.02	
			4 weeks	39.29	5.84	39.00	5.50	
Energy expenditure								
Matsushita, 2015	Energy expenditure change (kJ/day)							
	All	KP 100 mg/day vs placebo	Baseline	6213.00	143.00	6196.00	150.00	No significant in the placebo group but significant difference between the groups at 30 and 60 minutes, difference from baseline and maximal rise at 60 minutes
			60 minutes	6442.00	212.00	NR	NR	
	High-BAT	KP 180 mg/day vs placebo	Baseline	6076.00	184.00	6103.00	184	No significant in the placebo group but significant difference between the groups at 30 and 60 minutes, difference from baseline at 30, 60, 90 minutes and maximal rise at 60 minutes
			60 minutes	6427.00	234.00	NR	NR	
	Low-BAT	KP 180 mg/day vs placebo	Baseline	6418.00	223.00	6334.00	261.00	No significant effects
			60 minutes	NR	NR	NR	NR	
Erectile response								
Wannanon, 2012	Penile circumference (cm)							
	Resting state	KP 25 mg/day vs placebo	Baseline	9.40	0.79	9.00	0.73	No significant effects
			1 month	9.00	0.79	8.70	0.59	
			2 months	9.40	0.79	8.80	0.59	
			Delay[b]	9.15	3.10	9.15	3.10	
		KP 90 mg/day vs placebo	Baseline	9.20	0.69	9.00	0.73	After 1 and 2 months of treatment, significant increase in the length and width of penis when compared with the placebo treated group
			1 month	10.20	0.79	8.70	0.59	
			2 months	10.15	0.79	8.80	0.59	
			Delay[b]	9.65	2.71	9.15	3.10	
	Erection state	KP 25 mg/day vs placebo	Baseline	10.90	3.87	11.50	3.87	No significant effects
			1 month	10.50	3.68	10.60	3.10	
			2 months	11.50	4.26	11.80	2.71	
			Delay[b]	11.70	3.10	11.70	2.71	
		KP 90 mg/day vs placebo	Baseline	10.80	4.26	11.50	3.87	After 1 and 2 months of treatment, significant increase in the width when compared with the placebo treated group
			1 month	12.10	4.26	10.60	3.10	
			2 months	11.90	4.26	11.80	2.71	
			Delay[b]	11.70	0.39	11.70	2.71	
	Penile length (cm)							
	Resting state	KP 25 mg/day vs placebo	Baseline	9.70	4.26	9.95	7.55	No significant effects
			1 month	9.65	3.87	9.90	3.49	
			2 months	10.90	3.87	10.00	3.10	
			Delay[b]	10.60	3.49	10.25	0.07	

(continued)

Table 2. (continued)

Outcomes, Study	Sample Subgroup	Interventions	Time or Methods of Measurement	*Kaempferia parviflora*		Control		Summary
				Mean	SD	Mean	SD	
		KP 90 mg/day vs placebo	Baseline	9.40	4.07	9.95	7.55	After 1 and 2 months of treatment, significant increase in the length when compared with the placebo treated group
			1 month	11.25	3.49	9.90	3.49	
			2 months	11.10	2.71	10.00	3.10	
			Delay[b]	10.65	3.49	10.25	0.07	
	Erection state	KP 25 mg/day vs placebo	Baseline	12.50	5.27	13.10	4.96	No significant effects
			1 month	12.95	4.03	12.20	3.87	
			2 months	13.10	4.34	12.40	4.18	
			Delay[b]	13.55	3.87	13.20	2.79	
		KP 90 mg/day vs placebo	Baseline	12.90	4.34	13.10	4.96	After 1 and 2 months of treatment, significant increase in the length when compared with the placebo treated group
			1 month	13.75	4.34	12.20	3.87	
			2 months	13.90	4.03	12.40	4.18	
			Delay[b]	13.50	4.65	13.20	2.79	
	Latency time (mins)							
	Erection state	KP 25 mg/day vs placebo	Baseline	10.90	13.94	11.60	12.39	No significant effects
			1 month	8.60	12.39	11.70	11.81	
			2 months	8.00	12.39	10.00	10.65	
			Delay[b]	7.80	0.59	10.90	12.78	
		KP 90 mg/day vs placebo	Baseline	10.40	9.30	11.60	12.39	Significantly decreased the response latency to sexual erotic stimuli and still showed the significant changes during the delay period
			1 month	5.50	7.17	11.70	11.81	
			2 months	5.50	6.58	10.00	10.65	
			Delay[b]	7.40	6.20	10.90	12.78	
	Serum hormones concentrations							
	Testosterone (ng/mL)	KP 25 mg/day vs placebo	Baseline	4.11	1.56	4.14	0.92	No significant effects
			Single dose	4.79	4.63	5.28	2.76	
			1 month	5.11	3.13	5.92	5.49	
			2 months	4.64	1.22	5.65	1.23	
			Delay[b]	5.71	2.38	5.14	0.92	
		KP 90 mg/day vs placebo	Baseline	4.11	1.30	4.14	0.92	No significant effects
			Single dose	4.89	2.63	5.28	2.76	
			1 month	4.26	0.83	5.92	5.49	
			2 months	5.74	2.60	5.65	1.23	
			Delay[b]	6.06	3.19	5.14	0.92	
	FSH (IU/L)	KP 25 mg/day vs placebo	Baseline	8.80	4.29	7.88	4.34	No significant effects
			Single dose	7.35	4.23	6.73	2.54	
			1 month	7.23	5.37	6.52	5.51	
			2 months	7.96	3.32	5.95	2.34	
			Delay[b]	8.81	5.12	5.88	3.34	
		KP 90 mg/day vs placebo	Baseline	7.53	2.92	7.88	4.34	No significant effects
			Single dose	6.14	2.26	6.73	2.54	
			1 month	6.29	2.25	6.52	5.51	
			2 months	6.01	2.79	5.95	2.34	
			Delay[b]	7.03	2.35	5.88	3.34	

(continued)

Table 2. (continued)

Outcomes, Study	Sample Subgroup	Interventions	Time or Methods of Measurement	*Kaempferia parviflora*		Control		Summary
				Mean	SD	Mean	SD	
	LH (IU/L)	KP 25 mg/day vs placebo	Baseline	7.25	5.90	7.14	5.62	No significant effects
			Single dose	8.12	2.72	7.59	3.21	
			1 month	7.04	5.34	7.30	4.24	
			2 months	8.48	4.64	7.82	2.34	
			Delay[b]	8.72	4.67	8.14	3.23	
		KP 90 mg/day vs placebo	Baseline	6.99	4.37	7.14	5.62	No significant effects
			Single dose	7.65	1.88	7.59	3.21	
			1 month	8.55	3.64	7.30	4.24	
			2 months	7.41	4.67	7.82	2.34	
			Delay[b]	8.82	4.44	8.14	3.23	

Abbreviations: KP, *Kaempferia parviflora*; VO_2, oxygen consumption; ROM, range of motion; high-BAT, high brown adipose tissue; low-BAT, low brown adipose tissue; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

[a]Post: immediately after exercise.

[b]Delay: 1 month after the cessation of KP administration.

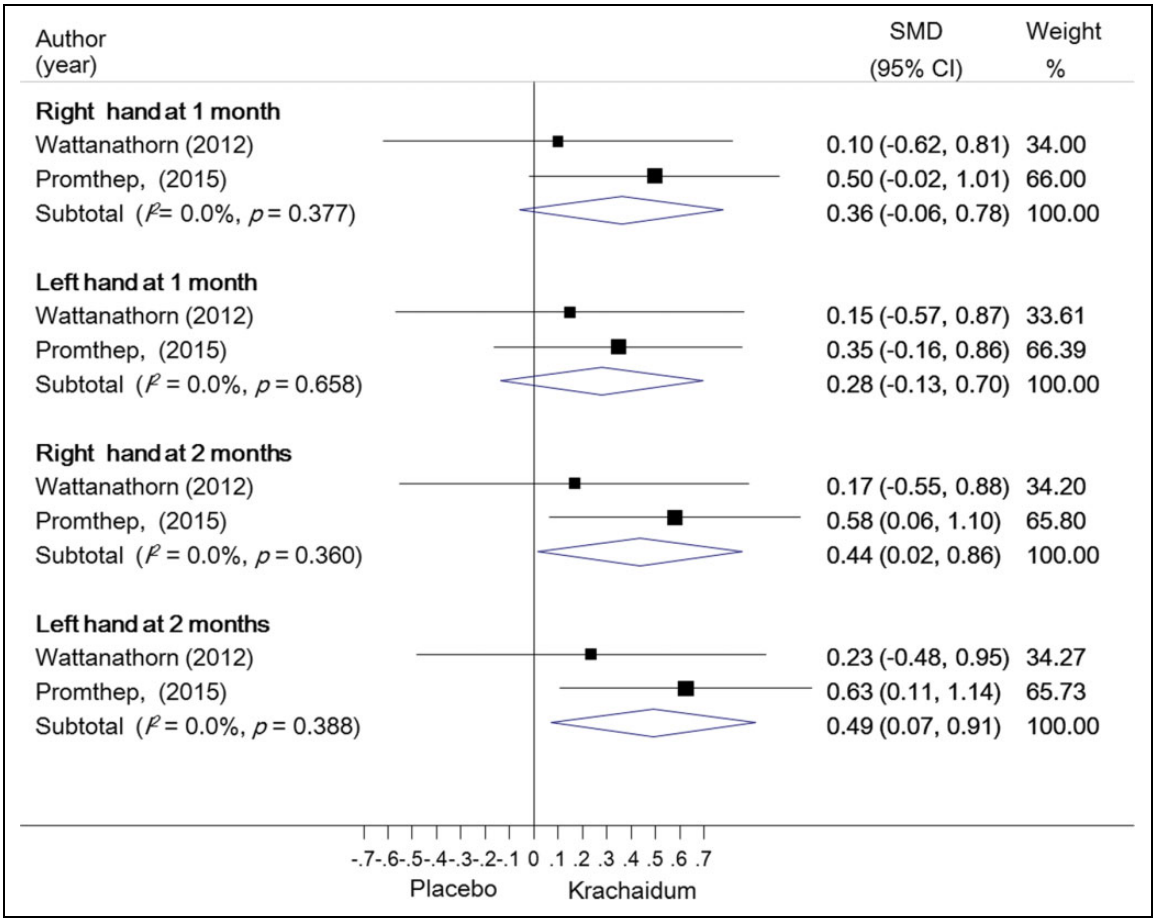

Figure 3. Forest plot illustrating the effect of Krachaidum on hand grip strength.

change compared with placebo. They found that when comparing with baseline, Krachaidum showed significant increase in energy expenditure at 30 minutes and 60 minutes in both groups. However, compared with placebo, no significant additional benefit of Krachaidum on energy expenditure was found (Table 2).

Discussion

This systematic review provides a critical summary of clinical evidence of Krachaidum for all indications. We found a wide variety of use of Krachaidum including physical or exercise performance, erectile response, pain indicators, and energy expenditure. The methodological quality of the 7 randomized controlled trials included in the systematic review was high according to Jadad score, and was ranked as unclear according to Cochrane risk of bias tool. From the included clinical trials, the benefits of Krachaidum remained inconclusive.

Our pooled effect on physical or exercise performance outcomes showed that Krachaidum 90 to 180 mg/day significantly enhanced hand grip strengths compared with placebo.[32,33] This might be explained by the increased blood flow effect of Krachaidum.[37] A previous study demonstrated that Krachaidum supplementation could increase blood flow to the organs due to vasorelaxation induction. This partly was mediated through cyclooxygenase and nitric oxide–dependent pathways,[38] and Krachaidum also showed anti-inflammatory effects.[37,39,40] Therefore, the combination effect of increased blood flow and anti-inflammatory effects may facilitate muscle strength.[32,33]

For erectile response outcome, although only one study was included,[34] it showed that subjects receiving Krachaidum 90 mg/day exhibited a significant enhancement in all parameters (ie, response latency time to visual erotic stimuli, size and length of penis both in flaccid and erectile states) after 1 and 2 months of treatment compared with placebo. The authors explained that the effects involved nitric oxide. The experimental studies reported that Krachaidum extract could induce an increase of endothelial nitric oxide synthase and protein expression in human umbilical vein endothelial cell.[41] Thus, abundance of endothelial nitric oxide synthase in endothelium of penile vasculature and sinusoidal endothelium within the corpora carvernosa might increase penile erection.[42-44]

For pain indicators, a study comparing Krachaidum cream with analgesic cream in knee osteoarthritis was found.[35] Although the findings demonstrated significant pain reduction in all indicators at 4 weeks compared with baseline, but there

was no significant difference when compared with analgesic cream. Since anti-inflammatory effect was studied only using oral administration of Krachaidum,[40,45,46] the mechanism of Krachaidum cream on pain reduction was still unclear.

Furthermore, the effect of Krachaidum on energy expenditure has been linked to the activity of brown adipose tissue, a site of nonshivering thermogenesis.[47] A previous study found that the components of Krachaidum extract activate hormone-sensitive lipase in adipocyte.[48] Furthermore, 5,7-dimenthoxyflavone, the major flavonoid in Krachaidum extract, was demonstrated to have a the potent inhibitory effect on eAMP-degrading enzyme.[20] Since eAMP is a signal of hormone-sensitive lipase in adipocyte, it activates brown adipose tissue thermogenesis. Thus, it is possible that the brown adipose tissue–mediated thermogenic effect of Krachaidum extract exist via the inhibition of phosphodiesterase in brown adipose tissue. A study showed that Krachaidum extract could potentially increase whole-body energy expenditure probably through the activation of brown adipose tissue, which might benefit as an antiobesity regimen.[36]

Considering safety issues, adverse events were not reported among all included studies. An animal study of Krachaidum extract on chronic toxicity was conducted.[23] They randomly divided 120 Wistar rats into 5 groups, 24 rats each (12 males and 12 females). Then, 3 treatment groups were orally administered with Krachaidum extract at doses of 5, 50, and 500 mg/kg/day for 6 months, respectively, which were equivalent to 1, 10, and 100 times that of human use, while 2 control groups were orally given distilled water and 1.0% tragacanth, respectively. The results showed that the histopathological study of visceral organs revealed no remarkable lesions related to the toxicity of Krachaidum extract.

The limitations of this study should be noted. First, we found limited number of studies to be included. Thus, pooling effect is impossible. Even when possible (ie, hand grip strengths), only 2 studies were pooled; therefore, conclusive findings could not be determined. Second, this systematic review had diversity of Krachaidum dosage regimens (ie, from 25 mg/day to 1.35 g/day), dosage forms (ie, capsule, cream), or extraction method (60% or 95% ethanol extraction) across studies. Applying the results to clinical practice is limited.

Conclusion

In summary, although various indications of Krachaidum were found with varying qualities of evidence, the positive benefits of Krachaidum were reported, and adverse events were not found. As a very small number of studies were included, it would be difficult to make reliable conclusions. Additional clinical studies with larger sample sizes are needed.

Authors' Note

The funding agency had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the article; and in the decision to submit the article for publication.

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Author Contributions

SS, PD, and NC conceptualized the study and developed the inclusion criteria. SS, PW, and PR collected the data, analyzed the data, developed the table, and wrote the first draft of the manuscript. SS developed the figure and analyzed the data. All authors conceptualized the study and reviewed the manuscript.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AC is currently a government official under the Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health, Nonthaburi, Thailand. The other authors have no potential conflicts of interest.

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Ethical Approval

This study did not warrant institutional review board review as no human subjects were involved.

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