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Author: Surachai Kotirum Shaiful Bahari Ismail Nathorn Chaiyakunapruk



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**Efficacy of Tongkat Ali (*Eurycoma longifolia*) on erectile function improvement: Systematic review and meta-analysis of randomized controlled trials**

Surachai Kotirum, PharmD<sup>1</sup>, Shaiful Bahari Ismail, MMED<sup>2</sup>, Nathorn Chaiyakunapruk, PharmD, PhD<sup>1, 3, 4, 5†</sup>

<sup>1</sup> School of Pharmacy, Monash University Malaysia, Selangor, Malaysia

<sup>2</sup> School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia

<sup>3</sup> Center of Pharmaceutical Outcomes Research (CPOR), Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand

<sup>4</sup> School of Pharmacy, University of Wisconsin, Madison, USA

<sup>5</sup> School of Population Health, University of Queensland, Brisbane, Australia

- It is believed that Tongkat Ali can improve erectile dysfunction (ED) in Asian men
- Efficacy of Tongkat Ali on ED improvement in men is not yet well proven
- A subgroup analysis suggested Tongkat Ali may improve ED among more severe ED cases

**†Corresponding author:**

Nathorn Chaiyakunapruk, PharmD, PhD

Professor of Health Economics

School of Pharmacy, Monash University Malaysia,

Jalan Lagoon Selatan, 46150 Bandar Sunway, Selangor, Malaysia

E-mail: nathorn.chaiyakunapruk@monash.edu

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**ABSTRACT**

**Objective:** To determine the efficacy of Tongkat Ali (*Eurycoma longifolia*) herbal extract on erectile function improvement.

**Methods:** Comprehensive electronic databases were searched from inception through October 2014. Randomized controlled trials investigating Tongkat Ali compared to placebo were included. Outcome of interest was the improvement of erectile dysfunction. The difference of changes from baseline of the outcome between Tongkat Ali and placebo was pooled using weighted mean difference (WMD). Methodological quality of included studies was assessed using Jadad's quality scale and Cochrane's risk of bias.

**Results:** Of the 342 articles identified, 2 studies involving a total of 139 participants were analyzed. No significant between group difference was found in the mean WMD of the change in the 5-item version of the International Index of Erectile Function (IIEF-5) at week-12 (0.91; 95% CI: -1.50 to 3.33 with  $I^2 = 89.5\%$ , P-value = 0.002) with statistical heterogeneity. Based on the subgroup analysis, significant improved IIEF-5 score of 2.15 (95% CI 1.03 to 3.27) was found in subjects with lower baseline IIEF-5 score, but this was not seen among those with higher baseline IIEF-5 score.

**Conclusion:** Based on current evidence, the herbal extract of Tongkat Ali may have clinical effect on erectile function. However, more efficacy trials are warranted to further support current evidence.

**Key words:** tongkat ali; eurycoma longifolia; root; extract; erectile dysfunction; alternative medicine

## INTRODUCTION

Sexual health plays an important role in quality of life of both genders. In males, erectile dysfunction (ED) can lead to dissatisfaction in sexual life and deterioration of sexual well-being.(1) ED is defined as a consistent or recurrent inability of a man to attain and/or maintain penile erection sufficiently for sexual activity, which occurs as a result of a lack of blood flow to the penis.(2) ED is an important sexual health problem worldwide with the estimated prevalence of 52% among men aged 40–70 years.(1) The prevalence of ED increases with age, with the highest prevalence in men in their seventies and eighties of between 50%-75%.(1, 2) Surveys among Asian countries showed that the prevalence of self-reported moderate ED in aging males (40–70 years) ranging from 17.7%, 22%, 28.3%, 32.2%, and 34% in Taiwan, Malaysia, China, Korea, and Japan, respectively.(3) Due to cultural differences in oriental countries compared to western countries including taboos and cultural restrictions, most Asian men with ED do not seek for formal medical treatment.(4) The Asian MALES study revealed that it was not uncommon for Asian men to consider traditional herbal medicine as a potential option to improve their sexual well-being.(5)

*Eurycoma longifolia*, from the Simaroubaceae family, is a native herb to the forests in Malaysia, Indonesia, and Thailand. It is traditionally known as ‘Tongkat Ali’ among Malaysian, which is believed to enhance sexual performance. Tongkat Ali is popular for its aphrodisiac property and has been commonly used as an energy enhancer.(6-8) Recent evidences suggest that water extract of the roots of Tongkat Ali can enhance testosterone level in men and can improve ED. Even though the mechanism of the effect of Tongkat Ali on ED remains unknown, it was postulated that a wide range of bioactive compounds including phenolic compounds, polypeptides, diterpenoids, alkaloids, and quassinoids may contribute to such effect.(3, 6) However, little is known on the efficacy of Tongkat Ali on aphrodisiac effect in human.(9) Using systematic review to summarize clinical evidence of herbal therapy has been considered as one of the best tools to synthesize overall findings and to define future research direction for the herbal

intervention of interest.(10-12) Therefore, this study aims to determine the effect of Tongkat Ali's roots water extract on the ED performance using systematic review and meta-analysis approach.

## **METHODS**

### ***Data sources and searching strategy***

This systematic review was conducted according to the Cochrane Collaboration framework guidelines (13), and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.(14) The following databases were systematically searched: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov and AMED (The Allied and Complementary Medicine Database). Databases were searched from their inception to October 10, 2014. Search terms were 'Tongkat Ali', 'Eurycoma longifolia (Jack)', and 'pasak bumi'. References of relevant articles were examined to identify potential studies not indexed in the above databases. Authors of relevant articles were inquired if they were aware of other relevant published or unpublished studies. The PICO (participants, interventions, comparators, and outcomes) study question is specified to determine the clinical effect of Tongkat Ali's extract compared to placebo on erectile function improvement outcome among male subjects with or without erectile dysfunction.

### ***Inclusion criteria***

The inclusion criteria were the followings: (i) randomized controlled clinical trial (RCT) in human subjects and ii) investigating the clinical effect of Tongkat Ali on erectile function. There was no language and study design restriction. Studies that were not original articles such as comments, letters, reviews, meta-analyses, guideline, case reports, surveys or editorials were excluded. Studies from the same population (duplicate studies), not reporting or obtaining effect estimates or with insufficient information to compute effect estimates were also excluded.

### ***Quality assessment of included study***

Screening for eligibility of all retrieved articles from searching and decision making on studies or clinical trials to be included were performed by 2 independent researchers (SK and NC). In addition, the methodological quality of each included clinical trial was appraised by them using a scale developed by Jadad et al (15) and Cochrane risk of bias criteria.(13, 16) Disagreements between the reviewers were resolved by discussion and consensus. The Cochrane risk of bias (16) evaluates bias in intervention studies based on a number of criteria including: sequence generation; allocation concealment; blinding; incomplete outcome data; selective reporting; and other sources of bias. Studies in which baseline characteristics were different among studies groups or not tested for their difference were considered as high risk for the domain of ‘other risk of bias’. The overall risk of bias for each study was based on the risk of bias of all domains. 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). For Jadad score (15), items for methodology evaluation include random allocation, blinding, and description of dropouts and withdrawals. We also determined whether the investigators assayed the amount of active ingredients in each Tongkat Ali preparation.

### ***Data extraction and summarizing study results***

Characteristics and results of included studies were extracted by 2 independent researchers (SK and NC), using a data extraction form in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting herbal interventions.(17) We extracted the number and characteristics of patients, the amount of Tongkat Ali administered, dosage form of herbal extract, duration of intervention, and outcome measurement. ED score measured by IIEF-5 was the outcome of interest (lower score implies a higher degree of ED symptoms). Information not available in the included studies was enquired directly with the corresponding authors.

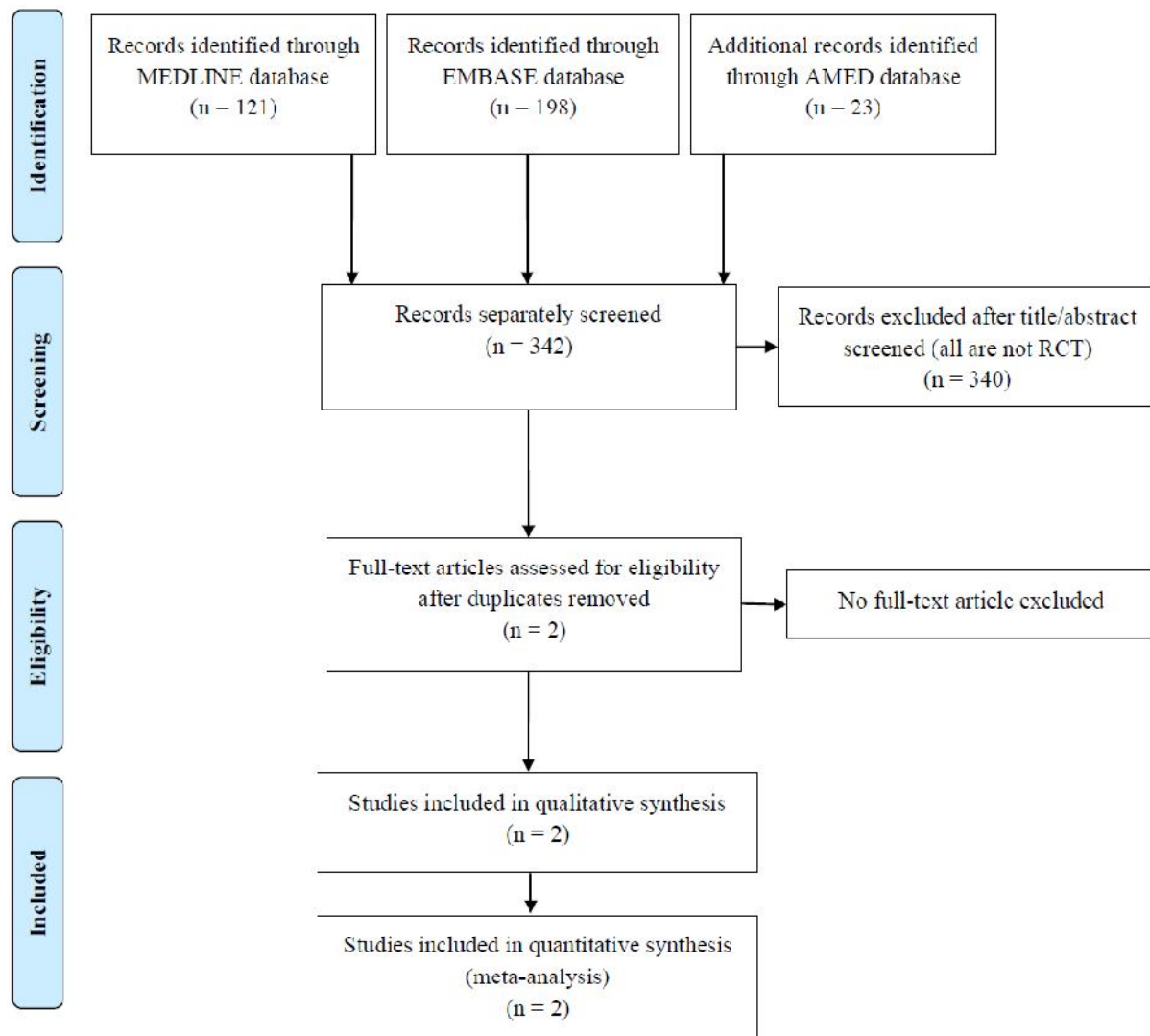
### *Statistical analysis*

Data from all studies were pooled in a meta-analysis to determine the overall effect size with 95% confidence interval (CI). The effect of Tongkat Ali on IIEF-5 was pooled at week 6 and 12 using WMD. In case of baseline imbalance, the difference of changes from baseline of the outcome variables between intervention and comparator arms were pooled instead. Statistical heterogeneity between studies was assessed using the chi-squared test and  $I^2$ .(18) A P-value of 0.10 or less indicated heterogeneity between-studies. I-squared values < 50 % denoted no/minimal heterogeneity across studies.(13) The Dersimonian and Laird random-effects model was employed for all analyses.(19) Meta-analyses were conducted using STATA<sup>®</sup> version 10 (STATA Corp, College Station, TX, USA). Studies included reported ED scores in different forms of standard questionnaires. IIEF-15 was used in Ismail et al and the score was reported for intervention arm only. In order to analyze combined scores on ED performance, we requested the corresponding author to provide us the IIEF-5 score for both intervention and placebo arms, which is obtainable due to 5 question items in IIEF-5 (20) are subset of IIEF-15 question items.(21)

## **RESULTS**

### *Study selection*

Our search yielded a total of 342 potential articles. Three hundred and forty studies were excluded because they were not RCT (Figure 1). No further published or unpublished studies were identified after contacting the experts in the field (Ismail SB, Udani JK). Finally, we included a total of 2 studies involving 139 participants in our analysis.(3, 22)



**Figure 1** Flow chart of the identified articles, the screening and inclusion process.

### *Study characteristics*

Table 1 gives an overview of all included studies. Both studies were randomized, placebo-controlled trials. Subjects were described as healthy American males, aged 40-65 years with stable heterosexual relationship in Udani et al (22), and healthy married Malay males aged 30-55 years in Ismail et al (3). Both studies did not specify that subjects need to be medically diagnosed with ED as one of their inclusion criteria. The average age was reported as approximately 43 years old in Ismail et al, whereas it was not



reported in another trial. The baseline IIEF-5 was in the range of 12.36 to 15.77 in Udani et al (22), and 21.30 to 22.29 in Ismail et al.(3) IIEF-5 score lower than 21 indicates ED.

Both studies used freeze-dried water extract of Tongkat Ali's root in their trials. Treatment group was given 1 tablet of 200 mg of Tongkat Ali root's extract plus 100 mg *Polygonum minus* daily in Udani et al (22), while two capsules (75 mg) 2 times daily after lunch and dinner (i.e. daily dosage of 300 mg Tongkat Ali's root extract) was administered to treatment group in Ismail et al.(3) Both studies stated that the control group received placebo identical to Tongkat Ali. The duration of intervention in both studies was 12 weeks. No concomitant intervention was given in both studies. Both studies reported no information on subject's adherence assessment. The ED score was assessed using IIEF-5 and compared to baseline value at week-6 and week-12.(20, 21)

The primary endpoint of Udani et al (22) was to compare the proprietary Tongkat Ali/*Polygonum minus* combination to placebo with regard to sexual performance, using 6 surveys-the EDITS (Erectile Dysfunction Inventory for Treatment Satisfaction) questionnaire, the SIA (Sexual Intercourse Attempts) diary and logs, the EHS (Erection Hardness Scale) scale, the SHIM (Sexual Health Inventory Questionnaire for Men) questionnaire, the AMS (Aging Male Symptom Score) score, and the IIEF-5 questionnaire. Primary endpoints of Ismail et al (3) were Quality of Life using SF-36 questionnaire and physical fitness tests and the secondary endpoints were Sexual Health Questionnaires (SHQ) for measuring overall sexual life and IIEF-15 for measuring ED. Safety endpoints were clinical and laboratory measures, for example, complete blood count, comprehensive metabolic panel, urinary analysis, , and adverse event monitoring in both studies. All endpoints were measured at week-6 and week-12.

### ***Quality of included studies***

All subjects were randomly allocated into the treatment or control groups. The overall risk of bias within the studies yielded that both trials were prone to high risk of bias as outcomes were reported selectively

(Table 2). In addition, imbalance of IIEF-5 baseline score between treatment and control arms was observed in Udani et al (22) that also resulted in high-risk of bias. Allocation concealment procedure was also not reported in both original articles, but correspondences with the authors of both studies revealed that random sequence generation, allocation concealment, and blinding procedure were undertaken appropriately. Both studies had high Jadad scores: 5 for Udani et al (22) and 4 for Ismail et al.(3) None of the included studies reported the amount of active ingredients or the qualitative fingerprint for quality assurance of Tongkat Ali preparation.

**Table 2** Quality assessment result of included studies.

<b>Jadad item</b>	Udani et al (2014)	Ismail et al (2012)
Q1. Was the study described as randomized? (this includes the use of words such as randomly, random, and randomization)	1	1
Give 1 additional point if: For Q1., the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.)	1	1
Q2. Was the study described as double blind?	1	1
Give 1 additional point if: For Q2., the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)	1	1
Q3. Was there a description of withdrawals and dropouts?	1	0
<b>Total</b>	<b>5</b>	<b>4</b>
<b>Risk of bias item</b>	Udani et al (2014)	Ismail et al (2012)
Sequence generation	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Low risk of bias
Blinding of participants, personnel and outcome assessors	Low risk of bias	Low risk of bias
Selective outcome reporting	High risk of bias	High risk of bias
Other sources of bias	High risk of bias	Low risk of bias
<b>Overall</b>	<b>High risk of bias</b>	<b>High risk of bias</b>

### ***Efficacy of Tongkat Ali's root water extract on erectile dysfunction performance***

The WMD of the effect of Tongkat Ali on IIEF-5 score was not statistically different from the placebo at both week-6 (WMD of 1.49 (95% CI: -0.89 to 3.87),  $I^2 = 88.7\%$ , P-value = 0.003) and week-12 (WMD of 3.11 (95% CI: -1.68 to 7.90),  $I^2 = 97.3.7\%$ , P-value < 0.001) with high heterogeneity. This pooled analysis might be invalid because of the significant imbalance of baseline IIEF-5 score between both arms in the

study of Udani et al (Tongkat Ali arm: 15.770, placebo arm: 12.360). Therefore, we chose to perform meta-analysis based on the changes of IIEF-5 from baseline at week 6 and 12.

At week-6, the WMD of the change of IIEF-5 score was -0.70 (95% CI: -1.49 to 0.09) with  $I^2 = 0\%$ , P-value = 0.995) without statistical heterogeneity (Table 3). This implies that the effect of Tongkat Ali is not statistically significant after 6 weeks of therapy. At week-12, the WMD of the change of IIEF-5 score was 0.91 (95% CI: -1.50 to 3.33) with  $I^2 = 89.5\%$ , P-value = 0.002) with statistical heterogeneity (Table 3). The potential cause of this heterogeneity was the lower mean baseline IIEF-5 score of 15.77 and 12.36 in Udani et al (22), compared to 22.29 and 21.30) in Ismail et al.(3) In subjects with lower baseline IIEF-5 score (22), the effect of Tongkat Ali on IIEF-5 score was clearly demonstrated with an increase in IIEF-5 score of 2.15 (95% CI: 1.03 to 3.27) in Udani et al (22), while there is a lack of effect of Tongkat Ali among those who have higher baseline score as shown in Ismail et al.(3)

#### ***Adverse effects of Tongkat Ali's root water extract***

Safety outcomes were reported in both studies and no significant differences of adverse events were found between treatment and placebo groups.(3, 22) No serious adverse events were report from Udani et al (22) while one subject was hospitalized in Ismail et al (3) under the treatment group, but it was not due to treatment.

**Table 1** Description of randomized controlled trials of Tongkat Ali for erectile function.

Authors (Year)	Target population	Tongkat Ali	Control	Outcome of interest	Assessment tool
Udani et al (2014)	40-65 years old healthy American males with stable heterosexual relationship	200 mg + 100 mg of <i>Polygonum minus</i> Physta tablet <sup>#</sup>	Identical tablet	ED score at week-6 and week-12 compared to baseline	IIEF-5 or SHIM <sup>##</sup>
Ismail et al (2012)	30-55 years old healthy Malay males	300 mg Physta capsule <sup>†</sup>	Matching capsule	ED score at week-6 and week-12 compared to baseline	IIEF-15 <sup>††</sup>

<sup>#</sup> Proprietary freeze-dried water extract of Tongkat Ali (*Eurycoma longifolia*) root plus 100 mg of *Polygonum minus*

<sup>†</sup> Freeze-dried water extract of Tongkat Ali (*Eurycoma longifolia*) root

<sup>##</sup> 5 items of International Index of Erectile Function (IIEF) or Sexual Health Inventory for Men (SHIM) questionnaire with 0-5 rating scale (maximum score = 25)

<sup>††</sup> 15 items of International Index of Erectile Function (IIEF) questionnaire, consisted of 6 items of erectile function score with 0-5 rating scale (maximum score = 30)

**Table 3** IIEF-5 outcomes of meta-analysis measured in clinical trial of Tongkat Ali with adjusted baseline imbalance.

Authors and Year	Udani et al 2014		Ismail et al 2012	
Group	Tongkat Ali	Control	Tongkat Ali	Control
Subject (n)	12	14	52	50 <sup>††</sup>
<b>Comparison week-0 VS week-6</b>				
Week-0; IIEF-5 score in Mean (SD)	15.770 (1.320)	12.360 (1.450)	22.289 (2.782)	21.300 (3.066)
Week-6; IIEF-5 score in Mean (SD)	16.920 (1.460)	14.210 (1.560)	21.423 (2.739)	21.140 (2.893)
Difference from baseline <sup>†</sup>	1.150 (1.392)	1.850 (1.506)	-0.865 (2.761)	-0.160 (2.980)
Mean difference (within trial)	<b>-0.70 (-1.81, 0.41)</b>		<b>-0.71 (-1.81, 0.42)</b>	
Pooled WMD (95% CI, I <sup>2</sup> , P-value)	<b>-0.70 (-1.49 to 0.09, 0.0%, 0.995)</b>			
<b>Comparison week-0 VS week-12</b>				
Week-0; IIEF-5 score in Mean (SD)	15.770 (1.320)	12.360 (1.450)	22.289 (2.782)	21.300 (3.066)
Week-12; IIEF-5 score in Mean (SD)	19.850 (1.210)	14.290 (1.810)	22.173 (2.534)	21.500 (2.830)
Difference from baseline <sup>†</sup>	4.080 (1.266)	1.930 (1.640)	-0.115 (2.661)	0.200 (2.950)
Mean difference (within trial)	<b>2.15 (1.03, 3.27)</b>		<b>-0.32 (-1.41, 0.78)</b>	
Pooled WMD (95% CI, I <sup>2</sup> , P-value)	<b>0.91 (-1.50 to 3.33, 89.5%, 0.002)</b>			

$$s_{pooled}^2 = \frac{(df_1)s_1^2 + (df_2)s_2^2}{df_1 + df_2} \quad \text{OR} \quad s_{pooled}^2 = \frac{SS_1 + SS_2}{df_1 + df_2}$$

df<sub>1</sub>=df for 1st sample; n<sub>1</sub>-1  
df<sub>2</sub>=df for 2nd sample; n<sub>2</sub>-1

<sup>†</sup>SD = Standard deviation (Pooled SD is based on the formulae:

<sup>††</sup>Requested data on mean and SD from author of the study due to no report in the original article

## DISCUSSION

This study summarizes evidence from randomized, placebo-controlled trials evaluating the efficacy of Tongkat Ali herbal for improvement of ED among men participants. In this meta-analysis, we did not find a significant effect of Tongkat Ali extract on ED. The results suggest that the subgroup of subjects with more severe ED may benefit from Tongkat Ali extract, but this would need to be confirmed in further well-designed studies in humans.

Recent evidence suggest that based on animal studies and anecdotal evidence in humans (9), *Eurycoma logifolia* increases sexual desire, coitus attempts and testosterone levels. Therefore, its extract as herbal medicine may help improving erectile function especially among more severe cases which was revealed in subgroup analysis. However, the 2.15 points increment of IIEF-5 score is not met the minimal clinically important difference (MCID) because the MCID for mild to moderate ED severity baseline (15.77 for treatment and 12.36 for placebo) in Udani et al's study should be at least 5 points increment.(23) IIEF-5 scores were classified into five ED severity including severe (5 to7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21) and no ED (22 to 25).(24) In addition, there remains unclear which active compounds are responsible for such effect. A wide range of bioactive compounds including phenolic compounds, polypeptides, diterpenoids, alkaloids, quassinoids, and others (3, 6) have been isolated from Tongkat Ali. Furthermore, it is important to note that there is no report on any standardized assay to quantify the amount of those ingredients in Tongkat Ali preparations used in the included studies.(3, 22)

There are a number of possible reasons that could explain the differences of findings of both studies (significant improvement of ED score at week 12 in Udani et al while no significant improvement in Ismail et al). Firstly, they use different formulation of investigational herbal medicine. Secondly, the subjects in Ismail et al have lower severity of ED, compared to that of Udani et al. The baseline IIEF-5 score was higher in Ismail et al (22.29 for treatment and 21.30 for control) indicating low ED severity, compared to Udani et al (15.77 for treatment and 12.36 for placebo) indicating moderate ED severity.

Lastly, another reason is that participants' ages were not comparable between the two studies. Subjects recruited in Ismail et al aged 30-55 years with the average age around 43, while Udani et al recruited males aged 40-65 years with no reported average age. In addition, participants with different culture (i.e. western and oriental) may respond differently to standardized questionnaires used in the trials.

It might be argued that the benefits seen in trial are not due to Tongkat Ali since *Polygonum minus*'s ingredient was included in the study product by the most recent clinical trial.(22) However, the effect of Polygonum is demonstrated mostly as antioxidant (25, 26) without any effect on ED performance. However, it cannot be concluded that the effect on ED performance is solely from Tongkat Ali in this trial as well, although Tongkat Ali could be the compound contributing to such benefit.

Our study was undertaken in accordance with high standard of systematic review and meta-analysis and reported aligned with PRISMA.(27) At review level, our search was as comprehensive as possible. There were no further published or unpublished studies identified by the experts in the field (Ismail SB, Udani JK). The quality assessment was done using standard approaches (15, 16) which revealed some bias (Table 2) in both included studies. At outcome level, both included studies were prone to high risk of bias as outcomes were reported selectively and no report on amount of active ingredients or the qualitative fingerprint for quality assurance of Tongkat Ali preparation. These gaps or caveats are needed to be addressed in order to define a reliable of Tongkat Ali's efficacy.

In summary, based on the results of our review, it suggests that Tongkat Ali's root water extract may have a clinical benefit on improving ED performance. However, further evidence of efficacy trial is warranted to make any firm recommendation. Monitoring of adverse events should be undertaken to ensure safety of the product. The potential of Tongkat Ali as an effective herbal ED treatment will be elucidated, when more future evidence data based on rigorous RCT is available.

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**Conflict of interest statement:**

Kotirum S and Chaiyakunapruk N declare no conflict of interests in regards with the present study. Ismail SB was one of the authors of an article included in this study, but had no role in screening and selecting of eligible studies.

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