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Efficacy of Triphala Formulation on Blood Lipid and Glucose: A Review of the Literature.

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Abstract

Introduction: Triphala is one of the oldest polyherbal formulation used in Thailand**.** Previous study indicated could be used in blood lipid and glucose lowering. However, the efficacy is supported by limit evidence and seems to be contradicted. This study aimed to conduct a systematic review and meta-analysis that investigates the efficacy of Triphala on blood lipid and glucose. **Method:** Published and unpublished papers were searched from accessible database such as Pubmed, CENTRAL, ScienceDirect, SciSearch, and Thailis including a hand search. Study designed randomized controlled trial in human, written in English or Thai, published before or in year 2014 were recruited. **Results:** From 1,194 potentially relevant articles identified, only 3 studies met our selection criteria and were included for data analysis. Two articles used Triphala as powder and another one was not identified. The mean differences for LDL lowering was -0.29 mmol/L [95%CI (-0.42, -0.17), p<0.00001]. The mean difference for reducing TG and FBS level were -0.37mmol/L, [95%CI (-0.90, 0.16), p=0.17] and -1.86 mmol/L [95%CI (-5.02 to 1.29), p=0.25] respectively. **Conclusion:** Triphala seemed to have effect on LDL lowering when compared to placebo but was unlikely to reduce level of TG and blood glucose. More well-designed trials are needed to determine the efficacy of Triphala for lipid and blood glucose lowering.

Keywords : Triphala, dyslipidemia, dibetics, blood lipid profile, blood glucose

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1. Introduction

Triphala is one of the oldest polyherbal formulation used in Thailand, recommended by the Ayuravedic medicine. Triphala formula is normally composed of three medicinal myrobalans; *Terminaria chebula*, *Terminalia bellirica* and *Phyllanthus emblica*. To date, Tripala can be formulated in several dosage forms, such as powder, tablet and also mixture. (Savarikar *et al.,* 2011; Bhattacharjee *et al.,* 2014). Previous reports indicated that Triphala had various therapeutic actions, therefore could be used in treating various biological activities, for example; antioxidant, chemopreventive, radioprotective effect, immu nomodulation activity, antimicrobial activity, anti-inflammatory and other disease for example; lipid lowering, blood glucose lowering, antiobesity, antidiarrhoeal, mouthwash for dental care, etc (Baliga *et al*., 2012; Kamali *et al*., 2013).

At present, Triphala has been increasingly used as a complementary therapy to treat chronic conditions especially cardiovascular diseases (CVDs) (Borgohain, 2012); World Health Organization (WHO) estimates 17.5 million people died of CVD in 2005 (Downs *et al*., 1998). Meanwhile, hyperlipidemia and hyperglycemia are significant risks to CVD, controlling these factors are of benefit to reducing this event. Previous clinical trials indicated that reduction in LDL level about 10% could reduce incidence of ischemic heart disease by 12-20% over a 5 year period (Wu *et al*., 2009). The previous study showed that efforts to improve blood glucose control significant redu ction in cardiovascular complications (Davidson *et al.,* 2009). As mentioned above, Triphala exhibited lipid and glucose lowering activities, thus, is surely of interest. Previous study suggested that Triphala had favorably efficacy on lipid lowering in *in vitro* (Kamali *et al*., 2013). Although, a few clinical trials reported efficacy on lipid and glucose reduction by Triphala, results of existing studies seem to be contradictory. Therefore, to minimize uncertainty, this study was to conduct a systematic review and perform a meta-analysis in order to determine efficacy of Triphala on lipid profile and blood glucose. We also summared descriptively adverse events found in the pooled studies.

2. Methods

Search strategy

Existing literature was reviewed system atically by using international electronic database including Pubmed, CENTRAL, Scopus, Science Direct and Scisearch. Literature search was also carried out with Thai electronic database; Thailis. A hand search was additionally conducted at the final step to identify other relevant studies from reference lists of retrieved articles. The biblio graphic databases were searched from inception to July 2014. The following MeSH terms used were Triphala, ItrifalSaghir, *Phylantus emblica, Terminalia bellirica, Terminalia chebula*, efficacy, clinical trial, ayurvedic medicine, lipid lowering, hyperlipidemia, dyslipidemia, LDL, cholesterol, triglyceride, blood glucose.

Inclusion criteria and study quality assessment

From the retrieved abstracts, firstly, the principle investigator considered all titles of articles and selected ones that seem to be clinical

trials of Triphala. All abstracts of those selected articles were consequently evaluated using an abstract evaluation form. Studies, written in English or Thai, were included at this stage if lipid profile (HDL, LDL, triglyceride, cholesterol) or blood glucose were stated clearly as clinical outcomes. Afterward, two researchers independently assessed full details of all selected articles using the data extraction form. Each article was assessed in its quality on the basis of study design (randomized or non-randomized controlled trial), pharmaceutical dosage form and dosage of Triphala, number of participants, methodological quality and outcome measurement. In addition, Jadad scoring system (Table 1) was also used as a guideline to evaluate methodological quality of clinical trial. Studies that met at least 3 points out of 5 criteria were classified as high quality. Articles with score less than 3 indicating low quality or having high risk of bias, were thus excluded. The third opinion was sought if disagreements appeared by the first two researchers. The study did not involve human study. Therefore, we are advice that ethical consider is not necessary.

Table 1 Quality Criteria List for Randomized Controlled Trials (Jadad scoring system).

Item	Maximum points	Description
Randomization	2	1 point if randomization is mentioned. 1 additional point if the method of randomization is appropriate. Deduct 1 point if the method of randomization is inappropriate.
Blinding	2	1 point if blinding process is mentioned. 1 additional point if the method of blinding is appropriate. Deduct 1 point if the method of blinding is inappropriate.
Withdrawal	1	1 point if the number and the reasons for withdrawal in each group are stated.

Statistical analysis

Efficacy between Triphala and control group was statistically tested using mean difference and 95% confident interval. Unit used to report blood lipid or blood glucose level was in mmol/L. Values expressed in mg/dL were converted to mmol/L by using the conversion factors: for TC, LDL, and cholesterol were multiplied by 0.0258, for TG the value was divided by 88.2 and for blood glucose was multiplied by 0.055. The statistical analysis was undertaken with Review Manager (Revman^{Ò}) program version 5.3 (Cochrance collaboration). Firstly, heterogeneity of included studies was examined using Q-statistic, result presented in I^2. Value of 50% or higher (P<0.1000) indicates heterogeneity of included studies. Random effects model was used if included studies were heterogeneous, otherwise the fixed effects model if homogeneity was found. Outcome related to safety of Triphala was also considered

and reported descriptively but the meta-analysis was not performed regarding this aspect.

3. Results

From the electronic search, a total of 1,194 articles were retrieved. Of those, 1,191 studies were excluded by the following reasons (1) not clinical trial, (2) did not measure level of blood lipid or glucose, (3) no control group, (4) unable to access full text and (5) used Triphala mixed with other herbs as intervention. However, we eventually exclude one more study conducted by Sing RB (1998) since outcomes reported in proportion of improved participants, thus were unable to convert the outcome into mmol/L unit. (Figure 1 illustrates the study selection process and review procedure. Characteristics of three studies and their assessment measures, details of intervention are presented in table 2.

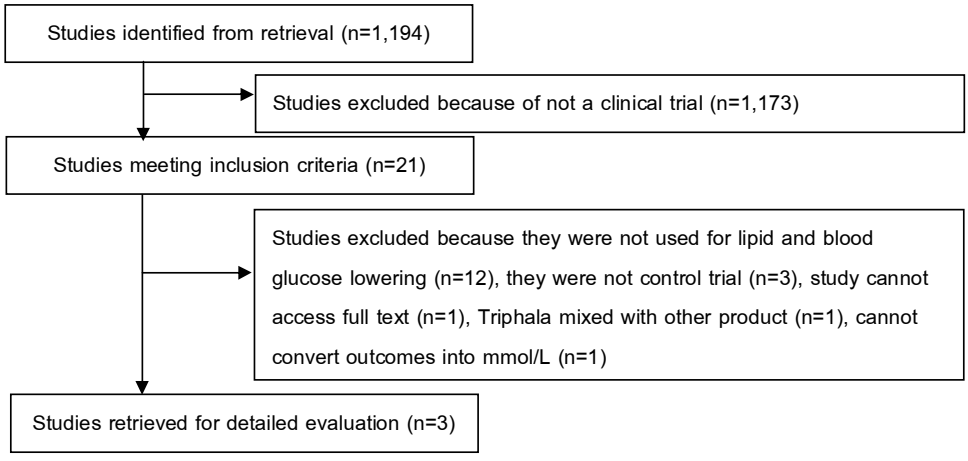

Figure 1 show Trial flow depicting the selection process of studies included in this study.

Efficacy on lipid lowering

Two RCTs, included in our analysis, examined efficacy of Triphala on lipid lowering; measuring blood level of TG and LDL. (Table 2) One study was conducted in Thailand, written and published in a Thai national journal (Wichiansaen *et al.*, 2014). The other was performed in Iran, written in English, and published in an interna tional journal (Kamali, 2013). Both studies were randomized double blinded controlled trials. Wichi ansaen and colleagues (2014) compared efficacy between Triphala 500 mg twice daily and placebo in healthy volunteers, treating for four weeks, however dosage form used, blinding process, and concealment were not described. Kamali and colleagues (2012), studied in obese patients, compared efficacy of Triphala powders 5 g twice daily to the use of identical appearance placebo, treating for three months. Two meta-analyses were performed separately to examine efficacy of Triphala on LDL and TG. Fixed and random effect model was used respectively, based on hetero-

geneity of the pooled data. As shown in Figure 1, the pooled mean difference of LDL level was -0.29 mmol/L, indicating lower LDL found in the Triphala group (95%CI -0.42 to -0.17; *P*<0.00001). Similar trend found for TG level, the pooled mean difference was as of -0.37mmol/L (95%CI -0.90 to 0.16; *P*=0.17) which means TG level of the Triphala group was lower than that of the control, but not statistically significant. (Figure 2)

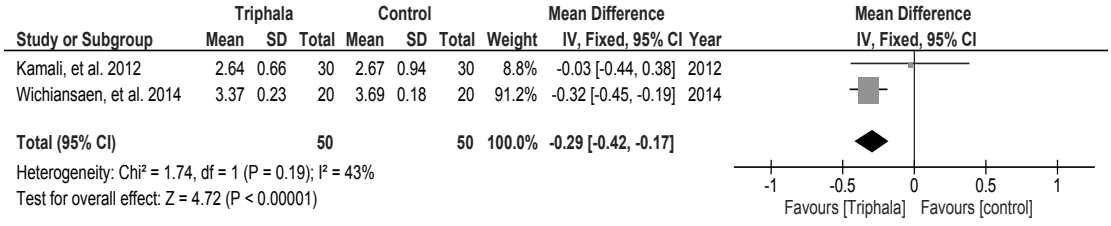

Figure 1 Mean difference (95%Confidence interval) in LDL level for Triphala versus placebo

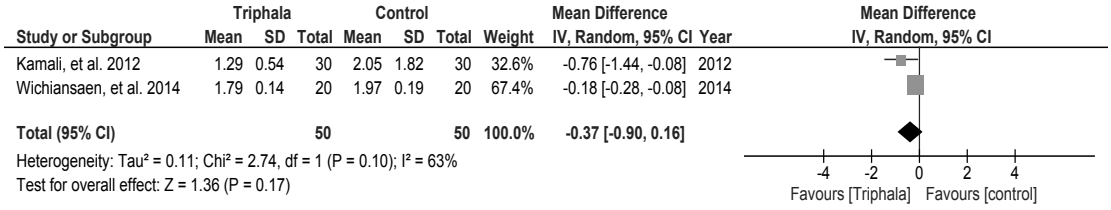

Figure 2 Mean difference (95%Confidence interval) in TG level for Triphala versus placebo

Efficacy on blood glucose lowering

Two RCTs were included in the meta-analysis for blood glucose lowering. Kamali and colleagues (2012), as aforementioned, also looked at efficacy of Triphala on fasting blood glucose (FBS), in addition to measuring lipid level. The other was Iranian trial, done by Rajan and colleagues (2008). This study examined efficacy of taking Triphala 5 g daily for 45 days in diabetic patients, compared to taking placebo. Outcome assessment was FBS. Since the heterogeneity of pooled data shows significant (p<0.00001, I^2=98%), thus the random effect model was used. As shown in Figure 3, the pooled mean difference in FBS was -1.86 mmol/L (95%CI -5.02 to 1.29; p=0.25). This means the use of Triphala provided better efficacy than placebo in terms of FBS, but not statistical significant.

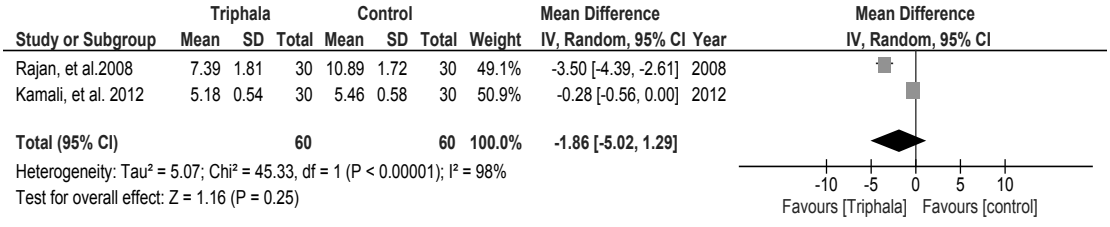

Figure 3 Mean difference (95%Confidence interval) in blood glucose level for Triphala versus placebo

Safety

Only two studies, Kamali *et al*. (2012) and Wichiansaen *et al*. (2014), mentioned descrip tively about adverse events of Triphala use. Both studies monitored some vital laboratory tests including liver function test (AST, ALT and ALP), blood urea nitrogen (BUN), serum creatinine and completed blood count; however all tests were found normal. Noticeably, Kamali *et al*. (2012) reported significantly decreased alanine transam-inase (ALT) and fasting serum insulin in the Triphala group than in the placebo (*P*=0.03 and 0.01, respectively), whereas Wichiansaen *et al.* (2014) did not find this phenomenon.

4. Discussion

This is a systematic review and meta -analysis conducted to determine the efficacy of Triphala for improving lipid profile and blood glucose. Existing evidence demonstrates that regimen used and dosage form of Triphala was varied. Patients participating in the Rajan *et al*. (2008) and Kamali *et al.* (2012) studies were already diagnosed as diabetic and obese respec tively. Consequently, they possibly taking anti-diabetics or other medicines related to dyslipidemia, but Kamali and colleagues (2012) did not specify patients' medication use. Such factors may have effected the clinical outcome, however, bias may be minimized because of the comparison with the control group. Regarding efficacy on LDL level, although no heterogeneity was detected among the included studies (I^2=43%), there were, nonetheless, some variations in terms of data presentation, dose, frequency and duration of Triphala use. This meta-analysis shows that Triphala tends to reduce LDL level. This might be an effect of gallic acid as was previously reported (Puntithavathi *et al.,* 2011 and Bok *et al*., 2002). Recently, Jantaboon and colleagues (2014) also found inhibitory effect of Triphala extract on HMG CoA reductase, with a similar mechanism as has pravastatin. Therefore, this herbal formulation might be useful as a supplementary treatment in dyslipidemia condition. The meta-analysis also shows trend in reducing TG, but this is not statistically significant [mean difference -0.37 (95%CI -0.90-0.16)]. Our findings are in contrast to Kamali and colleagues (2013) reporting that Triphala was able to control TG level in preclinical trial. Remarkably, one possible confounding factor in our analysis was the differences of participant health conditions in the two included studies; one conducted with

dyslipidemia patients, while the other with healthy volunteer. This variation might cause problems to conclude any effect on TG level. In terms of efficacy on blood glucose, Kamali and colleagues (2013) found efficacy on blood sugar lowering, while the present meta-analysis shows that Triphala was unlikely to improve blood glucose [mean difference -1.86 (95%CI -5.02-1.29)]. This is probably because regimen, including frequency and duration of Triphala used were inconsistent, making heterogeneous input. Another limitation of our study is that we did not consider the standardization of active ingredient which is necessary for quality control process. In this analysis, preparation used was different, affecting amount of active ingredients and clinical outcomes.

Our descriptive finding demonstrates that, seemingly, Triphala was safe for enteral use. Participants in all studies reported neither withdrawal nor serious adverse effect, apart from arising of ALT and insulin serum. However, these signs were common and other adverse reactions were not different from the placebo group.

Patients enrolled in the included studies were different in status; diabetic patients in Rajan *et al* (2008), obese patients in Kamali *et al* (2012) and healthy volunteer in Wichiansaen *et al* (2014). In addition, two trials (Wicheansan *et al*, 2014 and Rajan *et al*, 2008) did not conceal physical appearance of intervention used, whereas the concealment is an important procedure of RCT. These factors should be noted as our limitations, thus possibility of measurement bias exists. Publication bias is another concern for conducting meta-analysis since its existence can result in biased conclusion. Meanwhile, the number of studies was considerably small, a test for publication bias, therefore, was impossible to be performed. The results of the study can be used as prior knowledge to conduct more comprehensive study.

5. Conclusion

The number of studies regarding efficacy of Triphala on blood lipid and glucose is still limited. Although based only on 3 papers, this meta-analysis of existing evidence demonstrates efficacy of Triphala in LDL lowering when compared to placebo. Results also suggest that Triphala formulation was unlikely to reduce level of TG and blood glucose. However, well-designed trials with sufficient detail of active ingredients should be carried out further, to determine the efficacy of Triphala for lipid and blood glucose lowering activity.

Table 2 Characteristics of included studies

First author, year (location)	Quality score	Participants	Control (n)	Intervention (n)	Main outcomes	Results	
						Control	Treatment
Rajan *et al*., 2008 (Iran)	3/5	Diabetic patients	Placebo (30)	Triphala 5 g was mixed with butter milk daily 2 hr after dinner for 45 days (30)	FBS, PPG	FBS : 198±31.20 PPG : 43.84±35.81	FBS : 134.44±32.86 PPG : 209.0±31.64
Kamali *et al*. 2012 (Iran)	4/5	Outdoor patients age 16–60 years, a body mass index (BMI) between 30 to 50 kg / m^2	Placebo (30)	10 g of ItrifalSaghir/ day (30) for 3 months	BMI, lipid profile, blood sugar, HbA_{1C}, liver function test, CBC, renal function test, PT, INR	FBS: 99.20±10.55 LDL: 103.60±36.53 TG: 181.17±160.93	FBS: 94.20±9.78 LDL: 102.50±25.66 TG: 114.06±47.68
Wichiansaen, *et al*. 2014 (Thailand)	3/5	Healthy volunteer	Placebo (20)	Triphala 500 mg bid 4 weeks (20)	Weight, lipid profile, liver function test, CBC	LDL:142.95±7.09 TG : 173.95±16.36	LDL:130.80±8.83 TG : 157.25±12.52

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