Original Article

Anti-hyperlipidemic Property of Cinnamon Stomachic Mixture: A Pilot Study

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Introduction: Cinnamon stomachic mixture, one of the Thai traditional herbal recipes, is in the National herbal drug lists in Thailand. It has long been prescribed for treating flatulence and dyspepsia. As already known, cinnamon demonstrated the potential for reducing blood lipid and glucose. In this pilot study, we investigated the anti-hyperlipidemic property of cinnamon stomachic mixture.

Materials and methods: The open-label, one single arm, prospective, pilot study was conducted at Ampur Muang District Primary Care Center, Prapokkloa Branch, Chanthaburi province, Ministry of Public Health, Thailand. Cinnamon stomachic mixture was produced from the GMP certified pharmaceutical company (Thongtong Osoth). The quality control was performed at Faculty of Pharmacy, Mahidol University. Subjects were recruited with specific inclusion and exclusion criteria. Blood chemistry including complete blood count were investigated for evaluation of the safety. All subjects were advised to take 2 tablespoons of the mixture after mealtime, 3 times daily for total 2 months. At the end of the first and second months, all subjects were asked to follow up with physical examination, blood chemistry tests, the same as done at the beginning. The anti-hyperlipidemic effects of the cinnamon stomachic mixture were assessed as the primary outcome.

Results: Based on our results, the decreasing of total blood cholesterol and triglyceride, before and after herbal recipe ingestion, was detected, but no statistical difference was observed. Other blood chemistry and complete blood count were not statistically changed. Interestingly, the statistical difference with p value = 0.034 was found in AST level, at 2 months.

Conclusion: Cinnamon stomachic mixture could reduce total cholesterol and triglyceride level, but not significant. The potent hepatoprotective property of cinnamon stomachic mixture is shown in this investigation. However, more clinical studies are still needed to be assure of the lipid lowering property of cinnamon stomachic mixture in patients with dyslipidemia.

Keywords: anti-hyperlipidemic property; Cinnamon stomachic mixture; hepatoprotective effect

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INTRODUCTION

Cinnamon stomachic mixture, one of the Thai traditional herbal recipes, is in the National herbal drug lists in Thailand. It has long been prescribed for treating flatulence and dyspepsia. This herbal recipe is composed of several kinds of herbal plants, for example, the barks from *Cinnamomum zeylanicum*, the fruits from *Amomum verum*, the barks from *Cinnamomum bejolghota*, the dried flowers from *Syzagium armaticum*, and the roots from *Glycyrrhiza glabra*. From all these components, *Cinnamomum zeylanicum* plays a vital role with its therapeutic active compound in this recipe. *Cinnamomum zeylanicum* (as called Cinnamon) is the plant in the genus of Cinnamomum which has generally two main varieties [1]. The part used in this recipe is obtained from the inner bark of this tree with cinnamaldehyde as the primary constituent, approximately 65-80%. In traditional medicine, cinnamon has the medicinal properties for digestive ailments. Other important activities include anti-inflammatory, antimicrobial, antioxidant, and antidiabetic agents [2]. *Amomum verum* is in the family of Zingiberaceae containing approximately 10% of essential oil, such as camphor, myrcene, and limonene [3]. The therapeutic properties of its fruit include antimalarial and immunomodulatory effects. *Glycyrrhiza glabra*, in the family Fabaceae, has many properties for treating various kinds of illness, such as heartburn, chronic bronchitis with intense coughing and secretion, and supporting health. The secondary metabolites of this plant root have about 20 triterpenoids and nearly 300 flavonoids, which glycyrrhizin and glycyrrhetinic acid are the main components [4]. The traditional uses of Glycyrrhiza glabra are chronic inflammatory conditions of air passage and cough, including antiulcer activity [5]. *Cinnamomum bejolghota* is in the family of Lauraceae. The bark of this plant, containing the essential oil, alpha-terpineol, and cineole, has the medicinal properties for treating syncope, palpitation, and flatulence [6]. *Syzagium aromaticum*, known as clove, is in the family of Myrtaceae. It is used as the antioxidant and antimicrobial agents, with its therapeutic property for treating nausea and vomiting, flatulence, and bowel disorders. It is the main source of phenolic molecules [7]. As named, this cinnamon stomachic mixture is composed of *Cinnamomum zeylanicum* and *Cinnamomum bejolghota* at the proportion of 1600 mg to the total herbal weight of 4100 mg (w:w ~ 40:100).

From previous study, the cinnamon stomachic mixture is effective and safe for treating the patients with functional dyspepsia, similar to simethicone [8]. However, the clinical research as an anti-hyperlipidemic recipe has never been studied. As already known, cinnamon demonstrated the potential for reducing blood lipid and glucose [9,10,11]. With the highest percentages of cinnamon in this recipe, we hypothesized that cinnamon stomachic mixture could reduce the blood lipid, and this prompted us to investigate the anti-hyperlipidemic property of cinnamon stomachic mixture in this pilot clinical study.

MATERIALS AND METHODS

Production of cinnamon stomachic mixture

All herbal plants were purchased from a well-known Thai Herbal Pharmacy in Bangkok (Vejpongosot), and the cinnamon stomachic mixture was produced from the GMP certified pharmaceutical company (Thongtong Osoth). The mixture was derived from 40 grams of dried cinnamon, 20 grams of *Amomum verum*, 35 grams of *Cinnamomum bejolghota*, 25 grams of *Glycyrrhiza glabra*, and others in small amount. They were boiled together in 450 ml distilled water. After boiling, the crude was got rid by passing the mixture through the clean cloth before bottling the solution into each 100 ml plastic bottle and labeling for the experiment.

Quality control of cinnamon stomachic mixture

To address the chemical components and evaluate the herbal formula, high performance liquid chromatography (HPLC) was performed at Faculty of Pharmacy, Mahidol University. The herbal biomarkers used as the standard for this mixture was cinnamaldehyde. Gradient elution of 1% acetic acid in water and 1% acetic acid in acetonitrile were used in the mobile phase in this study. In addition, the heavy metal measurement and bacterial contamination of the cinnamon stomachic mixture were also performed.

Study designed

This is the open-label, one single arm, prospective, pilot study which conducted at Ampur Muang District Primary Care Center, Prapokkloa Branch, Chanthaburi province, Ministry of Public Health, Thailand. All volunteers provided the written informed consent. The study was approved by the Institutional Review Board's Ethics Committee at Prapokkloa Hospital, in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local laws. The study was approved with the NO. CTIREC 090/60.

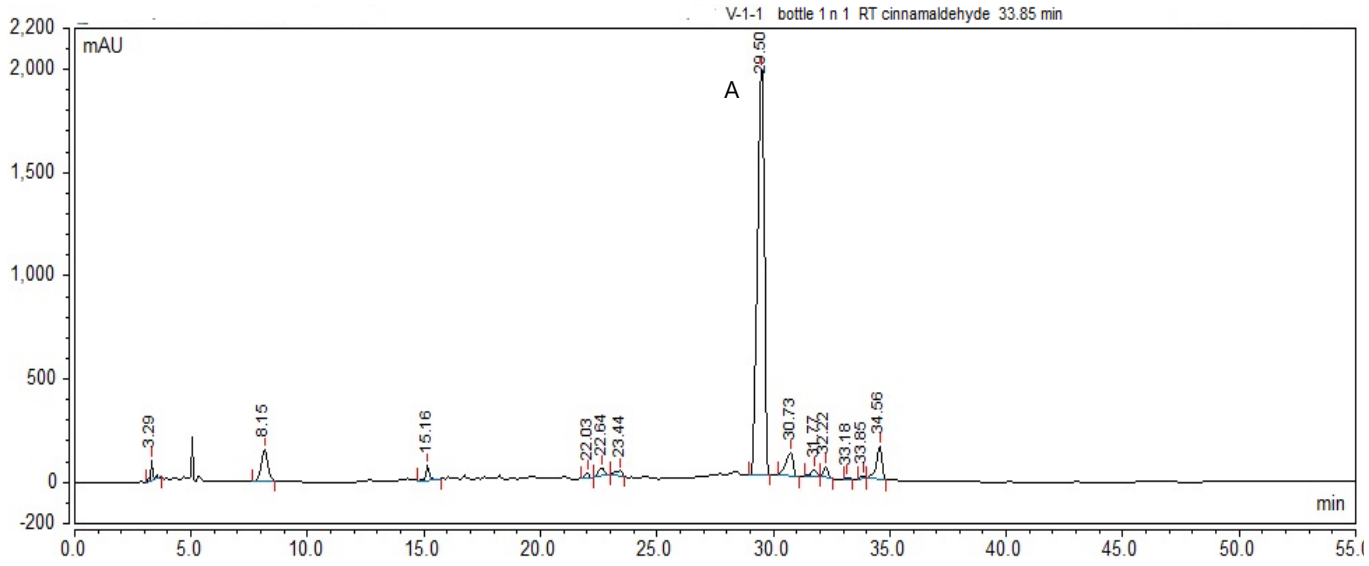

Figure 1. HPLC chromatogram of cinnamon stomachic mixture. (A- cinnamaldehyde)

Volunteers and Treatment protocol

The eligibility criteria for the study were: 1) age between 20-80 years of any sex; 2) fasting blood sugar less than 126 mg/dL; 3) total cholesterol level over 200 mg/dL; 4) LDL level less than 190 mg/dL; 5) Thai CV risk score less than 10; 6) urine pregnancy test negative; 7) willing to sign the informed consent. The exclusion criteria were: 1) those who are taking lipid-lowering drugs; 2) decline of renal and liver functions; 3) those who had history of allergy to herbal medicine; 4) have breast feeding; 5) continuously consuming alcohol; 6) history of recent cancer, coronary artery diseases (CAD), cerebrovascular diseases (CVD), and hepatitis.

This study was prospective, open-label, one single arm, pilot study. The total number of subjects was 18 persons in this one single arm, starting from July 2018 through October 2019. After subject was recruited in the study, physical examination was performed and blood was drawn for studying the lipid profiles (cholesterol, triglyceride, LDL, HDL), renal function test, (BUN, creatinine, eGFR), liver function test (AST, ALT, alkaline phosphatase, albumin, globulin), uric acid, urine exam, complete blood count (CBC), including urine pregnancy test for those who were in the reproductive period. All subjects were advised to take 2 tablespoons of the cinnamon stomachic mixture after mealtime, 3 times daily for total 2 months. At the end of the first and second months, all subjects were asked to follow up with physical examination, blood chemistry tests, the same as done at the beginning.

Outcome measurement

The anti-hyperlipidemic effects of the cinnamon stomachic mixture were assessed as the primary outcome of this study. For the efficacy, the comparison between the first and the third lipid profiles of each volunteer was analyzed.

Safety and adverse events monitoring

For safety, complete blood count and blood chemistry were evaluated before enrollment and every 4-week cycle, total for 2 times. All the adverse events were recorded, reported, and graded using the Terminology criteria for Adverse Events, version 4.0. Those with the adverse events over or equal to grade 3 were considered as severe events and had to stop the trial.

Statistical analysis

Data were analyzed by descriptive statistics, mean ± SD, Paired t-test, compared before and after treatment with cinnamon stomachic mixture. The p-value of less than 0.05 was considered statistically significant.

RESULTS

HPLC chromatogram of cinnamon stomachic mixture

In this study, the content of marker compound; cinnamaldehyde, in cinnamon stomachic mixture sample was quantified by High Performance Liquid Chromatography (HPLC). The result showed that the content of cinnamaldehyde was 2.11±0.02 µg/ml, as demonstrated in Figure 1.

Table 1. Age analysis of the 18 volunteers in this study with the oldest one at 76 years old, and the youngest one at 32 years old.

Age Characteristics	Years
Mean age	50.33
Median age	50.50
Standard deviation	10.81
Minimum age	32
Maximum age	76

Volunteer characteristics

During the study period, 18 volunteers were enrolled for participation. All volunteers strictly complied with the protocol, with no deviation. The mean age in this study is shown in Table 1. The oldest person was 76 years old, while the youngest one was 32 years old. Mean age and standard deviation were 50.33±10.81 years old. There were 14 females, accounting for 77.8%, and 4 males, accounting for 22.2%, recruited in this research. This data obviously exhibits the tendency that female has more frequent hyperlipidemia than male.

Table 2. Characteristics of 18 volunteers in this study, comparing before and after 2-month treatment.

Characteristics	Mean±SD (before)	Mean±SD (after)	p-value
BMI	26.60±3.99	26.40±4.35	0.353
Cholesterol	229.07±15.31	219.21±21.69	0.171
Triglyceride	132.86±60.61	124.79±42.61	0.367
LDL	165.74±16.96	168.29±25.38	0.650
ALT	21.86±12.45	18.14±7.03	0.071
AST	19.50±5.03	17.43±0.90	**0.034***
Hemoglobin	13.29±1.28	13.19±1.16	0.646
WBC	7.05±2.43	6.81±2.24	0.343
Platelet	255.21±26.07	255.857±32.169	0.919

BMI= body mass index; cholesterol= total cholesterol; LDL=low density lipoprotein; ALT=alanine aminotransferase; AST=Aspartate transaminase; WBC=total white blood cell count
* Significant p-value < 0.05

Table 2 demonstrated the characteristics of all volunteers in this study. Most of them had overweight and obesity, with mean BMI before and after treatment at 26.60 kg and 26.40 kg, respectively, but no statistical difference. In Thailand, BMI over 25 is considered as obesity, whereas BMI over 23 is considered as overweight. Complete blood count, including hemoglobin, total white blood cell count (WBC), and platelet count showed no difference before and after the study. Based on our results, the decreasing of total blood cholesterol, before and after herbal recipe ingestion, was detected, but, surprisingly, no statistical difference was observed. This evidence was also occurred in triglyceride level. Interestingly, statistical difference with p-value = 0.034 was found in AST level, at 2 months. The ALT level was declined after 2-month therapy, but no difference was detected. LDL level and renal function test was not statistically changed in this study group.

Side effects and adverse events

In this pilot study, the adverse events related to the cinnamon stomachic mixture were not detected. All physical examination and laboratory investigations of all volunteers recruited, especially liver function and renal function tests were within normal limit at the end of the study.

DISCUSSION

This herbal recipe, cinnamon stomachic mixture, is commonly found in the market, as it is announced in the Thai National Herbal Drug Lists. It has long been used for treating flatulence and dyspepsia. However, this is the first pilot study of cinnamon stomachic mixture demonstrated as lipid lowering herbal regimen. The products used in this study had quality control by using HPLC. In HPLC, the spikes of cinnamaldehyde in this recipe are derived from *Cinnamomum zeylanicum*, and *Cinnamomum bejolghota*, respectively. The products were safe for ingestion, as we found no bacterial nor heavy metal contamination.

In terms of lipid profiles, our results showed that cinnamon stomachic mixture could decrease the total cholesterol and triglyceride level, but no statistical significance. A number of interventions on lipid profiles have been performed using cinnamon. From previous double-blind, randomized-controlled trial with two parallel groups in non-alcoholic fatty liver (NAFLD) patients taking 2 capsules of cinnamon per day, equally to 1500 mg of cinnamon, for 12 weeks could reduce blood total cholesterol, and triglyceride [12]. Significant improvement of liver function tests, such as AST, ALT, and GGT, was also recognized in this clinical trial. In fact, it showed that cinnamon could be effective in improving NAFLD characteristics, as well. Other research group performed the phase I clinical trial evaluated for the efficacy and safety of cinnamon. Their results demonstrated no significant side effects and toxicities, similar to our study. In addition, they also revealed the

beneficial anti-hyperlipidemic and blood pressure lowering effects of cinnamon among healthy adults [13]. The effects of cinnamon consumption on lipid profile in patients with T2DM were also investigated. After 3 grams per day of cinnamon for 8 weeks, the levels of fasting blood glucose, HbA1c, triglyceride, weight, BMI, and body fat mass decreased significantly compared to baseline, but not in placebo group [14]. Moreover, from a systemic review and meta-analysis, the effects of cinnamon supplementation significantly reduced blood triglycerides and total cholesterol concentrations without any significant effect on LDL and HDL [15]. Quite similar results on lipid lowering effects were also obtained and reported in another research group [16]. The possible mechanism of cinnamon reducing lipid profiles might be from cinnamate, a phenolic compound found in the inner bark of cinnamon. This compound lowers cholesterol level in high fat fed rats by inhibiting hepatic HMG Co-A reductase activity. It can also suppress lipid peroxidation by enhancement of hepatic antioxidant enzyme activity [17]. As known, HMG Co-A reductase is an enzyme that regulates the cholesterol biosynthetic pathway. Thus, inhibition of this enzyme can reduce blood cholesterol level [18].

In addition, liver enzyme, especially AST, was significantly reduced with p value at 0.034, comparing to ALT with p value at 0.071. This hepatoprotective result is similar to previous reports. The cinnamon extract reduced the toxicity of CCl4 and preserved the hepatic tissue in rats [19]. As mentioned earlier, significant improvement of liver enzyme, such as AST, ALT, and GGT was seen in patients taking 1500 mg of cinnamon for 12 weeks [12]. This hepatoprotective property might come from the antioxidant activity of the cinnamon [20].

CONCLUSION

The ability of cinnamon in reducing blood sugar is well-known, however, the lipid lowering property of cinnamon is needed to be investigated. Based on our report, cinnamon stomachic mixture could reduce total cholesterol and triglyceride level, but not significant. The potent hepatoprotective property of cinnamon stomachic mixture is shown in this investigation. However, more clinical researches are still needed to be assure of the lipid lowering property of cinnamon stomachic mixture in patients with dyslipidemia.

Conflicts of Interest: Declare of no conflict of interest

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