Original Research

Cinnamon and Aspirin for Mild Ischemic Stroke or Transient Ischemic Attack: A Pilot Trial

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ABSTRACT

Purpose: Cinnamon can reduce levels of blood lipids, blood glucose, and inflammation, which are risk factors for ischemic stroke and transient ischemic attack (TIA).The goal of this study was to observe the safety and efficacy of aspirin combined with cinnamon in the treatment of patients with mild stroke or TIA.

Methods: This pilot study included patients with mild stroke or TIA treated at Guangdong Provincial People's Hospital–Nanhai Hospital between January 2014 and December 2016. The primary end point was recurrent stroke (within 90 days after the first attack; intention-to-treat analysis). The secondary end points included biochemical indices, carotid color Doppler ultrasound, safety indices, and adverse reactions.

Findings: A total of 122 patients were included, including 62 in the aspirin-cinnamon group (41 men and 21 women; mean age, 62.0 [3.5] years) and 60 in the aspirin-placebo group (40 men and 20 women; mean age, 63.0 [3.2] years). The number of participants with recurrent stroke was two (3.2%) and nine (15.0%) in the aspirin-cinnamon group and the aspirin-placebo group, respectively ($P = 0.002$). Compared with aspirin-cinnamon, aspirin-placebo rates of unstable plaque and severe vascular stenosis were higher, whereas the rate of mild vascular stenosis with aspirin-cinnamon was higher than with aspirin-placebo ($P < 0.05$). One case of mild to moderate upper gastrointestinal bleeding in each group was observed.

Implications: Among patients with TIA or mild ischemic stroke, the combination of cinnamon and aspirin could be superior to aspirin alone for reducing the risk of 90-day recurrent stroke. (*Clin Ther.* 2022;44:482–490.)

Key words: aspirin, cinnamon, ischemia, ischemic attack, stroke, transient.

INTRODUCTION

Acute ischemic stroke is an episode of acute neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction. The common complications after ischemic stroke include persistent neurologic dysfunction, secondary brain injury due to cerebral edema, swallowing dysfunction, pneumonia, urinary tract infections, deep vein thrombosis, pulmonary embolism, myocardial ischemia, heart failure, cardiac arrhythmias, seizures, fever, and delirium.[1,2] In patients with mild stroke, the

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symptoms usually disappear after a few minutes, but the brain sustains some degree of damage.[3,4] The risk factors are the same as for moderate and severe stroke,[4] but the incidence of mild ischemic stroke is vastly underestimated.[5] Transient ischemic attack (TIA) is a temporary episode of neurologic dysfunction caused by focal ischemia of the brain, spinal cord, or retina, with no evidence of acute infarction on neuroimaging.[6] In the United States, the reported incidence of TIA is 0.7 to 0.8 per 1000 people, and the prevalence is 2.3%.[6]

Currently, in terms of risk factors and pathogenesis of mild stroke or TIA, guidelines mainly focus on controlling blood pressure and levels of blood lipids, blood glucose, and vascular inflammation.[7–10] Aspirin and clopidogrel are both recommended as basic or routine drugs to prevent stroke,[7–10] but resistance to aspirin and clopidogrel has been reported, and their preventive effect is reduced.[11] In addition, their long-term use has some side effects such as increased bleeding risk.[12]

Studies indicated that cinnamon could reduce levels of blood lipids, blood glucose, and inflammation.[13–17] Therefore, cinnamon, a commonly used Chinese herbal medicine, has the potential to prevent ischemic stroke. Currently, there is no relevant study on the combination of cinnamon and antiplatelet drugs (eg, aspirin) in the treatment of mild stroke or TIA. The goal of the present pilot study was to observe the effect of cinnamon combined with aspirin in the treatment of patients with mild stroke or TIA.

PARTICIPANTS AND METHODS

Study Design and Participants

This pilot study was conducted in patients with mild stroke or TIA treated at Guangdong Provincial People's Hospital–Nanhai Hospital between January 2014 and December 2016. The study was approved by the ethics committee of the Guangdong Provincial People's Hospital–Nanhai Hospital. All participants provided a signed informed consent form.

Referring to the 2014 Chinese Expert Consensus on Antiplatelet Therapy for TIA and Mild Stroke,[18] mild ischemic stroke was defined as a sudden focal mild neurologic dysfunction (defined as National Institutes of Health Stroke Scale score <3) due to blood vessel occlusion and lasting ≥24 hours, or neurologic dysfunction owing to ischemic infarction associated with imaging and clinical symptoms rather than cerebral hemorrhage detected by imaging. TIA was defined either by using a time-based definition (TIA is a sudden focal neurologic dysfunction [brain, spinal cord, or retina] caused by vascular causes, lasting <24 hours) or a histology-based definition (TIA is a transient neurologic disorder caused by ischemia in the brain, spinal cord, or retina without acute infarction).

The inclusion criteria were:(a)Diagnosis of an acute minor ischemic stroke or TIA and the ability to start the study drug within 24 hours after symptom onset.(b)TIA was defined as focal brain ischemia with resolution of symptoms within 24 hours after onset plus a moderate to high risk of stroke recurrence (defined as a score ≥4 at the time of randomization on the ABCD2 score, which assesses the risk of stroke on the basis of blood pressure, age, presence or absence of diabetes, duration of TIA, and clinical features; scores range from 0–7, with higher scores indication greater short-term risk). (c)Acute minor stroke was defined by a score ≤3 at the time of randomization on the National Institutes of Health Stroke Scale (scores range from 0–42, with higher scores indicating greater deficits).[19] (d) All patients were diagnosed independently by 2 neurologists after onset.(e)patients aged ≥40 years.(f)No long-term use of cinnamon and related preparations within 3 months before onset. (g)Patients or family members were informed and agreed to participate in the study.

Exclusion criteria were: (a) bleeding tendency; (b) vascular malformations; (c) tumors; (d) abscesses; (e) nonischemic diseases of the brain; (f) aspirin contraindications; (g) history of intracranial hemorrhage; (h) cardiogenic stroke; (i) long-term use of antiplatelet drugs (eg, clopidogrel, ticagrelor, warfarin) affecting platelet function; (j) gastrointestinal hemorrhage or major surgery within 3 months; (k) planned revascularization within 3 months; (l) combined with multiple noncardiovascular diseases with a life expectancy not exceeding 3 months; or (m) hyperactivity of fire and excess heat syndromes by traditional Chinese medicine syndrome differentiation.

Randomization and Blinding

The patients were assigned to the aspirin-cinnamon group and the aspirin-placebo group by using sequential sealed envelopes prepared by an independent biostatistician using a random number table. The patients, physicians, and data assessors were blinded to grouping.

Therapeutic Regimens

All patients received 100 mg of labeled aspirin (lot no. BJ27410; Bayer Schering Pharma, Berlin, Germany) once a day on the first day after admission. From the second day, 100 mg/d aspirin was given for 90 consecutive days. The patients in the cinnamon-aspirin group were given 5 g of cinnamon granules (Chinese herbal formula granules, batch no. 408234T; Guangdong Yifang Pharmaceutical Co, Ltd, Guangdong, China) on the first day of admission, together with 200 mL of boiled water, and for 90 consecutive days. The patients in the aspirin-placebo group were given placebo granules on the first day (placebo and cinnamon granules were similar in color, taste, and appearance, and were provided by Guangdong Yifang Pharmaceutical Co, Ltd, with the same dosage, method, and course of treatment) for 90 consecutive days.

End Points

The primary end point was recurrent stroke (within 90 days after the first attack). The secondary end points included biochemical indices, carotid color Doppler ultrasound, safety indices, and adverse reactions.

Data Collection

The levels of total cholesterol, triacylglycerol, LDL-C, HDL-C, plasma lipoprotein–related phospholipase A_2 (Lp-PLA_2), and high-sensitivity C-reactive protein (hs-CRP) were measured within 24 hours and at 30, 60, and 90 days after stroke or TIA. The biochemical indices were measured by using an automatic biochemical analyzer (C8000; Abbott Laboratories, Abbott Park, IL, USA).

After admission, carotid artery color Doppler ultrasonography was performed in each group, and after 90 days of treatment, carotid artery color Doppler ultrasound (ProSound SSD-α10; Hitachi-Aloka, Tokyo, Japan) was performed to evaluate the carotid artery lesions. Morphologic and echocardiographic properties of carotid atherosclerosis were evaluated, referring to the diagnostic criteria for color Doppler flow imaging of the carotid artery, which was divided into the normal carotid artery, stable plaque, and unstable plaque.[20] The stable plaque group and the unstable plaque group were divided into 3 groups according to the degree of stenosis: mild (0%–49%), moderate (50%–69%), and severe (70%–99%),[21] referring to ECST (the European Carotid Surgery Trial).

Possible side effects were observed, including cerebral hemorrhage, gastrointestinal tract hemorrhage, urinary hemorrhage, and hemorrhage at other possible sites. Routine testing of Body temperature, pulse, blood pressure, respiration, blood routine, urine routine, stool routine, liver and kidney function, blood electrolyte and other indicators of patients were detected 1 day before treatment and 90 days after treatment.

Statistical Analysis

This was a preliminary test performed with patients who were admitted to the neurology department at our hospital between January 2014 and December 2016. The incidences π_1 and π_2 of recurrent stroke after 90 days of treatment were calculated in both groups, and the sample size was estimated according to the equation:

$$N = \left(Z_\alpha / \sqrt{\pi_c(1-\pi_c)\left(Q_1^{-1} + Q_2^{-1}\right)} + Z_\beta \sqrt{\pi_1(1-\pi_1)Q_1 + \pi_2(1-\pi_2)Q_2} / (\pi_1 - \pi_2))^2 \right)$$

where $\alpha = 0.05$, $\beta = 0.10$, $\pi_c = Q_1\pi_1 + Q_2\pi_2$, Q_1 and Q_2 are ratios of the sample size of the 2 groups, and π_1 and π_2 are recurrence rates of stroke in the 2 groups of preliminary test. After calculations, the difference in the stroke recurrence rate between the 2 groups (π_c) was 20.3%. The sample size was calculated as 122 patients using this equation.

SAS version 9.3 (SAS Institute, Inc, Cary, NY, USA) was used to analyze the data. The centralized tendency of the data was expressed as mean (SD) of the measurement data in each group. The *t* test or Mann-Whitney *U* test was used to compare the means of the 2 groups, as appropriate. Categorical data are expressed as no. (%). Comparisons between the 2 groups were made by using the χ^2 test. All statistical *P* values were two-sided (when possible), and *P* values <0.05 were considered as statistically significant.

RESULTS

Characteristics of the Participants

This study enrolled 122 participants between January 2014 and December 2016 (Figure I). There were 41 men and 21 women in the aspirin-cinnamon group, aged 43 to 75 years (mean age, 62.0 [3.5] years). There were 40 men and 20 women in the aspirin-placebo group, aged 42 to 73 years (mean age, 63.0 [3.2] years). No significant differences in

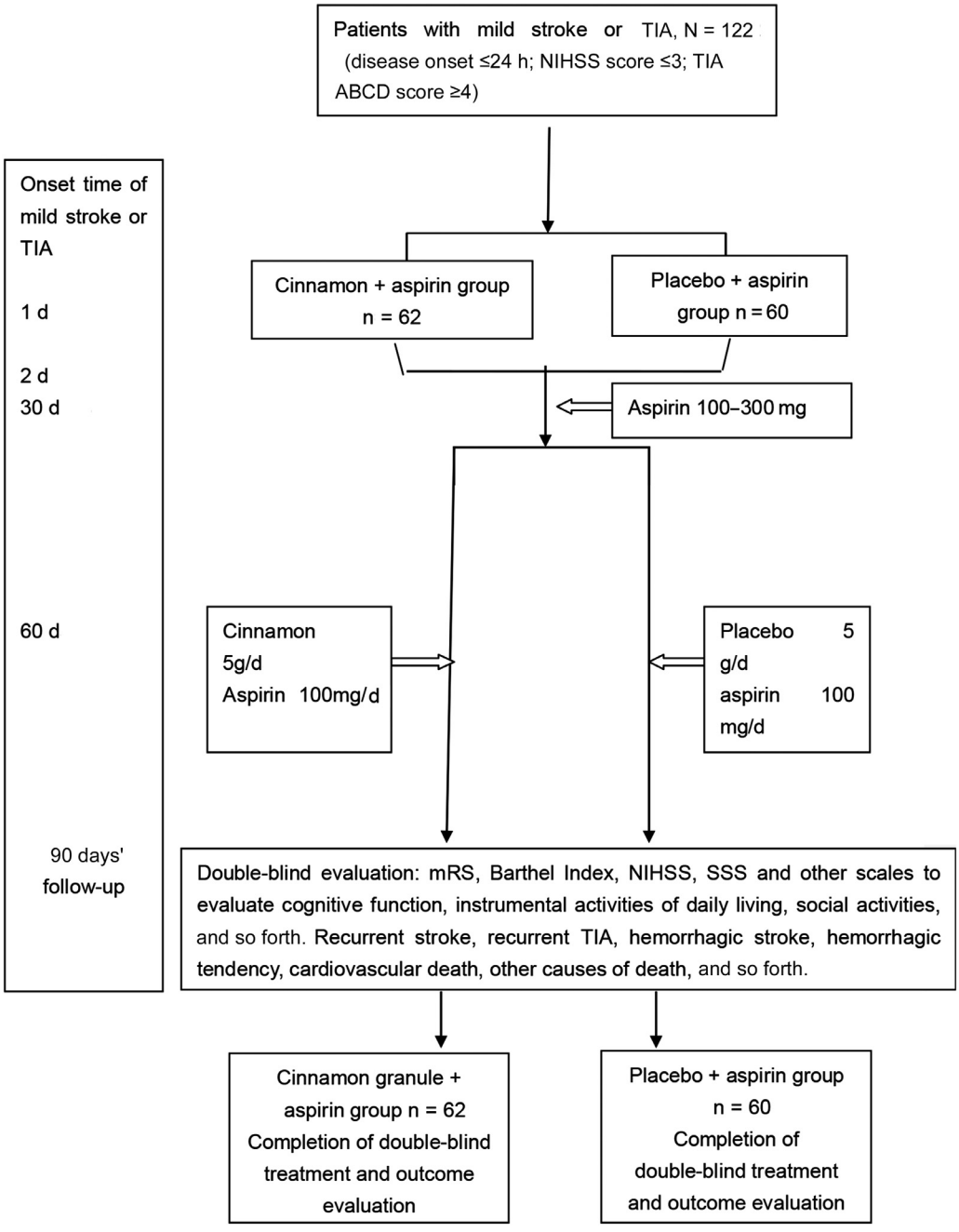

Figure I. Flowchart. mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; SSS = Scandinavian Stroke Scale; TIA = transient ischemic attack.

characteristics, including age and sex, were noted between the 2 groups (all, $P > 0.05$). The only exception was the frequency of diabetes, which was higher in the aspirin-placebo group (Table I).

Recurrent Stroke

The number of participants with recurrent stroke was 2 (3.2%) and 9 (15.0%) in the aspirin-cinnamon group and the aspirin-placebo group, respectively

Table I. Characteristics of the participants. Values are given as mean (SD) unless otherwise indicated.

Variable	Aspirin-Cinnamon (n = 62)	Aspirin-Placebo (n = 60)	*P*
Age, y	62.0 (3.5)	63.0 (3.2)	0.098
Female	21 (33.9%)	20 (33.3%)	0.950
Systolic pressure, mm Hg	150 (10)	151 (12)	0.626
Diastolic pressure, mm Hg	91 (9)	90 (7)	0.493
Body mass index, kg/m^2	25.0 (1.5)	25.0 (1.9)	>0.999
History			
Stroke	12 (19.4%)	12 (20.0%)	0.929
Transient ischemic attack	2 (3.2%)	2 (3.3%)	>0.999
Myocardial infarction	1 (1.6%)	1 (1.7%)	>0.999
Congestive heart failure	1 (1.6%)	0	>0.999
Atrial fibrillation/flutter	1 (1.6%)	1 (1.7%)	>0.999
Hypertension	40 (64.5%)	39 (62.9%)	0.955
Diabetes	13 (21.0%)	27 (45.0%)	0.005
Hypercholesterolemia	7 (11.3%)	8 (13.3%)	0.731
Pulmonary embolism	0	0	>0.999
Smoking history	26 (41.9%)	27 (45.0%)	0.733
Onset time			
12 h	30 (48.4%)	30 (50.0%)	0.859
≥12 h to ≤72 h	32 (51.6%)	30 (50.0%)	0.859
Transient ischemic attack	17 (27.4%)	16 (26.7%)	0.925
Mild stroke	45 (72.6%)	44 (73.3%)	0.753

($P = 0.002$). The 2 recurrent cases in the aspirin-cinnamon group were both TIA, but 2 recurrent cases in the aspirin-placebo group were ischemic stroke (3.3%), and 7 cases were TIA. No hemorrhagic stroke occurred.

Biochemical Indices

Compared with the aspirin-placebo group, levels in the aspirin-cinnamon group at 30, 60, and 90 days after treatment of triacylglycerol, LDL-C, fasting plasma glucose, glycosylated hemoglobin, Lp-PLA$_2$, and hs-CRP were significantly lower (all, $P < 0.05$), and levels of HDL-C were significantly higher (all, $P < 0.05$). No significant differences were found in total cholesterol levels between the 2 groups (all, $P > 0.05$) (Table II).

Comparison in Carotid Artery Examination After Treatment

Before treatment, there was no statistical significance in plaque stability or different degree of vascular stenosis between the aspirin-placebo group and the aspirin-cinnamon group. After treatment, compared with the aspirin-placebo group, rates in the aspirin-cinnamon group of unstable plaque (24.2% vs 53.3%; $P < 0.05$) and severe vascular stenosis (3.2% vs 23.3%; $P < 0.05$) were significantly lower, but the rate of mild vascular stenosis was significantly higher (56.5% vs 26.7%; $P < 0.05$) (Table III).

Safety and Adverse Reactions

One case of mild to moderate upper gastrointestinal bleeding in each group was observed after treatment. No significant abnormality was found in the results of blood routine, urine routine, stool routine, liver and kidney function, and electrolytes. There were no cases of rash, allergic reactions, or other serious adverse reactions, as well as no changes in vital signs.

DISCUSSION

Cinnamon can reduce levels of blood lipids, blood glucose, and inflammation,[13–17] which are risk factors for ischemic stroke and TIA. The aim of the

Table II. Comparison of the biochemical indices.

Group	Aspirin-Cinnamon (n = 62)				Aspirin-Placebo (n = 60)			
Time	24 h	30 d	60 d	90 d	24 h	30 d	60 d	90 d
TG, mmol/L	1.86 (0.72)	1.58 (0.45)*	1.53 (0.47)*	1.51 (0.49)*	1.96 (0.80)	1.90 (0.51)	1.85 (0.55)	1.84 (0.59)
TC, mmol/L	4.82 (1.93)	4.70 (1.35)	4.69 (1.25)	4.50 (2.40)	5.02 (1.62)	4.96 (2.08)	4.87 (0.55)	4.77 (1.43)
HDL-C, mmol/L	0.85 (0.40)	1.52 (0.53)*	1.77 (0.43)*	1.78 (0.64)*	0.92 (0.65)	1.03 (0.72)	1.23 (0.86)	1.26 (0.69)
LDL-C, mmol/L	4.63 (0.79)	4.28 (0.53)*	4.35 (0.37)*	4.30 (0.33)*	4.70 (0.51)	4.65 (0.67)	4.63 (0.41)	4.62 (0.61)
FPG, mmol/L	6.03 (1.84)	5.20 (0.51)*	5.22 (0.46)*	5.23 (0.32)*	6.05 (0.62)	6.12 (0.87)	6.20 (0.96)	5.98 (1.09)
HbA_{1c}, %	6.5 (0.9)	6.3 (0.6)*	6.2 (0.6)*	6.0 (0.5)*	6.5 (0.7)	6.7 (0.4)	6.6 (0.7)	6.5 (0.5)
Lp-PLA_2, μg/L	44.2 (4.7)	26.5 (1.6)*	20.9 (8.3)*	19.3 (5.3)*	43.8 (5.3)	35.8 (4.5)	28.7 (6.0)	23.3 (3.8)
hs-CRP, mg/L	6.63 (0.26)	2.95 (0.24)*	2.68 (0.19)*	2.51 (0.36)*	6.59 (0.24)	5.63 (0.38)	4.80 (0.76)	4.23 (0.41)

FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; hs-CRP = high-sensitivity C-reactive protein; Lp-PLA_2 = lipoprotein-associated phospholipase A_2; TC = total cholesterol; TG = triacylglycerol.
* $P < 0.05$ versus the aspirin-placebo group at the same time point.

Table III. Carotid ultrasound findings. Values are given as no. (%).

Group	Aspirin-Cinnamon (n = 62)		Aspirin-Placebo (n = 60)	
	Before	After	Before	After
Type of plaque				
Normal carotid	10 (16.1)	10 (16.1)	8 (13.3)	8 (13.3)
Stable	23 (37.1)	37 (59.7)	18 (30.0)	20 (33.3)
Unstable	29 (46.8)	15 (24.2)*	34 (56.7)	32 (53.3)
Degree of plaque				
No	10 (16.1)	10 (16.1)	5 (8.3)	5 (8.3)
Mild	21 (33.9)	35 (56.5)*	15 (25.0)	16 (26.7)
Moderate	19 (30.6)	17 (27.4)	26 (43.3)	24 (40.0)
Severe	12 (19.4)	2 (3.2)*	14 (23.3)	14 (23.3)

* $P < 0.05$ versus the aspirin-placebo group after treatment.

present pilot study was to observe the effect of aspirin combined with cinnamon in the treatment of patients with mild stroke or TIA. The results suggest that among patients with TIA or mild ischemic stroke, the combination of cinnamon and aspirin groups could be superior to aspirin groups alone for reducing the risk of 90-day recurrent stroke.

Ischemic mild stroke, also named subclinical stroke, is a special type of common ischemic stroke and is characterized by an National Institutes of Health Stroke Scale score <3.[22] Acute ischemic mild stroke and TIA are both acute nondisabling cerebrovascular events. Several investigations reported that the recurrence of events during the acute phase after mild stroke/TIA is high,[23,24] and many studies strongly suggest the necessity of intensive antiplatelet therapy after TIA and mild stroke.[25–28] Unfortunately, some patients are resistant to antiplatelet drugs and develop recurrent stroke despite secondary prevention.[11]

Several common clinical conditions mimic TIA, including seizures, migraine, peripheral vertigo, syncope,

and anxiety.[29] To minimize the possibility of including patients with symptoms similar to TIA, we excluded patients with isolated sensory symptoms, simple visual changes, simple dizziness/vertigo, and no evidence of acute infarction on baseline head CT imaging or MRI. In addition, the inclusion of patients with TIA was mainly limited to those with ABCD2 scores ≥4. The objective was to increase the likelihood of enlisting patients with a true diagnosis of TIA and to ensure that these enrolled patients had a higher risk of recurrent ischemic events. [30] The risk of subsequent stroke was indeed high in this population, indicating that our strategy was successful.

Cinnamon is the dry bark of *Cinnamomum Presl*, a *Lauraceae* plant, and is one of the most important and popular spices worldwide. It is commonly used in traditional Chinese medicine.[31] It can go to the kidney, spleen, heart, and liver meridians; it possesses the functions of tonifying fire and helping yang, eliminating cold to stop the pain, and activating blood to promote menstruation. Cinnamon mainly contains volatile oil, diterpene and its glycoside, flavanol and its polymer, flavonoids, and polyphenols. The most important active component is cinnamaldehyde in the form of *trans*-structure in the volatile oil of cinnamon. Geng et al[32] isolated and identified 41 different components from different cinnamon volatile oils, including cinnamaldehyde, cinnamic acid, and cinnamyl alcohol acetate. The composition proportion mainly depends on its growth stage and origin. Tung et al[33] extracted the volatile oil from the twigs of *Cinnamomum cassia* at different distillation periods, and the main components were eugenol, caryophyllene oxide, β-caryophyllene, γ-cineole, δ-piper chengolene, δ-junitol, L-borneol, and E-neroli tertiary alcohol. Cinnamon has been shown to decrease blood lipids, blood glucose, and inflammation,[13–17] which are risk factors for stroke.[7–10] In 2007, the hypoglycemic and hypolipidemic effects of cinnamaldehyde were reported for the first time in streptourease-induced male diabetic rats.[34] Stimulating receptors activated by peroxisome proliferators improves insulin resistance and lipid metabolism.[35]

Currently, cinnamon extract and its active ingredients can reduce the risk of cardiovascular and cerebrovascular disease, Alzheimer disease, and vascular dementia by controlling hyperglycemia, while inhibiting apolipoprotein and improving vascular complications.[36,37] The present pilot study showed that the aspirin-cinnamon combination decreased blood lipids, blood glucose, Lp-PLA_2, and hs-CRP and increased HDL-C compared with the aspirin-placebo group. Those changes could explain, at least in part, the observation that the rate of recurrent stroke was lower in the aspirin-cinnamon group compared with the aspirin-placebo group. Consequently, the severity of carotid artery atherosclerosis was decreased by aspirin-cinnamon compared with aspirin alone.

This pilot study has limitations. The sample size was small, and the follow-up was short. In addition, atherosclerosis and ischemic stroke are also associated with multiple factors, including hyperlipidemia, hyperglycemia, hyperhomocysteinemia, and inflammation. Therefore, it is of great clinical significance to discover more comprehensive measures to further reduce the recurrence rate of stroke. Nevertheless, this study paves the way for a multicenter randomized controlled trial.

CONCLUSIONS

Among patients with TIA or mild ischemic stroke, the combination of cinnamon and aspirin groups could be superior to aspirin groups alone for reducing the risk of 90-day recurrent stroke. Blood lipids, blood glucose, inflammation, and carotid atherosclerosis were decreased by aspirin-cinnamon compared with aspirin alone.

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Mr Z. Li and Ms L. Zhang contributed to the conception of the study and contributed significantly to analysis and manuscript preparation; Ms L. Zhang and Mr J. Liang performed the data analyses and wrote the manuscript; Mr Y. Wu performed diagnosis and treatment based on an overall analysis of the illness and the patients' condition, and administration of Chinese medicine; and Ms Y. Fan, Mr Z. He, and Mr P. He helped collect clinical data. All authors read and approved the manuscript.

DECLARATION OF INTEREST

None declared.

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