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Research Article

Preventive effects of ginseng against atherosclerosis and subsequent ischemic stroke: A randomized controlled trial (PEGASUS trial)

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ABSTRACT

Background: Korean Red Ginseng (KRG) extract has been shown to have beneficial effects in patients with atherosclerosis, suggesting that KRG extract may be effective in preventing subsequent ischemic stroke in patients with severe atherosclerosis.
Methods: This double-blind, placebo-controlled trial randomized patients with severe atherosclerosis in major intracranial arteries or extracranial carotid artery, to ginseng group and placebo group. They were given two 500-mg KRG tablets or identical placebo tablets twice daily for 12 months according to randomization. The primary endpoint was the composite of cerebral ischemic stroke and transient ischemic attack during 12 months after randomization. The secondary endpoints were change in volumetric blood flow of the intracranial vessels and the incidence of newly developed asymptomatic ischemic lesions. Any adverse events were monitored.
Results: Fifty-eight patients were randomized from June 2016 to June 2017, 29 to ginseng and 29 to placebo, and 52 (28 and 24, respectively) completed the study. One patient in the placebo group, but none in the ginseng group, experienced ischemic symptoms ($p = 0.46$). Changes in volumetric blood flow and the presence of ischemic brain lesions did not differ significantly in the two groups, and none of these patients experienced adverse drug reactions.
Conclusion: Ginseng was well tolerated by patients with severe atherosclerosis, with these patients showing good compliance with ginseng dosing. Ginseng did not show significant effects compared with placebo, although none of the ginseng-treated patients experienced ischemic events. Long-term studies in larger patient populations are required to test the effect of ginseng.

1. Introduction

Intracranial atherosclerotic disease (ICAD) is one of the common causes of ischemic stroke worldwide, accounting for 8–10 % of stroke in North America and 30–50 % of strokes in Asia [1]. Patients with significant hemodynamic stenosis have a high risk of stroke [2,3]. The 1- and 2-year rates of subsequent stroke in the territory of the stenotic artery were found to be 23 % and 25 %, respectively, in patients with severe stenosis of 70 % or more [4]. Therefore, there is a necessity to improve stroke management for the prevention of stroke recurrence in patients with severe ICAD.

Generally, the mechanisms of ischemic stroke in ICAD are artery to artery embolism, hypoperfusion, and branch atheromatous disease [1]. Considering the results in the medical arm of the SAMMPRIS trial, most common mechanism causing ischemic stroke due to severe ICAD is hypoperfusion [5]. Severe stenosis (≥ 70 %), along with stenosis progression, poorly controlled hypertension, and elevated low-density lipoprotein cholesterol levels, is

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known as a predictor of recurrence in patients with a history of stroke [4]. It is reported that the degree of collateral circulation development is also closely related to recurrent stroke [6–8]. The extracranial carotid atherosclerotic disease accounts for about 18–25 % of ischemic stroke [9]. Atherosclerosis in the extracranial carotid artery is highly concurrent with intracranial atherosclerosis [10]. These concurrent lesions are also significantly associated with ischemic stroke [10,11]. Medical management of extracranial carotid atherosclerosis is similar to that of ICAD but still challenging [9]. In addition, collaterals are also important to protect against ischemic stroke events in patients with severe extracranial carotid artery stenosis [12]. Therefore, stopping the progression of the atherosclerosis and enhancing collaterals would be important to prevent recurrent stroke downstream to the atherosclerotic stenosis.

Preventing subsequent stroke in patients with ICAD requires improvements in endothelial function [1]. Nitric oxide (NO) is an important cell signaling molecule produced by endothelial nitric oxide synthase (eNOS) that maintains vascular endothelial homeostasis [13]. Enhancing eNOS activation has been shown to increase collateral perfusion by dilating leptomeningeal anastomoses [13]. Cilostazol is a phosphodiesterase III inhibitor, increasing intracellular cAMP content and activating protein kinase A [14]. These effects result in antiplatelet aggregation and peripheral vasodilation. Cilostazol also activates eNOS and increases NO production [15]. In randomized controlled trials, cilostazol showed the results of the prevention of non-cardioembolic stroke recurrence and the progression of the symptomatic intracranial arterial stenosis; and it showed lower tendency of vascular events in stroke patients with intracranial arterial stenosis [16–19]. One study suggested that its beneficial effects were related with antiatherogenic and antiproliferative action in addition to antiplatelet effect [19].

The roots of the Korean Red Ginseng (KRG) plant, *Panax ginseng*, have been used in traditional Korean herbal medicine for thousands of years. The major bioactive components of the ginseng extracts are the ginsenosides, with Rb1, Rg1, and Rg3 being the major ginsenosides in KRG preparations [20]. The ginsenoside Rb1, one of the most abundant components of KRG preparations, was shown to have beneficial effects in patients with atherosclerosis, such as decreasing the inflammatory responses of endothelial cells, stabilizing plaque, attenuating plaque formation, and reducing blood lipid levels. Rg1 and Rg3 also have therapeutic effects on atherosclerosis by affecting macrophages and vascular smooth muscle cells. Most ginsenosides, including Rb1, trigger NO production [20–23].

In the literature, the safety of *P. ginseng* has been investigated in many clinical trials. One systematic review reported that treatment with *P. ginseng* preparations for 12 weeks to 3 years was safe, as shown by the frequency and intensity of adverse events [24]. A multicenter, randomized, placebo-controlled trial confirmed that 2 g/day KRG extract for 24 weeks was safe and tolerable in healthy adults [25]. Ginsenoside-Rd has shown encouraging neuroprotective efficacy in acute ischemic stroke patients [26]. In the phase II study, ginsenoside-Rd significantly improved the overall distribution of scores on the modified Rankin scale (mRS) at 90 days [27]. Few studies, however, have assessed the long-term safety of KRG extract, and none to date have evaluated its safety and efficacy in stroke patients with severe ICAD.

The beneficial effects of ginsenosides led us to hypothesize that ginseng could prevent the subsequent ischemic strokes by atherosclerotic plaque stabilization and the collateral flow improvement. The aims of this study are to determine whether ginseng is effective in the prevention of both atherosclerosis and subsequent ischemic stroke and whether ginseng is tolerable in high-risk patients with severe ICAD.

2. Materials and methods

2.1. Study population

The patients who visited our medical center and who had undergone cerebral catheter angiography were screened. Patients were included if they (1) were aged 20–80 years; (2) had occlusion or severe stenosis (≥70 %) of the extracranial carotid artery and major intracranial arteries (intracranial carotid artery, middle cerebral artery, anterior cerebral artery, intracranial vertebral, basilar, or posterior cerebral artery) as documented by cerebral catheter angiography [4,12]; (3) had any risk factor for stroke, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol drinking, or previous stroke history; (4) had no adverse reactions to the administration of ginseng; and (5) agreed to participate in the trial. Patients were excluded if they (1) did not agree to participate in the trial; (2) had any genetic cerebrovascular diseases; (3) had adverse reactions to contrast medium; (4) were pregnant or planning to be pregnant; (5) had a history of cardioembolic stroke; (6) had an emboligenic cardiac disease such as atrial fibrillation, valve disease, congestive heart failure, or recent myocardial infarction; (7) had a risk of stroke of other determined etiology according to the TOAST classification [28]; (8) had undergone any neurointervention procedure or surgery, such as intraarterial thrombolysis, angioplasty procedures, carotid endarterectomy, or bypass surgery; (9) had chronic kidney disease (GFR <30 mL/min); or (10) had severe hepatic dysfunction. All participants provided written informed consent.

2.2. Study design

This was a 12-month, randomized, double-blind, placebo-controlled, and single center trial. A study drug was a 500-mg KRG extract tablet manufactured by Korean Ginseng Corporation, and A placebo was fabricated in identical appearance of the KRG extract tablet [25]. Each subject was randomized in a 1:1 ratio to the ginseng or placebo group according to random permuted blocks. All investigators, participants, and their caregivers were blinded to group assignment throughout the study period. The study protocol conformed to Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by the institutional review board of our institution (No. 2015-1350). This trial was registered at ClinicalTrials.gov (No. NCT02796664) (Fig. 1).

2.3. MRI acquisition and quantitative analysis

Mgnetic resonance imaging (MRI) and quantitative magnetic resonance angiography were performed at randomization and at 1-year follow-up. All the participants underwent cardiac-gated phase-contrast-MRI on a 3 T scanner (Ingenia CX, Philips Healthcare). The quantitative cerebral flow was measured using noninvasive optimal vessel analysis (NOVA) software (VasSol, Chicago, IL, USA). Prior to measuring flow, time-of-flight images were obtained for the 3D modeling of the blood vessels. The standard points for the quantitative measurement of flow in the 11 vessels were set; these included the cervical segments of the internal carotid arteries, the intradural segments of the vertebral arteries, the basilar trunk, the A1 segments of both anterior cerebral arteries, the M1 trunks of both middle cerebral arteries, and the P2 segments of both posterior cerebral arteries (Fig. 2). Arteries in which it was difficult to quantitatively analyze flow due to severe stenosis or occlusion were regarded as having no flow.

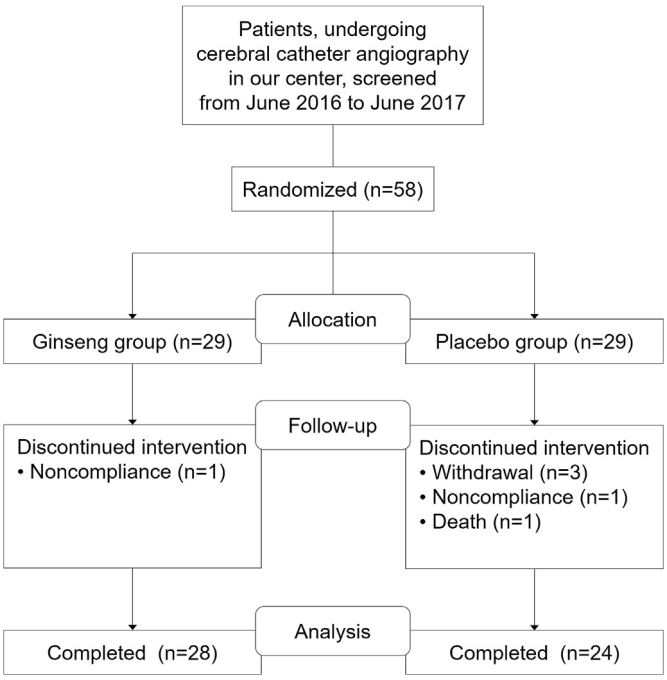

Fig. 1. Flow diagram of study patients.

To quantitatively analyze flow, the volumetric flow (mL/min) of the target arteries with occlusion or severe stenosis was measured, as was the sum of the arterial flow that may serve as collateral channels via either leptomeningeal flow or the circle of Willis. If patients had several steno-occlusive lesions, they were summed and analyzed. Measurements at baseline and 1-year follow-up were compared, with changes of <10 % considered insignificant, increases of ≥10 % considered 'improved', and decreases of ≥10 % considered 'aggravated'. The Fazekas scale was used to quantitate the amount of fluid attenuated inversion recovery hyperintense lesions in the periventricular and deep white matter [29]. The presence of ischemic lesions of the brain was also evaluated.

2.4. Study protocols and follow-up

All participants took two tablets twice daily for 12 months. The ginseng group took a total of 8 mg/day of the ginsenosides Rg1, Rb1, and Rg3, and the placebo group took a placebo, which was fabricated in the same appearance as the KRG extract tablet. Participants are checked for drug compliance and adverse events at 1, 3, 6, and 12 months after randomization by visiting the hospital or over the phone. Drug compliance was defined as the percentage of the actual dosing history with the prescribed drug regimen. Participants with poor drug compliance (<75 %) or who did not comply with the follow-up protocol were dropped out in the study.

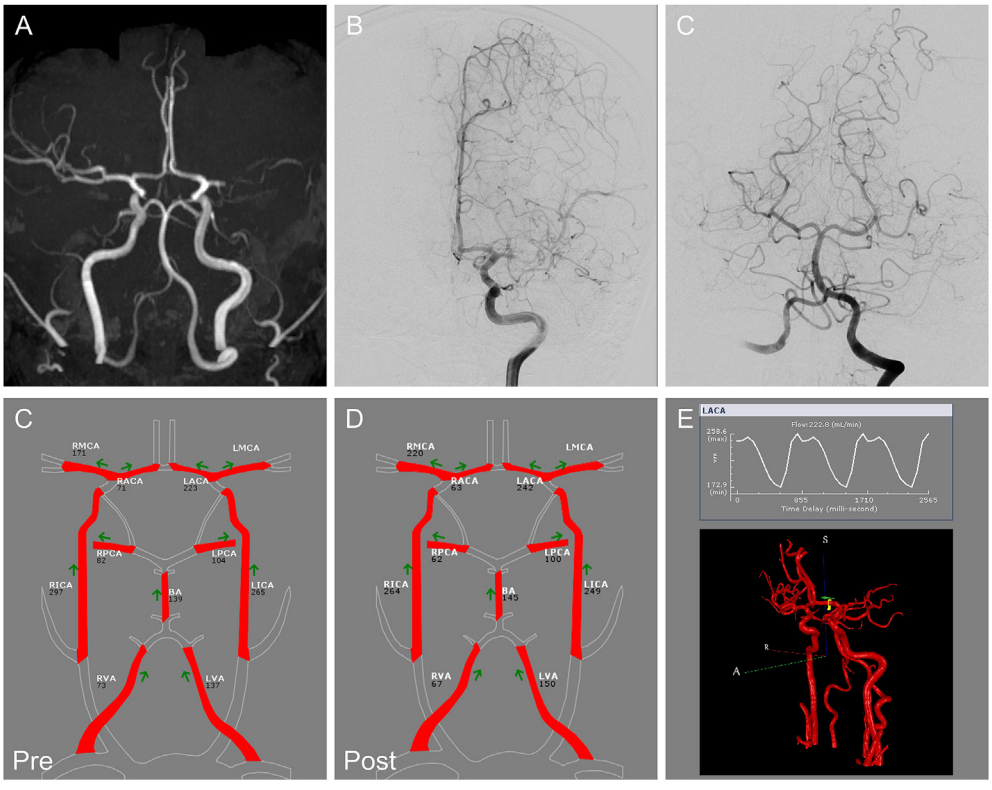

Fig. 2. Angiographic evaluation and quantitative flow analysis with noninvasive optimal vessel analysis (NOVA) software. (A) A representative patient (subject no. 4, ginseng group) showing total occlusion at the proximal M1 segment of the left middle cerebral artery on time-of-flight magnetic resonance angiography. (B, C) Digital subtraction angiography confirming the occlusion status and the leptomeningeal collaterals from the ipsilateral anterior and posterior cerebral arteries. The schematic vessel maps from the NOVA report show individual volumetric flow rate (mL /min) and direction of flow at baseline (D) and 1-year follow-up (E). The left middle cerebral artery flow was not large enough to be measured, increasing the flow of the ipsilateral anterior cerebral and posterior cerebral arteries contributing to the collateral. The sum of the collateral flow was slightly increased at follow-up. (F) Flow waveform and 3-dimensional tangentially oriented snapshot of the left A1 showing the collateral flow caused by the left M1 occlusion, as shown on the NOVA report.

The severity of adverse events and their relationship with ginseng or placebo were also evaluated. Adverse events were defined as undesirable and unintended signs, symptoms, or diseases that developed during the clinical trial regardless of a cause-and-effect relationship with the ginseng. Serious adverse events included permanent disability, death or life-threatening events.

2.5. Endpoints

The primary endpoints were the 1-year composite of cerebral ischemic stroke and transient ischemic attack downstream to an arterial lesion, and mRS at last follow-up. Primary endpoints were assessed at every follow-up visit. The secondary endpoints were the changes of volumetric blood flow in intracranial vessels, white matter hyperintensities, and parenchymal ischemic lesions. The secondary endpoints were assessed by quantitative magnetic resonance angiography with NOVA and by fluid attenuated inversion recovery in the brain MRI.

2.6. Sample size calculation and statistical analysis

Prior studies indicated that the stroke recurrence rate could be as high as 40 % [30,31], whereas the stroke recurrence rate during treatment was reported to be about 10 % [32]. To detect a ≥30 % difference in the primary outcome on equality tests, 29 subjects per group would be needed to reject the null hypothesis with a power of 0.8 and a two-sided alpha level of 0.05. The endpoints were analyzed in the per-protocol set. Categorical variables were analyzed using Chi-squared test or Fisher's exact tests. Continuous variables were analyzed using Student's t-tests or Wilcoxon rank-sum test. All statistical analyses were performed using SPSS (IBM Corp. version 21) and R (R Core Team. version 4.0.2) software, with a two-sided alpha of 0.05.

2.7. Role of the funding source

The funding source had no role in the design or performance of the study, in the analysis or interpretation of study results, and in the writing or approval of the manuscript.

3. Results

3.1. Study population and baseline characteristics

Between June 2016 and June 2017, 58 patients were randomized, 29 to the ginseng group and 29 to the placebo group, and 52 patients completed the study: 28 in the ginseng group and 24 in the placebo group. One patient in each group showed noncompliance with the study regimen. Of the four other non-completers in the placebo group, three withdrew consent, and one died, with a thorough investigation concluding that the death of this patient was unrelated to this study. Except for smoking, the baseline characteristics of the two groups did not differ significantly (Table 1).

Table 1
Baseline characteristics.

	Ginseng group (n = 28)	Placebo group (n = 24)	*P*-value
Age, years	63.4 ± 12.5	58.8 ± 13.6	0.21
Male sex	15 (53.6)	16 (66.7)	0.50
Risk factors			
Hypertension	20 (71.4)	14 (58.3)	0.49
Diabetes	10 (35.7)	4 (16.7)	0.22
Hyperlipidemia	23 (82.1)	15 (62.5)	0.20
Previous stroke history	13 (46.4)	9 (37.5)	0.71
Atrial fibrillation	0 (0)	0 (0)	
Myocardial infarction	0 (0)	0 (0)	
Angina pectoris	5 (17.9)	2 (8.3)	0.55
Alcohol drinking	6 (21.4)	9 (37.5)	0.33
Smoking	5 (17.9)	13 (54.2)	0.01
Medications			
Antiplatelet agents			0.78
Mono antiplatelet	8 (29.6)	9 (37.5)	
Dual antiplatelet	17 (63.0)	14 (58.3)	
Other antiplatelet	2 (7.4)	1 (4.2)	
Antihypertensive agent	21 (75.0)	13 (54.2)	0.20
Antidiabetic agent	9 (32.1)	3 (12.5)	0.18
Antihyperlipidemic agent	25 (89.3)	21 (87.5)	1.00
Baseline mRS			0.34
0	21 (75)	22 (91.7)	
1	5 (17.9)	1 (4.2)	
2	0	0	
3	2 (7.1)	1 (4.2)	
Drug compliance (%)	97.4 ± 4.7	97.8 ± 4.3	0.79

1) Data presented as mean ± standard deviation or n (%).
2) T-test or Wilcoxon rank-sum test for continuous measures.
3) Chi-squared test or Fisher's exact test for categorical variable.
4) Abbreviations: mRS, modified Rankin Scale.

Table 2
Clinical outcomes.

	Ginseng group (n = 28)	Placebo group (n = 24)	*P* value
Ischemic events			0.46
TIA	0	1 (4.2)	
Cerebral ischemic stroke	0	0	
Follow-up mRS			0.34
0	21 (75)	22 (91.7)	
1	5 (17.9)	1 (4.2)	
2	0	0	
3	2 (7.1)	1 (4.2)	

1) Data presented as mean ± standard deviation or n (%).
2) Chi-squared test or Fisher's exact test for categorical variable.
3) Abbreviations: TIA, transient ischemic attack; mRS, modified Rankin Scale.

3.2. Primary endpoint

The 1-year composite rate of cerebral ischemic stroke and transient ischemic attack downstream to an arterial lesion did not differ significantly in the two groups ($p = 0.46$) (Table 2). The only ischemic event observed in this study was a transient ischemic attack in one patient in the placebo group. That patient, with right middle cerebral artery stenosis, complained of a 15-min transient weakness on the left side. Diffusion-weighted MRI showed no evidence of a newly developed ischemic lesion. None of the patients in the ginseng group showed cerebral ischemic symptoms. Assessment of mRS at 1-year follow-up showed that 21 patients in the ginseng group were mRS 0, five were mRS 1, and two were mRS 3; in the placebo group, 22 patients were mRS 0, and one each was mRS 1 and mRS 3. There was no difference in mRS between baseline and follow-up in both groups.

3.3. Secondary endpoints

At baseline, there were no significant differences in mean flow amount of steno-occlusive lesions and collaterals between the ginseng and placebo groups (Table 3). At 1-year follow-up, the amount of steno-occlusive lesion flow was 6.8 % lower in the ginseng group (81.4 vs. 87.3 mL/min, $p = 0.16$) and 1.4 % higher in the placebo group (99.2 vs. 97.8 mL/min, $p = 0.81$). Collateral flow at 1-year was 1 % lower than at baseline in the ginseng group (295.1

Table 3
Lesion characteristics and quantitative flow analysis.

	Ginseng group (n = 28)	Placebo group (n = 24)	*P*-value
Location of steno-occlusions[§]			0.81
Extracranial ICA	5 (16.1)	6 (19.4)	
Intracranial ICA	5 (16.1)	4 (12.9)	
MCA, M1 segment	17 (54.8)	14 (45.2)	
ACA, A1 segment	0 (0)	2 (6.5)	
Basilar artery	3 (9.7)	3 (9.7)	
Vertebral artery	1 (3.2)	2 (6.5)	
Multiplicity	3 (10.7)	7 (29.2)	0.16
Lesion status			0.12
Stenosis	15 (48.4)	9 (29.0)	
Occlusion	16 (51.6)	22 (71.0)	
Steno-occlusion flow (mL/min)			0.60
Baseline	87.3 ± 113.7	97.8 ± 175.1	
Follow-up	81.4 ± 108.6	99.2 ± 162.8	
P-value[¶]	0.16	0.81	
Collateral flow (mL/min)			0.64
Baseline	298.0 ± 138.7	279.8 ± 141.1	
Follow-up	295.1 ± 134.9	275.1 ± 126.6	
P-value[¶]	0.77	0.68	
Steno-occlusion flow change			0.13
Improved	4 (14.3)	5 (20.8)	
No change	17 (60.7)	18 (75.0)	
Aggravated	7 (25.0)	1 (4.2)	
Collateral flow change			0.17
Improved	7 (25.0)	7 (29.2)	
No change	17 (60.7)	9 (37.5)	
Aggravated	4 (14.3)	8 (33.3)	

1) Data presented as mean ± standard deviation or n (%).
2) [§] The number of steno-occlusions was 33 in the ginseng group and 33 in the placebo group.
3) [¶] Comparing baseline to follow-up.
4) T-test or Wilcoxon rank-sum test for continuous measures.
5) Chi-squared test or Fisher's exact test for categorical variable.
6) Abbreviations: ICA, internal carotid artery; ECA, external carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

vs. 298 mL/min, $p = 0.77$) and 1.7 % lower in the placebo group (275.1 vs. 279.8, $p = 0.68$).

When analyzed by the patient, steno-occlusive lesions improved in four patients (14.3 %) in the ginseng group and in five (20.8 %) in the placebo group, and worsened in seven patients (25 %) in the ginseng group and one (4.2 %) in the placebo group. Collateral flow improved in seven patients each in the ginseng (25 %) and placebo (29.2 %) groups, and worsened in four patients (14.3 %) in the ginseng group and eight (33.3 %) in the placebo group. Categorical analyses, however, showed no significant differences between the two groups.

White matter hyperintensity and ischemic lesion were evaluated at 12 months. There were no significant between-group differences in the Fazekas scale and in the number of old ischemic lesions (Table 4). In two patients in the placebo group, the scale of the deep white matter hyperintensity increased by one step, and the rest remained unchanged from the baseline.

3.4. Drug compliance and adverse events

Drug compliance in both groups was 97.4 % in the ginseng group and 97.8 % in the placebo group, and there was no significant difference. One patient in the placebo group experienced a serious adverse event, which was femoral fracture and later died of sepsis. The investigators decided that this event was unrelated to the study. Two other adverse events, constipation and bruising, were reported in the placebo group and one, subjective hair loss, in the ginseng group.

4. Discussion

In this randomized, controlled, double-blind study, the effects of ginseng were evaluated on subsequent ischemic stroke prevention in patients with severe atherosclerosis in major intracranial arteries or extracranial carotid arteries. There was no significant difference in the occurrence of primary outcomes, which were defined as cerebral ischemic stroke or transient ischemic attack, between the ginseng and placebo groups. In addition, there was no difference between the two groups in the cerebral blood flow change or the occurrence of parenchymal lesions, which were considered as secondary outcomes. However, this study showed that ginseng was well tolerated with a good compliance, enabling study taking KRG extract daily for one year. Although most of the patients were taking antiplatelet agents, no serious adverse events such as hemorrhage were reported in the ginseng group.

Participants in this study, who had severe ICAD or extracranial carotid stenosis, were estimated to be at high risk of ischemic stroke [33,34]. In these patient group, restoring endothelial function, preventing inflammation, and inhibiting cholesterol deposition are needed to stabilize atherosclerosis and may lead to subsequent stroke prevention [35–37]. The ginsenosides in the KRG extract may have these potential protective roles against atherosclerosis [20]. Despite the promising hypothesis, this study did not prove any significant effect of the KRG tablet. The result is probably because the incidence of the primary outcome in this study group (1.9 %, 1/52) was not high enough to elicit significant results. The low incidence can be explained by the fact that most of the participants were relatively stable (mRS $\leq$ 3) and were

Table 4
Fazekas scale for white matter lesions and old ischemic lesions in FLAIR images.

	Baseline			Follow-up		
	Ginseng (n = 28)	Placebo (n = 24)	*P*-value	Ginseng (n = 28)	Placebo (n = 24)	*P*-value
PVWM			0.74			0.74
0	2 (7.1)	1 (4.2)		2 (7.1 %)	1 (4.2 %)	
1	9 (32.1)	11 (45.8)		9 (32.1 %)	11 (45.8 %)	
2	15 (53.6)	10 (41.7)		15 (53.6 %)	10 (41.7 %)	
3	2 (7.1)	2 (8.3)		2 (7.1 %)	2 (8.3 %)	
DWM			0.84			0.95
0	9 (32.1)	7 (29.2)		9 (32.1 %)	6 (25 %)	
1	15 (53.6)	15 (62.5)		15 (53.6 %)	15 (62.5 %)	
2	3 (10.7)	1 (4.2)		3 (10.7 %)	2 (8.3 %)	
3	1 (3.6)	1 (4.2)		1 (3.6 %)	1 (4.2 %)	
Ischemic lesion			0.23			0.23
Yes	22 (78.6)	15 (62.5)		22 (78.6 %)	15 (62.5 %)	
No	6 (21.4)	9 (37.5)		6 (21.4 %)	9 (37.5 %)	

1) Data presented as n (%).
2) Chi-squared test or Fisher's exact test for categorical variable.
3) Abbreviations: PVWM, periventricular white matter; DWM, deep white matter.

receiving strict medical therapy. Current therapeutic approaches in patients with ICAD highlight stroke risk factor management and best medical therapy [38]. Considering the baseline characteristics, the study participants were well-controlled in stroke risk factor management. Furthermore, most participants administrated statin. The impacts of statin therapy on atherosclerotic plaque include plaque regression, plaque stabilization, and reduction of inflammation in plaque [39]. Therefore, to detect small differences in the well-treated study population, a larger number of participants or longer study periods may be necessary to assess the beneficial effects of KRG extract.

Another effect of ginseng evaluated in this study was the capacity to increase collateral flows. The collateral flows compensate for hypoperfusion via the circle of Willis or leptomeningeal anastomoses [40,41]. Ginsenosides can enhance NO production by various pathways in endothelial cells, including the activation of eNOS [20]. Enhancing eNOS activation increased collateral perfusion by dilating leptomeningeal anastomoses [13]. Quantitative magnetic resonance angiography with NOVA is a useful tool for understanding cerebral hemodynamics and evaluating the changes in cerebral blood flow [42,43]. Although we hypothesized that ginseng would increase collateral flow through the circle of Willis or leptomeningeal anastomoses in patients with severe intracranial stenosis, the flow analysis showed no significant differences. The study period of one year may be short to lead significant hemodynamic changes, and there may be a limitation to detect subtle flow changes considering the margin of error of NOVA.

This study had several limitations. The lack of previous related studies made it difficult to determine the number of patients in the study population. The 1-year follow-up period was relatively short to determine clinical results, considering that atherosclerosis is a long-term chronic disease. An extended study period is needed to determine the long-term safety of ginseng administration. There is a lack of knowledge of the proper dose of KRG extract tablet in stroke patients for the prevention of stroke recurrence. Finally, this study did not measure levels of NO, anti-inflammatory activity, and antiplatelet activity in these patients due to the absence of surrogate biochemical markers. Studies of the pharmacological actions of ginsenosides and their potential interactions with different targets are required to further understand the pharmacokinetics and efficacy of the key components of KRG extracts. Both in vitro and in vivo studies including randomized controlled clinical trials are necessary to enhance in-depth knowledge of ginseng and its practical applications.

5. Conclusion and Recommendation

To our knowledge, this was the first randomized controlled trial assessing KRG extracts for stroke prevention. The outcomes were similar in the ginseng and placebo groups. The patients at high risk for stroke showed good compliance with ginseng dosing, without serious adverse effects. For future studies, several things are recommended. Firstly, the number of the study population should be increased for statistical power, and the study period should be extended considering the chronic process of atherosclerosis. Secondly, long-term safety should be studied in this high-risk stroke patients considering polypharmacy. Lastly, the dose of KRG extract tablet should be optimized for stroke patients by further pharmacokinetic or bioavailability studies.

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Declaration of competing interest

The authors declare no conflicts of interest.

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