Chinese Journal of Physiology 60(3): 158-165, 2017
DOI: 10.4077/CJP.2017.BAF452

A Randomized, Double-Blind Clinical Study on Blood Pressure Reduction and Blood Lipid Profile Amelioration on Treatment with Ankascin 568

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Abstract

Hypertension and cardiovascular complications are the leading causes of death worldwide. Antihypertensive drugs often cause various side effects, and improper use of antihypertensive medications can result in irreparable damage. Edible fungi of the *Monascus* species have been used as traditional Chinese medicines in Southeast Asia for several centuries. The fermented products of *Monascus purpureus* NTU 568 (ANKASCIN 568) possess a number of functional secondary metabolites including the anti-inflammatory pigments monascin (MS) and ankaflavin (AK). In this study, a double-blind, placebo-controlled clinical trial was performed in which patients with mild to moderate hypertension were randomly assigned to receive placebo or two 500-mg capsules of Ankascin 568 for 8 weeks. The effects of this treatment on the regulation of blood pressure (BP) were then examined. The results showed that systolic blood pressure (SBP) decreased from 141.6 ± 12.0 to 133.9 ± 14.4 mmHg ($P < 0.05$), and diastolic blood pressure (DBP) decreased from 91.7 ± 8.1 to 84.8 ± 7.4 mmHg ($P < 0.05$). Moreover, Ankascin 568 treatment effectively reduced serum triglycerides and total cholesterol (TC), increased high-density lipoprotein cholesterol (HDL-C), and reduced low-density lipoprotein cholesterol (LDL-C) levels, thereby improving the serum lipid profile. Additionally, administration of Ankascin 568 did not cause significant rhabdomyolysis nor impaired the metabolic or physiological functions of the liver or kidney. In conclusion, patients administered Ankascin 568 for 8 weeks exhibited significant in reduction of SBP, serum TC and LDL-C levels, which should contribute to better cardiovascular health.

Key Words: ankaflavin, Ankascin 568, hypertension, monascin, *Monascus purpureus* NTU 568

Introduction

Hypertension is a risk factor for metabolic syndromes and cardiovascular diseases. Many epidemiological studies have demonstrated that there is a relationship between increases in blood pressure (BP) and cardiovascular diseases (23). Worldwide prevalence estimates for hypertension may be as

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Received: June 20, 2016; Revised: October 5, 2016; Accepted: November 7, 2016.
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high as one billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension (6). The prevention and management of hypertension have been major public health challenges. Many epidemiological and experimental studies have demonstrated that metabolic syndrome affects almost half of adult population over 50-60 years of age (4, 20-22). An excess of body fat, especially when it is localized in the abdominal region, leads to an imbalance of the metabolism of fats and sugars that induces hyperinsulinemia (15, 25). In addition to strategies based on changing lifestyle, natural substances are frequently utilized with beneficial properties (3, 9, 27, 28). A central tenet of the lipid hypothesis is that elevated plasma cholesterol levels are associated with increased chances of developing atherosclerosis or coronary heart disease (CHD). Hypertension, or high BP, is common in older adults and represents a primary risk factor for cardiovascular diseases, including cerebrovascular stroke (25). In particular, studies have shown that increased systolic BP (SBP) is more deleterious to health than increased diastolic BP (DBP). Indeed, isolated systolic hypertension (ISH) is a major risk factor for stroke in the elderly, and the incidence of cardiovascular events may be effectively reduced by treating ISH [#]. Hypertension and coronary artery disease may be treated with amlodipine, a long-acting calcium channel blocker, which belongs to the dihydropyridine (DHP) class and the statin group of drugs (8).

For several centuries, *Monascus (M.)* species have been used as traditional food fungi in Southeast Asia. Interestingly, the secondary metabolite monacolin K has been proven to inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway (7). Accordingly, red mold rice (RMR) has gradually gained popularity as a functional organic food for the treatment of hyperlipidemia (19). *Dioscorea* is a traditional Chinese herb and an ideal substrate for *M.* fermentation. Furthermore, red mold dioscorea (RMD) has been reported to be a stronger HMG-CoA reductase inhibitor with higher hypocholesterolemic activity than RMR (14). In our previous study, we showed that *M. purpureus* NTU 568-fermented products contained monascin (MS) and ankaflavin (AK), which possess anti-inflammatory ability (13). These products include the yellow pigments MS and AK, the orange pigments monascorubrin and rubropunctanin, and the red pigments monascorubramine and rubropuctamine (26). MS and AK have numerous biological effects such as inhibition of non-alcoholic fatty liver, amelioration of pancreatic damage and hyperglycemia in diabetes, and antioxidant and anti-inflammatory effects (11). We further demonstrated the effects of a combination of *M.*-fermented products and lovastatin on increased risk of rhabdomyolysis in hyperlipidemic hamsters (4). Previous animal experiments have revealed that MS and AK can reduce the concentrations of serum triglyceride and hepatic cholesterol (17, 18). In addition, MS and AK can inhibit the activity and expression of inflammatory factor tumor necrosis factor alpha (TNF-α) and endothelial nitric oxide synthase (eNOS), thereby reducing the formation of nitric oxide (12). Analysis of the mechanisms of action of MS and AK has shown that these compounds are peroxisome proliferator-activated receptor (PPAR)-γ agonists that subsequently initiate the transcription of downstream genes (10, 11, 15). Based on the reported health benefits of MS and AK as the major constituents of Ankascin 568, we evaluated in the current clinical trial the effects of Ankascin 568 on hypertension.

Materials and Methods

Materials

The study material consisted of an Ankascin 568 product fermented by *M. purpureus* NTU 568, which was obtained from SunWay Biotech., Co., LTD. (Taipei, Taiwan). Total of 3 mg of MS and 1.5 mg AK is contained in one capsule. Material made of maltodextrin was used as the placebo.

Subjects

The clinical study was conducted from January 2012 to December 2014 at Taipei City Hospital, Renai Branch, Taipei, following acquisition of approval of the study by the Institutional Review Board (IRB) of Taipei City Hospital (TCHIRB No: 1001013). The inclusion criteria for selection of participants for the study were as follows: age 20–65 years, sound mind and ablility to communicate, clinical diagnosis of essential hypertension, SBP or DBP range of 130–179 mmHg or 85–109 mmHg, respectively, no antihypertension medications within 2 months before participation in the study, and no other serious medical problems, including cancer, heart failure, liver cirrhosis, severe liver, kidney dysfunction and other chronic diseases. The exclusion criteria were as follows: moderate or severe hepatic, renal dysfunction, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels more than three times higher than the normal level, diagnosed with hepatic

[#] World Health Report 2002. Reducing risks, promoting healthy life. World Health Organization, Methods Summaries for Risk Factors assessed in Chapter 4. pp. 47-97, 2002.

cirrhosis, or creatinine level higher than 1.5 mg/dl, administration of antihypertension drugs, statins, or red yeast rice as a Chinese herbal medicine, surgery within 1 month prior to starting the study, pregnancy or breast-feeding, drug allergies, other serious diseases, major damage, or organ impairment, known to have allergies to a component of the test product, or any medical or surgical condition that could lead to inconsistent adherence to the study protocol.

Based on these inclusion and exclusion criteria, 60 patients were screened through a series of stages. In the first stage of screening, healthy patients were screened for essential hypertension, and patients with SBP or DBP in the range of 130–179 or 85–109 mmHg, respectively, were included. Of these, 39 patients withdrew from the trial because of the development of some illness; thus, 21 patients completed this study. Written informed consent was obtained from all enrolled patients. The treatment and placebo groups included 11 and 10 patients, respectively.

During the Ankascin 568 treatment, patients with hypertension were not allowed to use depressor drugs unless their BP was suddenly elevated, and those with CHD were also not allowed to use analgesics unless they were experiencing symptoms of angina pectoris. All patients were on a low-cholesterol diet throughout the entire treatment period. Carotid ultrasound examinations and plasma biochemical assays were performed at the end of the treatment.

Randomization, Treatment and Follow-Up

The participants were visited by the investigators and were informed about the rationale and main aims of the study. A written informed consent was obtained from the participants. Block randomization was used for treatment allocation. The participants were randomly assigned to two groups. One group received Ankascin 568 standard (the treatment group), and the other group received placebo (control group). The study was double-blind. The participants were also advised not to use hypertension drug regimen during the study.

Endpoints

The designated study endpoint of both treatment groups was the incidence of adverse events. Additional safety endpoints included serious adverse events, adverse events leading to the discontinuation of the study health food (for patients in the Ankascin 568 group), and abnormalities in creatine kinase levels, liver and kidney functions, and electrolyte imbalance. A prespecified exploratory outcome was defined as the incidence of confirmed cardiovascular events, which were ascertained over the course of the study.

Table 1. Baseline characteristics of patients

Group	Placebo	Treatment
Male	4	6
Female	6	5
Age (years)	47.4 ± 9.2	51.5 ± 8.4
SBP (mmHg)	138.5 ± 9.6	141.6 ± 12.0
DBP (mmHg)	86.7 ± 7.5	91.7 ± 8.1

Student's *t*-tests were used. Data are expressed as means ± SD; placebo, n = 10; treatment, n = 11.

Statistical Analysis

Data are expressed as the mean ± standard deviation (SD). The statistical significance of the biochemical analyses was determined using one-way analysis of variance (ANOVA) with the general linear model procedure of the statistical package for the social sciences (SPSS 16.0) software (SPSS Institute, Inc., Chicago, IL, USA). This was followed by ANOVA with paired *t*-tests to evaluate the differences before and after sample and placebo administration, whereas Student's *t*-test was used to compare difference between the treatment and placebo groups ($P < 0.05$).

Results

Anthropometric Measurements

The body weight, body mass index (BMI), waistline and BP of the participants in this trial increased normally with age (Table 1). In the placebo group, 10 subjects included 4 male and 6 female, the 11 subjects in the treatment group included 6 male and 5 female. There were no differences in physical examination between the groups during the course of the study. In addition, the appearance and health conditions of the participants were maintained.

Effects of Ankascin 568 on BP Index

Following treatment with the same sample dosages, the BP of the study group was measured once every 2 weeks over a span of 10 weeks. The SBP values of the participants in the treatment and placebo groups during the 10 weeks are shown in Fig. 1A. The results demonstrated that there were significant decreases in SBP in both groups. Changes in the DBP in the treatment and placebo groups during the test are

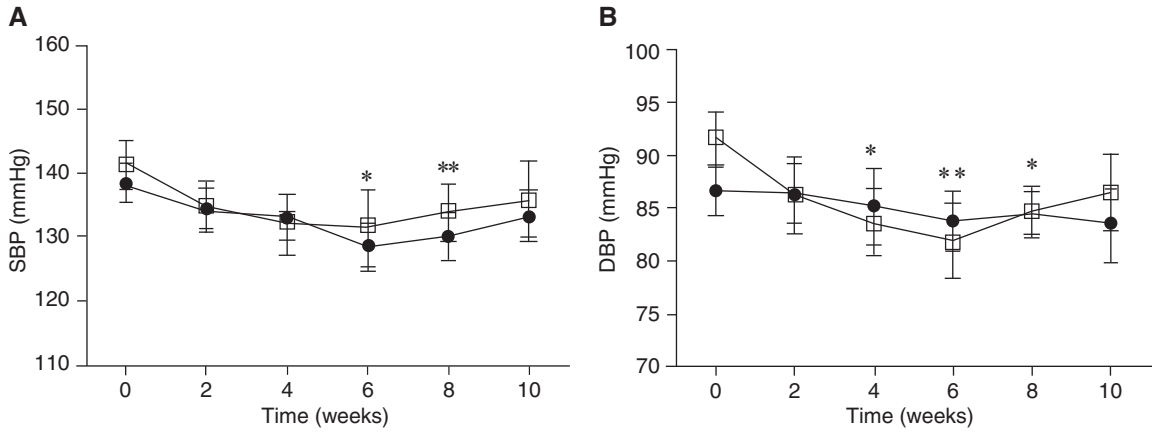

Fig. 1. Effects of 8-week administration of Ankascin 568 or placebo on (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) in participants. Data are expressed as mean ± SEM (standard error of the mean); placebo [●], n = 10; treatment [□], n = 11. Student's *t*-tests were used for comparisons within groups. $*P < 0.05$ and $**P < 0.01$ versus the baseline in the same group.

shown in Fig. 1B. In the treatment group, the effects of Ankascin 568 on DBP began to show at week 4, with the effects peaking at week 6 and the effects were maintained until the end of week 8. However, the effects disappeared at 2 weeks after stopping Ankascin 568 therapy.

Evaluation of differences in the treatment and placebo groups showed no significant changes in DBP, suggesting the occurrence of the placebo effect. The use of placebo in clinical trials has been vigorously debated. Placebo control may be useful in disease states, such as hypertension as defined by the sixth report of the joint national committee on detection, evaluation and treatment of high BP, in which response rates for placebo are high or close to response rates for effective therapies, or when established interventions have significant adverse effects (2).

Effects of Ankascin 568 on Blood Lipid Levels

The total triglyceride (TG) content is an important diagnostic factor in metabolic syndrome. TG content greater than 200 mg/dl was defined as hyperlipidemia, and that greater than 150 mg/dl was defined as exceeding the standard of metabolic syndrome. Serum TG levels in the treatment and placebo groups were compared at weeks 0, 4 and 8 (Fig. 2A); the results revealed that there were no differences between the groups. There were no significant differences in TG levels between week 0 (baseline) and week 8 in the placebo group. However, in the treatment group, the mean of TGs decreased over time, the results being 110.5 ± 47.4, 81.5 ± 35.9 and 85.5 ± 40.7 mg/dl in weeks 0, 4 and 8, respectively), with significant differences compared with the baseline levels at weeks 4 and 8 ($P < 0.01$).

Normal total cholesterol (TC) levels are between 130 and 200 mg/dl in humans; high or low TC levels can cause adverse effects on health. Moreover, abnormalities in TC levels can be associated with blood cholesterol levels and cardiovascular disease. Notably, there were no significant differences in TC levels at week 0 between the placebo and treatment groups (Fig. 2B). The mean TC levels in the placebo group at weeks 0, 4 and 8 were 204.5 ± 26.6, 176 ± 21.4 and 189.3 ± 27.3 mg/dl, respectively, whereas those in the treatment group were 196 ± 42.7, 166.4 ± 36.7 and 169.3 ± 37.0 mg/dl, respectively. For both groups, the TC levels were significantly lower after 8 weeks of treatment compared with that at the baseline ($P < 0.05$). However, there were no differences between the treatment and placebo groups in each week; this may be because of the large standard deviations among the groups. Interestingly, however, serum TC levels were significantly decreased in the treatment group compared with that in the placebo group.

Effects of Ankascin 568 on Serum Lipid Profiles

Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels can be used to determine the lipid metabolic status; in humans, the standards are less than 130 and greater than 40 mg/dl, respectively. Extremely low HDL-C or high LDL-C levels are thought to have a considerable impact on cardiovascular health. In this study, the LDL-C level in the placebo group was not significantly different from that in the treatment group at week 0 (Fig. 2C). However, the LDL-C levels were significantly different in the treatment group at weeks 4 and 8 compared with that of the baseline ($P < 0.001$ and $P <$

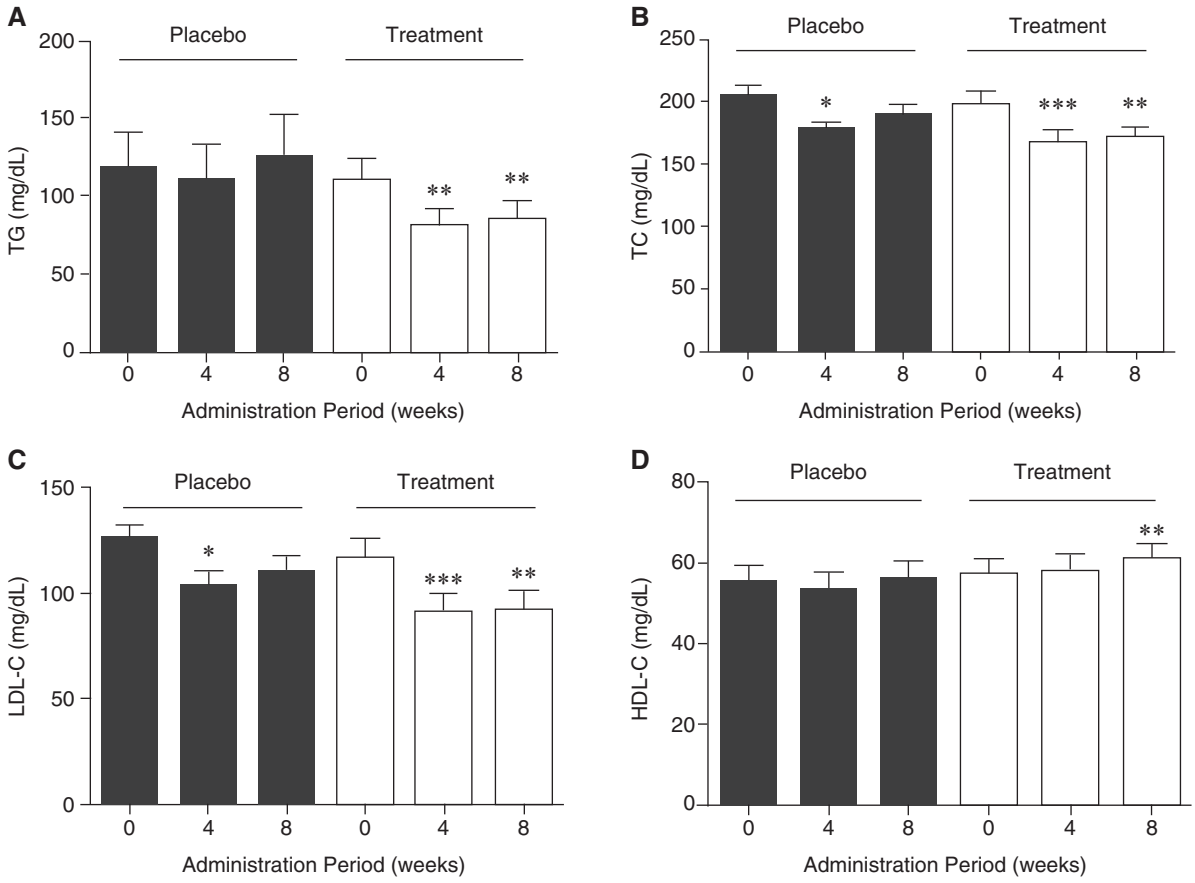

Fig. 2. Effects of administration of Ankascin 568 product or placebo on (A) triglycerol (TG), (B) total cholesterol (TC), (C) LDL-C and (D) high-density lipoprotein cholesterol (HDL-C) levels in participants. Placebo, n = 10; treatment, n = 11. $^{**}P < 0.01$ versus the baseline within the same group.

0.01, respectively). In the placebo group, a significant difference was only observed between week 4 and the baseline ($P < 0.05$). There were no differences between the groups at any time point. The reduction of LDL-C within the treatment group was significantly greater than that in the placebo group.

Changes in HDL-C concentrations are shown in Fig. 2D. Notably, there were no differences in the HDL-C levels between the treatment and placebo groups at any time point. In the placebo group, the HDL-C levels were not significantly altered over time. However, in the treatment group, significant differences were noted at week 8 compared with that at the baseline ($P < 0.01$).

These statistical results indicated that HDL-C and LDL-C levels were significantly improved in the treatment group over time. However, there were no significant differences between the groups; therefore, although Ankascin 568 treatment may improve blood lipid factors, the data do not support that this compound can improve blood lipid metabolism in patients.

Safety Assessment of the Effects of Ankascin 568 on Liver Functions

Citrinin is a toxic secondary metabolite produced by *M. purpureus* during the fermentation process. Moreover, citrinin is a mycotoxin that inhibits some gram-positive bacteria and prevents the growth of spoilage bacteria. Citrinin has been shown to cause damage to the liver, kidney and other organs in animals and humans (1).

To assess the safety of the products, we assayed the serum levels of hepatic AST, ALT, gamma-glutamyl transpeptidase (γ-GTP), total bilirubin, and total protein, including albumin and globulin. There were no significant differences in AST, ALT, γ-GTP, total bilirubin and total protein levels between the placebo and treatment groups (Table 2). Therefore, Ankascin 568 did not affect liver secretion or maintenance of hepatic protein levels in the serum.

Safety Assessment of the Effects of Ankascin 568 on Serum Thyroid Functions and Creatine Phosphokinase Levels

Table 2. Effects of 8-week administration of Ankascin 568 or placebo on liver functions

Group	Placebo			Treatment		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
AST (U/L)	21.2 ± 5.5	23.3 ± 6.3*	23.5 ± 7.2	23.1 ± 6.2	23.1 ± 6.9	24.9 ± 6.4
ALT (U/L)	24.5 ± 10.7	27.1 ± 10.8	30.4 ± 11.8*	24.4 ± 10.5	27.6 ± 15.0	28.8 ± 17.4
γ-GTP (U/L)	26.9 ± 13.1	28.0 ± 12.3	26.4 ± 12.3	24.9 ± 11.9	23.9 ± 11.0	24.7 ± 12.8
Total bilirubin (mg/dl)	0.7 ± 0.3	0.7 ± 0.3	0.8 ± 0.4	0.7 ± 0.3	0.7 ± 0.4	0.7 ± 0.2
Total protein (g/dl)	7.4 ± 0.3	7.4 ± 0.4	7.5 ± 0.4	7.4 ± 0.5	7.3 ± 0.5	7.5 ± 0.5
Albumin (g/dl)	4.6 ± 0.2	4.7 ± 0.3	4.7 ± 0.2	4.5 ± 0.2	4.5 ± 0.3	4.6 ± 0.3
Globulin (g/dl)	2.8 ± 0.3	2.8 ± 0.2	2.8 ± 0.3	2.9 ± 0.4	2.8 ± 0.4	2.9 ± 0.5
A/G	1.61 ± 0.3	1.7 ± 0.1	1.7 ± 0.2	1.6 ± 0.3	1.7 ± 0.3	1.6 ± 0.3

Abbreviations used: AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; A/G: albumin/globulin ratio; U/L: enzyme activity units per liter. Student's *t*-test was used in the statistical analysis. *Significantly different ($P < 0.05$) versus baseline in each group. Data are expressed as the mean ± SD.

Table 3. Effects of administration of Ankascin 568 or placebo on kidney and electrolyte balance

Group	Placebo			Treatment		
	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
BUN (mg/dl)	12.0 ± 2.2	11.8 ± 2.1	12.7 ± 1.9	13.7 ± 3.83	12.1 ± 3.0	13.0 ± 3.8
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.15	0.9 ± 0.2	0.9 ± 0.2
Uric acid (mg/dl)	6.0 ± 1.6	6.0 ± 1.5	5.9 ± 1.3	5.8 ± 0.95	5.6 ± 1.1	5.5 ± 1.2
Calcium (mEq/l)	9.5 ± 0.2	9.6 ± 0.2	9.5 ± 0.3	9.6 ± 0.35	9.3 ± 0.3*	9.4 ± 0.4
Sodium (mEq/l)	141.7 ± 1.2	141.4 ± 1.8	141.1 ± 1.7	142.1 ± 1.97	142.0 ± 2.1	141.8 ± 1.9
Potassium (mEq/l)	4.1 ± 0.3	4.1 ± 0.4	4.3 ± 0.3*	4.0 ± 0.2	4.1 ± 0.4	4.2 ± 0.2*
Chloride (mEq/l)	102.0 ± 1.8	102.1 ± 1.9	102.7 ± 1.1	103.5 ± 3.2	103.1 ± 3.0	103.9 ± 4.0

BUN: blood urea nitrogen. Student's *t*-test was used. *Significantly different ($P < 0.05$) versus baseline in each group. Data are expressed as the mean ± SD.

Blood urea nitrogen (BUN) is a protein metabolite, and high concentrations of BUN are indicative of a weak renal excretory mechanism. In this study, BUN, creatinine and uric acid levels were not significantly different between groups ($P > 0.05$) (Table 3). Furthermore, there were no significant differences in serum electrolytes, including calcium, sodium, potassium, and chloride ions, between the groups ($P > 0.05$) (Table 3). These results implied that Ankascin 568 did not have significant effects on renal metabolism or physiological functions. Therefore, Ankascin 568 did not relieve increases in DBP by altering the electrolyte contents of the body.

Discussion

RMR has been used as a dietary supplement for several centuries in Eastern Asia, particularly in China and Japan. However, healthcare professionals have become skeptical about dietary supplements and herbal products because of a lack of studies and safety regulations in the era of evidence-based medicine. Thus, it is important that healthcare practitioners become aware of the advantages of prescribing herbal products that could be used instead of biomedical drugs. RMR has also become a popular functional food for the management of hypolipidemia because monacolin K, a secondary metabolite found in RMR, inhibits HMG-CoA reductase in the cholesterol biosynthesis pathway (7).

In this clinical trial, we aimed to determine the effects of Ankascin 568 capsules on BP. In a previous study, Ankascin 568 was shown to reduce BP in SHR rats (5). This was a placebo-controlled, double-blind study and was expected to exclude the possibility of placebo effects or errors caused by laboratory

personnel biases (2). In this study, BP was recorded by nurse under standard protocols when participants returned to the hospital once every 2 weeks. Patients were administered Ankascin 568 for 8 weeks, followed by a 2-week washout and BP was recorded and tracked to determine the occurrence of sequelae. The composition of incubation substrates is critical for the growth of *M.* spp. and the production of secondary metabolites, including MS and AK, which are major inhibitory neurotransmitters in the sympathetic nervous system, and play important roles in cardiovascular functions. Thus, these compounds may contribute to the antihypertensive effects of Ankascin 568. However, other *M.* fermented metabolites are also likely to be involved in mediating these antihypertensive effects.

A previous study showed synergistic anti-atherogenic effects of lipid-lowering therapy with statin drugs, such as pravastatin, in combination with calcium antagonists (14). This combination therapy more effectively retarded the progression of stenosis and reduced the number of new lesions compared with statin therapy alone. Thus, the combination of calcium antagonists with statins may represent an alternative approach for the prevention and regression of atherosclerosis.

Atherogenic modification of lipoproteins in the form of small dense LDL does not appear to be affected by amlodipine or amlodipine-RMD cotreatment because the LDL particle size remains unchanged in both cases (27). In this study, we investigated the effects of Ankascin 568 on the major parameters responsible for the atherogenic modification of LDL. Ankascin 568 therapy had beneficial effects on all parameters except LDL levels, which remained unchanged. Indeed, of all the known LDL modifications, amlodipine affects only the sialic acid content (24). In conclusion, patients administered two 500-mg capsules of Ankascin 568 for 8 weeks exhibited significant reductions in the progression of existing hypertension and in serum TC and LDL-C levels.

Conflict of Interest

The authors declared no conflicts of interest.

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