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Research Article

A Randomized, Double-Blind, Parallel Group Clinical Study to Evaluate the Efficacy and Safety of UO ABG 01 in the Management of Borderline Cardiovascular Risk Factors

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Abstract

The growing incidence of cardiovascular disease presents a substantial risk to developed and developing countries alike, thus necessitating prompt intervention. This clinical study was carried out to investigate the efficacy and safety of UO ABG 01, an aged black garlic extract containing 0.5% SAC and 2% polyphenol in the management of cardiovascular risk factors. In this randomized, double-blind, placebo-controlled study, 56 subjects at risk for cardiovascular factors were enrolled. Participants received either UO ABG 01 or placebo for 84 days. Serum triglycerides, serum HDL cholesterol, serum LDL cholesterol and total cholesterol were measured as the primary efficacy endpoints and fasting blood glucose and blood pressure were measured as secondary endpoints. UO ABG 01 supplementation significantly ($p<0.05$) reduced with a percentage reduction of 19.93% in serum triglycerides, 15.48% in serum LDL cholesterol, 13.45% in total cholesterol, 7.08% in systolic blood pressure, 8.34% in diastolic blood pressure and 11.67% in fasting blood glucose. Subjects in the UO ABG 01 group also reported significantly ($p<0.05$) greater improvement with 17.97% in serum HDL cholesterol. The findings of this study indicated that UO ABG 01 is an effective and safe alternative therapy for the treatment of cardiovascular disease (CVD).

Keyword: Aged black garlic; CVD; HDL; LDL

Introduction

The cardiovascular system comprises the heart and blood vessels. The term "cardiovascular disease" (CVD) encompasses several related pathologies that are commonly recognised as coronary heart disease (CHD), venous thromboembolism, peripheral arterial disease, rheumatic and congenital heart illnesses [1,2].

Despite advancements in molecular medicine and in the identification, prevention, and management of CVDs, these conditions continue to be the leading cause of mortality and disability globally [3]. Herbal medicines are being used in modern medical systems with an unprecedented zeal. This desire is fueled by a number of causes, the most important being the belief that

they are safe and have the potential to be more cost-effective therapeutic options than the present standard of care [4].

Since the beginning of human history, garlic (*Allium sativum*) has been used for both medical and nutritional purposes. The role of garlic as a potential herb has been acknowledged for over five thousand years [5]. Additionally, it is regarded as a crucial component of Indian traditional medicine, including Ayurveda, Tibbi, and Unani. Furthermore, it is asserted to have positive effects on the prevention of dyslipidemia and hypertension, two additional factors of cardiovascular disease [6].

Fresh garlic bulbs are fermented at high temperatures (60–90 °C) and high humidity levels (70–90%), followed by an incubation period of 10–80 days, to yield aged black garlic [7]. Humidity, fermentation time, and temperature vary depending on the manufacturer which affects the composition of bioactive substances [8,9]. These conditions modify the organoleptic properties turning garlic black, sweet, and completely odorless. The elevated temperature required to produce aged black garlic is responsible for the changes in bioactive compounds, showing an increase in total phenols, S-alkyl-cysteine compounds (SAC), coumaric acid, and flavonoids [10].

Dyslipidemia has been demonstrated to be a substantial risk factor for the development of atherosclerosis and cardiovascular disease [11]. Lipid abnormalities encompass elevated low-density lipoprotein (LDL) cholesterol, increased triglycerides, and lowered high-density lipoprotein (HDL) cholesterol levels. Cholesterol found in α-lipoprotein (HDL) helps lower serum cholesterol levels, whereas β-lipoprotein (LDL) and pre-B-lipoprotein are deposited into blood vessels[12].

To determine the impact of various garlic preparations on lipid levels, several randomized, controlled experiments were conducted. An experiment conducted on human subjects in the early 1980s [13] showed a significant decrease in total cholesterol and triglyceride levels following administration of 40 gm of garlic. In a similar vein, a 16 week trial by Mader [14] in 1990 in individuals suffering from dyslipidemia with 800 mg of garlic (standardised to 1.3% of Alliin) revealed a 12% and 17% decrease in serum cholesterol and triglyceride levels, respectively, compared with placebo.

One significant risk factor that might contribute to cardiovascular disease is hypertension. Presently, it impacts one billion individuals globally, and by 2025, this figure is anticipated to increase to 1.6 billion [15,16]. Regular garlic consumption has been linked to the regulation of blood pressure. Garlic's ability to lower blood pressure is associated with its ability to produce hydrogen sulphide [17], release allicin from alliin, and activate the enzyme alliinase [18], which is thought to have angiotensin II inhibitory qualities and causes vasodilator.

Garlic offers a preventive effect against platelet adhesion or aggregation which is a risk factor associated with cardiovascular disease. In addition to garlic's putative role in inhibiting platelet aggregation, allicin and ajeones' self-condensation products are reported to possess antithrombotic activity. Garlic enhances fibrinolysis, which is the process by which clots and thrombi dissolve [19].

Garlic mostly prevents CVDs by lowering cholesterol levels, but recent research indicates that it also hasbenefits on endothelium and vascular dilatation by inhibiting the oxidation process. According to a research by Chan et al. [20], allicin increased the generation of glutathione and decreased reactive oxygen species, which improved the antioxidant status. In a similar vein, garlic guards against cardiovascular disease by blocking LDL oxidation, which in turn inhibits arterial atherosclerosis, one of the major risk factors for the condition[21].

Thus, this study is to investigate the efficacy and safety of UO ABG 01, an aged black garlic extract containing 0.5% SAC and 2% polyphenol, developed by Xtractiva Lifescience using a solid liquid fusion technology for the management of borderline cardiovascular risk factors.

Materials and Methods

Study Participants

The study was conducted at Chennai Meenakshi Multispecialty Hospital in Mylapore, Chennai, from October 2023 to February 2024. Male or female subjects who had borderline cardiovascular risk factors were included.

The inclusion criteria were as follows: male or female subjects between 25 to 65 years of age; ability to understand the risks/benefits of the protocol; female subjects of childbearing potential must be using a medically acceptable form of birth control; female subjects of non-childbearing potential must be amenorrheic for at least 1 year or have had a hysterectomy and/or bilateral oophorectomy; serum triglycerides > 115mg/dL and < 199 mg/dL; if a former smoker (previously smoked ≥10 cigarettes/day for at least 1 year, cessation for at least 6 months); willing to give written informed consent and willing to comply with trial protocol.

The exclusion criteria were as follows: pregnant or breast-feeding women; serum glucose levels higher than 126 mg/dL; use of cholesterol-lowering medications or supplements; use of blood pressure-lowering medications; subjects with abnormal liver or kidney function tests (ALT or AST > 2 times the upper limit of normal; elevated creatinine, males > 125 μmol/L, females > 110 μmol/L, renal insufficiency, thyroid or other endocrine disease;

any other condition that, in the opinion of the investigator, would adversely affect the subject's ability to complete the study or its measures; hypersensitivity to any ingredient used in the study supplements; alcohol consumption exceeding the definition of moderate drinking (2 drinks/day for men or 1 drink/day for women); and subjects who participated in any investigational study medication within thirty (30) days prior to screening.

Test Product Details

The investigational product UO ABG 01 (GARL-X 500 mg) is an aged black garlic extract developed by Xtractiva Lifescience using a solid liquid fusion technology containing 0.5% SAC and 2% polyphenol. The proprietary technology uses either water or ethanol as a solvent. The process uses low temperature drying that helps the retention of its active ingredient to its maximum level.

Overview of the Study Design

The study was a randomized, placebo-controlled, double-blind, parallel-group design. The subjects with borderline cardiovascular risk factors were included and randomly assigned to either aged black garlic extract UO ABG 01 or placebo group for 84 days.

This clinical study included 5 study visits (Figure 1). During the first visit (day -7 to 0), informed consent was obtained from subjects who satisfied the inclusion criteria but did not match any of the exclusion criteria. During this visit, subjects underwent physical examination, recording of disease history, concomitant illness, previous and concomitant medication, vital signs assessment, clinical laboratory tests (hematology, biochemistry and urine analysis) and urine pregnancy test for female subjects. The clinical assessments, such as lipid profile, blood pressure, and fasting blood glucose, were also performed during this visit. During the second visit (day 0), the participants were randomized to receive either UO ABG 01 or placebo in a double-blinded manner. The randomised sequence was created by an impartial statistician. To blind the subjects and investigators, product labels were substituted with labels that included a computer-generated blinded sequence designed by a statistician.

In visit 3 (Day 28±3), visit 4 (Day 56±3) and visit 5 (Day 84±3), all subjects were assessed by the principal investigator for their vital signs, clinical symptoms, and tolerability of the study product, any AEs and concomitant medications. Lipid profile, blood pressure, fasting blood glucose were assessed as efficacy assessment.

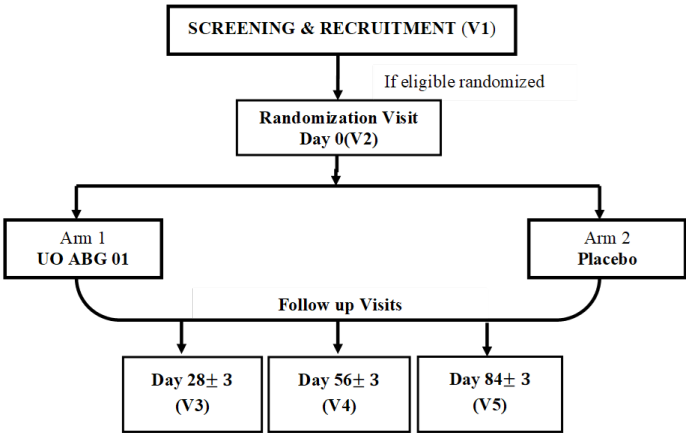

Figure 1: Study Design.

Study Endpoints

Efficacy Endpoints

The change from baseline to end of the study in serum triglycerides, serum LDL cholesterol, serum HDL cholesterol and total cholesterol was the primary efficacy endpoint.

The changes in blood pressure and fasting blood glucose from baseline to the end of the study were the secondary outcomes of the study.

Safety Endpoints

The safety assessment included changes in vital and laboratory data, the percentage of patients who stop their study treatment because of adverse events (AEs) and the frequency and severity of AEs.

Study Assessments

Serum triglycerides

A triglyceride is an ester of glycerol with three fatty acids. These are the most common type of fat in the body. Several meta-analyses and reviews have highlighted the relationship between triglyceride levels and the risk of CVD among the general population. An increase in triglyceride concentration is associated with a higher risk of CVD events [22,23].

Serum LDL cholesterol

LDL has been found to be the primary risk factor for CVD in numerous epidemiological and interventional

investigations. It is essential to the pathophysiology of atherosclerosis and it is also referred to as "bad" cholesterol. LDL has largely taken the place of total cholesterol as the main lipid indicator used to forecast the risk of cardiovascular disease in recent years [24,25].

Serum HDL cholesterol

HDL (high-density lipoprotein) cholesterol is also known as the "good" cholesterol. Research demonstrates that HDL-C, which is regarded as an anti-atherosclerotic lipoprotein, has an inverse relationship with the risk of vascular problems [26].

Total Cholesterol

It is generally recognised that raised serum total cholesterol (TC) is linked to an increased risk of cardiovascular disease (CVD), and that elevated TC is the primary cause of coronary atherosclerosis [27].

Blood Pressure

One significant risk factor that might contribute to cardiovascular disease is hypertension. Presently, it impacts one billion individuals globally, and by 2025, this figure is anticipated to increase to 1.6 billion [15,16].

Fasting blood glucose

Cardiovascular disease is the leading cause of morbidity and mortality in diabetic patients. Patients with elevated blood glucose levels are more likely to have cardiovascular risk factors, such as obesity, hypertension, and dyslipidaemia, which puts them at risk for cardiac events. In addition, many studies have found biological mechanisms associated with high glucose levels that independently increase the risk of CVD.

Statistical Analysis

The change in primary and secondary endpoints from the baseline to the subsequent visits was used to evaluate the effectiveness of the treatment. The change from the baseline was defined as the difference between the post-treatment value and the baseline value.

ITT populations were used for the efficacy analysis. The ITT efficacy analysis set consisted of all subjects who took at least one dose of the study supplement and had at least one post-baseline assessment. Missing observations were imputed using the LOCF(Last Observation Carried Forward) approach.

The primary efficacy endpoints, i.e., the change in the serum triglycerides, serum LDL cholesterol, serum HDL cholesterol and total cholesterol between baseline and 28^{th}, 56^{th} and 84^{th} day of the study period, were compared within groups using an independent sample t-test and between groups using repeated measures of ANOVA.

Secondary efficacy endpoints, i.e., the change in blood pressure and fasting blood glucose between the baseline and 28^{th}, 56^{th} and 84^{th} day of the study period, were compared within groups using independent sample t-test and between groups using repeated measures of ANOVA.

In all cases, a p-value < 0.05 was considered statistically significant.

Results

Out of the sixty participants who were screened, four were deemed to be screen failures because they did not meet the eligibility criteria. Out of a total 56 number of subjects enrolled, 28 subjects were allocated to the UO ABG 01 group and 28 subjects were allocated to the placebo group. Subjects in both groups had nearly similar demographic and baseline characteristics (Table 1). Out of 56 subjects, 52 completed the study as per protocol requirement: 27 subjects in the UO ABG 01 group and 25 in the placebo group. Three subjects dropped out of the study.

	UO ABG 01	Placebo
	(N=28)	(N=28)
Age (years)		
Mean (SD)	47.43±11.03	46.71±9.15
Median	46.5	47
Range	27-65	34-64
Gender, N (%)		
Male	19 (67.86%)	12 (42.86%)
Female	9(32.14%)	16 (57.14%)
Weight (kg)		
Mean (SD)	71.64±13.67	73.42±15.92
Median	72.8	71.65
Range	42.9-104	50.5-114.8
Height (cm)		
Mean (SD)	162.72±9.78	159.20±8.68
Median	163	156.75
Range	144-186	143-175
BMI (kg/m^2)		
Mean (SD)	26.98±4.61	28.90±5.35
Median	26.45	29.70
Range	19.1-42.7	18.8-40.2

Table 1: Baseline Characteristics (ITT Population).

Efficacy

The primary endpoint of the study was the change in serum triglycerides, serum LDL cholesterol, serum HDL cholesterol, and total cholesterol from baseline, while the secondary endpoints were the change in blood pressure and fasting blood glucose from the baseline. The current study demonstrated clinically and statistically significant changes in both primary and secondary endpoints in the UO ABG 01 group compared to placebo (Figure 2 and Figure 3).

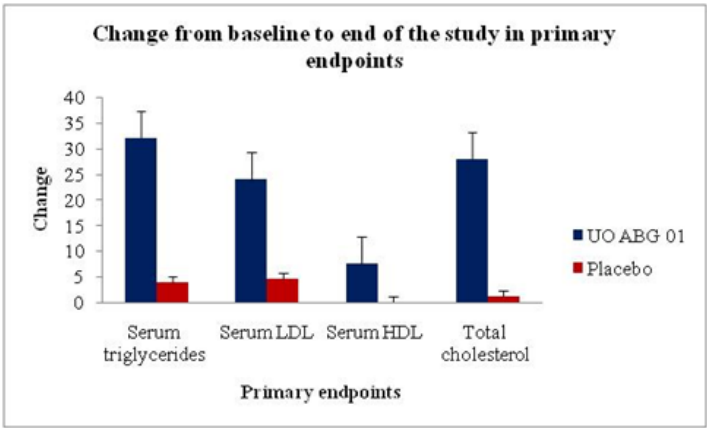

Figure 2: Change from baseline to end of the study in primary endpoints.

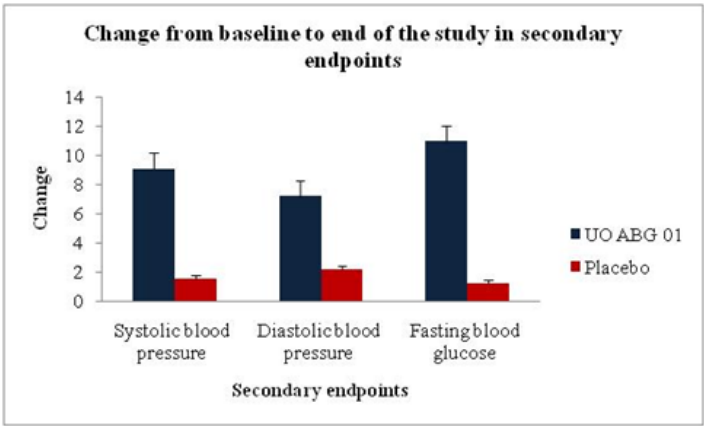

Figure 3: Change from baseline to end of the study in secondary endpoints.

Serum triglycerides

In the UO ABG 01 treatment group, the percentage reduction in serum triglycerides from baseline was 9.79% at visit 3, 15.37% at visit 4, and 19.93% at visit 5, whereas in the placebo group it was 0.73% at visit 3, 1.70% at visit 4, and 2.42% at visit 5.

Serum LDL

In the UO ABG 01 treatment group, the percentage reduction in serum was 5.38% at visit 3, 11.13% at visit 4, and 15.48% at visit 5 , whereas in the placebo group it was 0.79% at visit 3, 1.83% at visit 4, and 3.01% at visit 5.

Serum HDL

In the UO ABG 01 treatment group, the percentage reduction in serum HDL was 8.09% at visit 3, 12.61% at visit 4, and 17.97% at visit 5, whereas in placebo group it was 2.89% at visit 3, 3.76% at visit 4, and 0.17% at visit 5.

Total Cholesterol

In the UO ABG 01 treatment group, the percentage reduction in serum total cholesterol was 3.47% at visit 3, 8.08% at visit 4, and 13.45% at visit 5 , whereas in the placebo group it was 0.71% at visit 3, 1.46%at visit 4, and 0.61% at visit 5.

Systolic Blood Pressure

In the UO ABG 01 treatment group, the percentage reduction in systolic blood pressure from baseline was 5.46% at visit 3, 6.83% at visit 4, and 7.08% at visit 5, whereas in the placebo group it was 0.93% at visit 3, 1.74% at visit 4, and 1.18% at visit 5.

Diastolic Blood Pressure

In the UO ABG 01 treatment group, the percentage reduction in diastolic blood pressure from baseline was 6.51% at visit 3, 7.26% at visit 4, and 8.34% at visit 5, whereas in the placebo group it was 1.97% at visit 3, 2.98% at visit 4, and 2.52% at visit 5.

Fasting blood glucose

In the UO ABG 01 treatment group, the percentage reduction in fasting blood glucose from baseline was 4.99% at visit 3, 9.26% at visit 4, and 11.67% at visit 5, whereas in the placebo group it was 1.77% at visit 3, 1.77% at visit 4, and 1.24% at visit 5.

Safety

The overall incidence of AEs was 10.71% (3/28 subjects) in the UO ABG 01 group and 7.14% (2/28 subjects) in the placebo group, respectively. There was no statistically significant difference in the incidence of AEs between the UO ABG 01 and placebo groups. All the AEs were mild and moderate in severity in both groups and no clinically relevant AEs were identified. The AEs in UO ABG 01 group were nausea 1 (3.57%), cold 1 (3.57%) and heart burn 1 (3.57%), while in the placebo group the AEs were stomach pain 1 (3.57%) and diarrhea 1 (3.57%). Adverse events were classified by System Organ Class (Body System) / Preferred Term across treatment groups.

There were no significant changes in the laboratory parameters over time. Although some values, such as bilirubin, SGOT, SGPT and specific gravity, were found to be statistically significant, they were not clinically significant (Table 2).

Index	UO ABG 01 N=30			Placebo N=30		
	Baseline visit	Visit 5	Mean change	Baseline visit	Visit 5	Mean change
Haemoglobin	13.45±2.23	13.55±1.65	0.10±1.54	13.02±1.88	12.98±2.21	0.04±0.89
Platelet count	278.54±81.16	283.04±75.07	4.50±70.02	278.39±70.36	269.88±73.79	8.52±78.09
WBC	7731.43 ± 590.82	7398.57±2060.42	332.86±1460.34	7753.57±1772.45	7460.71±1768.08	292.86±1448.07
RBC	4.72±0.46	4.84±0.57	0.12±0.47	4.67±0.53	4.75±0.58	0.08±0.46
BUN	9.97±2.47	10.40±2.37	0.43±3.11	9.08±2.22	8.92±2.83	0.16±2.69
Bilirubin	0.50±0.17	0.60±0.29	0.11±0.22*	0.53±0.23	0.56±0.30	0.04±0.28
SGOT	20.96±4.54	24.25±5.32	3.29±3.93*	23.04±10.34	24.82±5.87	1.79±8.62
SGPT	22.68±10.85	25.57±11.37	2.89±7.04*	23.57±17.96	24.54±9.89	0.96±11.23
Creatinine	0.77±0.18	0.75±0.20	0.02±0.15	0.70±0.17	0.74±0.19	0.03±0.15
Urine PH	5.98±0.25	8.02±9.61	2.04±9.61	5.96±0.13	6.05±0.28	0.09±0.31
Specific gravity	1.02±0.01	1.01±0.01	0.00±0.01	1.02±0.01	1.01±0.01	0.00±0.01*
*P value < 0.05, values are presented in absolute value. Between the group analysis by Independent sample t-test.						

Table 2: Laboratory Parameters (ITT population).

Discussion

CVDs account for more than 17 million mortalities each year [28]. WHO studies identify that the predominant cause of mortality in low and middle income countries are mostly due to delays in diagnosis and the inaccessability of the healthcare services during CVD progression. As a conservative estimate, about three quarters of the world's deaths occur in low and middle-income countries [29]. Markedly, CVDs are expected to surpass the casualties that arise from deadly infectious diseases like TB, Malaria, HIV/AIDS by the year 2030 [30].

The prevention and management of CVDs involves lifestyle adjustment with disciplinary control over modifiable risk factors. Current conventional treatments mainly focus on controlling LDL cholesterol levels thereby leading to a substantial reduction in hyperlipidemia. Notably, the conventional treatment available for controlling hypertension and hyperlipidemia is affected by factors such as cost and availability of medicines. The major concern about the available agents is their dangerous side effects and complications [31]. The Complementary and Alternate Medicine (CAM) approach using natural products has gained global attention as a treatment strategy for managing risk factors in CVDs [32].

Garlic, a potential agent historically used as a flavoring agent in enhancing the flavor of the food and to improve stamina in athletes, has long been recognized for its benefits. CharakSamhita advocates the use of garlic in heart diseases [33].

The objective of the clinical trial was to test the efficacy and safety of UO ABG 01 in the management of borderline cardiovascular risk factors. *This study was a double-blind, placebo-controlled study involving 56 subjects with* borderline cardiovascular risk factors *and the study duration was 84 days involving 5 visits.* The study product was administered at a dose of 500 mg once daily in capsule form.

The change in serum triglycerides, serum HDL cholesterol, serum LDL cholesterol and total cholesterol from baseline to the final visit was the study's primary endpoint, while the secondary endpoints were the changes in fasting blood glucose and blood pressure from baseline to the end of the study. Primary and secondary endpoints were evaluated in all the visits during the study. Safety assessments included the evaluation of AEs, changes in vital signs and changes in laboratory parameters.

The study demonstrated significant benefits of UO ABG 01 over placebo in subjects with cardiovascular risk factors. Statistically significant improvements were observed over placebo in endpoints such as serum triglycerides, serum HDL cholesterol, serum LDL cholesterol, total cholesterol, fasting blood glucose and blood pressure.

Conclusions

Based on the results of this study, it was concluded that UO ABG 01, developed by Xtractiva Lifescience, was effective in the

management of cardiovascular risk factors. Additionally, it is safe and well-tolerated, and may serve as a potential alternative natural therapy for the management of cardiovascular risk factors.

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Ethical Considerations: This study was conducted strictly in accordance with the "Guidelines for Clinical Trials on Pharmaceutical Products in India- GCP Guidelines" issued by the CDSCO, the Ministry of Health, and the Government of India, as well as in accordance with the ethical principles derived from the Declaration of Helsinki and the Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonisation (ICH).

On 11th October 2023, this research was registered on Clinical Trials Registry-India (CTRI) [Registration No.: CTRI/2023/10/058501]. The Chennai Meenakshi Multispeciality Hospital acknowledged an independent ethics council, which evaluated and approved the protocol before the trial started. Before being included in the study, participants gave their signed, informed consent.

Conflicts of Interest: The authors do not have any conflicts of interest to declare.

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