

# Safety and Efficacy of NC120 for Improving Lipid Profile: A Double Blind Randomized Controlled Trial

Nafrialdi<sup>1,2,3</sup>, Johannes Hudyono<sup>2</sup>, Frans D. Suyatna<sup>1,2</sup>, Arini Setiawati<sup>1,2</sup>

<sup>1</sup> Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

<sup>2</sup> Clinical Research Supporting Unit, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

<sup>3</sup> Department of Clinical Pharmacology, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

## Corresponding Author:

Nafrialdi, MD., PhD. Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Indonesia. Jl. Salemba no. 6, Jakarta 10430, Indonesia. email: nafrialdi@gmail.com.

## ABSTRAK

**Latar belakang:** penggunaan obat golongan statin untuk menurunkan kolesterol darah sering disertai efek samping yang mengganggu seperti mialgia dan gangguan fungsi hati. NC120 adalah obat herbal yang mengandung ekstrak ragi beras merah, guggulipid, dan chromium picolinat yang diharapkan tidak menimbulkan efek samping seperti statin. Penelitian ini bertujuan mengevaluasi efektivitas dan keamanan NC120 dalam menurunkan lipid darah. **Metode:** penelitian ini merupakan uji klinik dengan disain acak tersamar ganda, membandingkan NC120 dengan plasebo pada subjek dengan hiperkolesterolemia. NC120 atau plasebo diberikan dengan dosis 2 kapsul dua kali sehari selama 28 hari. Kadar kolesterol total, kolesterol LDL dan trigliserida diukur pada hari-0, hari-7, dan hari-28. Uji t-test tidak berpasangan digunakan untuk membandingkan parameter penelitian antar kelompok, sedangkan uji ANOVA satu arah digunakan untuk analisis dalam satu kelompok. **Hasil:** 25 subjek mendapat NC120 dan 24 subjek mendapat plasebo. Penurunan bermakna pada kadar kolesterol total dan kolesterol-LDL terlihat pada kelompok yang mendapat NC120, sedangkan pada kelompok plasebo tidak terlihat perbedaan bermakna. Tidak terlihat penurunan yang bermakna pada kadar trigliserida pada kelompok NC120, maupun kelompok plasebo. Efek samping umumnya ringan dan seimbang pada kedua kelompok. **Kesimpulan:** NC120 efektif menurunkan kadar kolesterol total dan kolesterol-LDL, tapi tidak efektif menurunkan trigliserida. NC120 menunjukkan profil keamanan yang cukup baik, dan obat ini dapat dipertimbangkan tidak bisa merekomendasikan sesuatu berdasar satu RCT apalagi jumlah sampel masih terbatas terutama untuk pasien hiperkolesterolemia yang tidak toleran terhadap statin.

Kata kunci: Nutrafor, kolesterol, ragi beras merah, guggulipid.

## ABSTRACT

**Background:** the use of statin to lower blood cholesterol is often associated with bothersome adverse effects such as myopathy and liver dysfunction. NC120 is herbal lipid lowering drug containing red yeast rice (RYR) extract, guggulipid, and chromium picolinate, and expected to have better safety profile. The aim of this study was to evaluate the efficacy and safety profiles of NC120 in lowering blood lipid. **Methods:** this was a double blind randomized clinical trial comparing NC120 with placebo in subjects with hypercholesterolemia. Two capsules of NC120 or placebo were administered twice a day for 28 days. Blood total-cholesterol, LDL-cholesterol, and triglyceride were measured on day-0, day-7, and day-28. Unpaired t-test was used to compare study parameter between groups, and one-way ANOVA was used to compare within group. **Results:** 25 subjects received NC120 and 24 subjects received placebo. Significant decrease of total cholesterol and LDL-cholesterol were observed since day-7 in NC120 group, while the changes in placebo group were not significant at all time of observation.

No significant decrease of triglyceride was observed in NC120 group and in placebo group. Side effects were minor and comparable between the two groups. **Conclusion:** NC120 is effective in reducing total cholesterol and LDL-cholesterol, but not triglyceride. This drug shows a good safety profile, and thus can be considered for patients who can not tolerate statin drugs.

**Keywords:** Nutrafor, cholesterol, red yeast rice, guggulipid.

## INTRODUCTION

Data from the National Vital Statistics Report stated that cardiovascular disease is still the leading cause of mortality in the US in 2015.<sup>1</sup> Among cardiovascular death, coronary artery disease (CAD) represents the most common cardiovascular disease. Hypercholesterolemia is considered as the most important trigger of atherosclerotic formation.<sup>2</sup> Lipid lowering agents, especially statin groups are noted to have pivotal role in CAD prevention. This drug class has been used since 1990, and should be given to patients during acute heart attack, as well as chronic maintenance treatment.<sup>3</sup>

Despite its efficacy, the use of statins is often associated with some adverse effects, such as myopathy and liver dysfunction. Myopathy ranges from muscle pain (myalgia), myositis, and very rarely a life-threatening rhabdomyolysis. Myopathy, in the form of muscle pain might be the most common complaints of patients taking statin and become the most common reason for discontinuation of therapy.<sup>4,5</sup> Regarding the role of statin therapy in the prevention and treatment of coronary artery disease, alternative treatment should be found for those who can not tolerate statins. In this case, the use of natural products is hoped to be a good alternative due to its reputation of good safety profile.

NC120 is a food supplement with the indication to help reducing blood lipids.<sup>6</sup> Every capsule of NC120 contains 375 mg Red Yeast Rice (RYR) extract (comparable to 0.32 mg lovastatin), Guggulipid extract 110 mg (11 mg Guggulsterones), and 50 mg of chromium picolinate.<sup>6</sup> Red Yeast Rice (RYR) contains 0.4% monacolin K which is identical with lovastatin and reported to exhibit a cholesterol-lowering action through inhibition of the HMG-CoA reductase. In addition, other components in RYR,

such as plant sterols, isoflavones, selenium, and zinc, are also believed to have lipid lowering effects.<sup>7,8</sup> The effects of guggulipid for cholesterol lowering are less clear and various studies showed variable effects. Chromium picolinate is a food supplement with antioxidant activity and often recommended for diabetic patients. A study by Press et al.<sup>9</sup> reported a decrease in TC, LDL-cholesterol and apolipoprotein B, and an increase in HDL-cholesterol and apolipoprotein A.

A mixture of the 3 ingredients in NC120 has been marketed for reducing blood lipids. However, a formal clinical study has never been done. Therefore, this study was aimed to evaluate its efficacy as well as safety profile of NC120 in decreasing blood lipids in subjects with hypercholesterolemia.

## METHODS

This was a double-blind randomized controlled clinical trial to compare NC120 versus placebo. This study was conducted at the Clinical Research Supporting Unit (CRSU), Faculty of Medicine, Universitas Indonesia, between March 2016 to June 2018.

The protocol of this study has been approved by the Research Ethics Committee of the Faculty of Medicine, University of Indonesia with approval letter number 590/UN2.F1/ETIK/2015.

### Inclusion Criteria

Included in this study were men or women aged 18 to 60 years with LDL cholesterol 130 - 180 mg/dL, have never received lipid lowering drugs (including herbal or supplements) regularly within one month prior to the study, and willing to participate in the study by signing informed consent form. Those with the history of hypersensitive to any components of NC120, pregnant or lactating women, presence or a history of CV disease except grade 1 hypertension,

presence of diarrhea or inflammatory bowel syndrome, patients with liver dysfunction (ALT or AST > 3x ULN or a history of cirrhosis), patients with renal dysfunction (CICr < 50 mL/min), were excluded.

### Sample Size

This study was planned as a preliminary study. Thus, sample size was not calculated, and 2 x 30 evaluable patients were determined by the investigator. However, after an interim analysis, it turned out that the minimum sample size needed per group was only 25.

### Study Drugs

NC120 and placebo capsules were prepared by Novell Pharmaceutical Laboratories, and presented as identical capsule with similar colour. Allocation of patients to receive either products was done by random permutation blocks of size 4. Packaging product for individual patients was done by the Clinical Study Unit, Faculty of Medicine, Universitas Indonesia according to a pre-determined randomization list. Each drug package was labelled with the patient randomization number and dosage instruction. Each patient received drug supply for consumption during each period between visits plus a few days in excess, for compliance check and to allow additional days for patient visit.

### Drug Administration

After 2 weeks run-in period, each patient received either NC120 (NC) or Placebo, in a double-blind fashion, to be taken 2 capsules in the morning after breakfast and 2 capsules in the evening after dinner, for a duration of 4 weeks.

### Concomitant Medication

Use of chronic medications for other chronic diseases (eg. hypertension) was allowed if the use started more than 2 weeks prior to screening and the dose remained constant throughout the whole study.

### Efficacy Assessments

Total cholesterol, LDL-cholesterol, and triglyceride were measured as parameters of efficacy at day-0 (before treatment), day-7, and day-28 of the study.

### Data Analyses

The efficacy analysis was done as intent-to-treat (ITT) on all randomized patients without eligibility violation, who took at least one dose of study drug and returned at least once post-randomization.

Statistical tests was used to compare the decrease of LDL-C, TC, and TG from baseline following therapeutic response to NC and Placebo after 7 days and 28 days. Paired-t or Wilcoxon test was used to analyze the difference from baseline within each group (NC120 and Placebo), and unpaired-t or Mann-Whitney test was used to analyze the difference from baseline, at day 7 and 28 between NC and Placebo.

Safety analysis. All patients who took at least one dose of the study drug and returned at least once post-randomisation, were subject to safety analysis. All adverse events were listed per group (NC and Placebo), both the incidence and the percentage. The adverse events with possible and probable relationship to the study drug (ADRs) were also listed as the incidence and the percentage per group (NC120 and Placebo).

### Role of Funding Source and the Authors

This study was funded by PT Novell Industries. Nafrialdi was the principle investigator and wrote the final report; Frans D. Suyatna and Johannes Hudyono were the co-investigators; and Arini Setiawati made the protocol and had some contribution in data analysis and report writing.

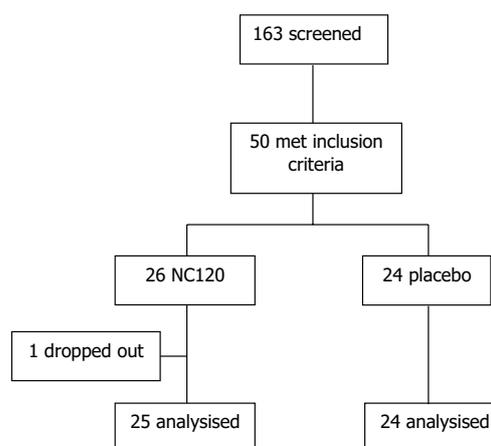


Figure 1. Recruitment of subjects during the study of NC120

## RESULTS

A total of 163 subjects were screened, but most of them failed to meet the inclusion criteria after run-in period of 2 weeks. Thus, only 50 subjects were eligible to enter the study. Twenty six subjects received NC120 and 24 received placebo. One subject in NC120 group was dropped-out due to unnoticed age that exceeded 60 year (**Figure 1**). Both groups were comparable in demography and baseline characteristics (**Table 1**).

**Table 1** shows demographic and baseline characteristics of patients. It can be seen that both groups are comparable in almost every parameter.

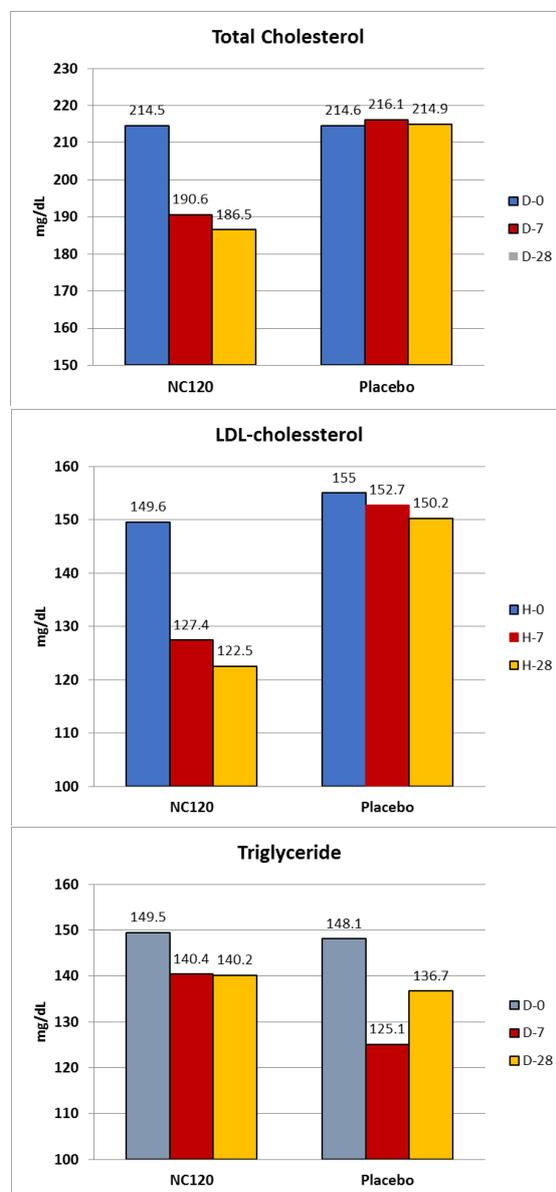
### Efficacy Analysis

NC120 showed significant decreases in total cholesterol and LDL-cholesterol since the first

**Table 1.** Demographics and baseline characteristics of study subjects.

Variables	NC120 (n = 25)	Placebo (n = 24)
<b>Demography</b>		
Gender		
- Male	8 (32.0%)	9 (37.5%)
- Female	17 (68.0%)	15 (62.5%)
Age (yrs), Mean (SD)	44.6 (9.25)	44.8 (8.95)
Weight (kg), Mean (SD)	68.8 (12.56)	64.9 (14.08)
Height (cm), Mean (SD)	155.6 (7.10)	155.6 (8.80)
BMI (kg/m <sup>2</sup> ), Mean (SD)	28.4 (4.91)	26.6 (3.79)
<b>Baseline characteristics</b>		
SBP (mmHg)	121.5 (15.70)	117.9 (16.88)
DBP (mmHg)	80.0 (9.35)	75.6 (9.48)
Heart rate (beats/min)	71.3 (8.20)	75.8 (8.67)
Haemoglobin (g/dL)	13.9 (1.62)	13.9 (1.39)
Hematocrit (%)	41.6 (3.93)	41.7 (3.80)
Platelet (103/ $\mu$ L)	305.8 (94.44)	320.4 (72.29)
Leukocyte (103/ $\mu$ L)	7.6 (1.54)	8.0 (1.98)
Ureum (mg/dL)	18.4 (9.61)	17.7 (6.49)
Creatinine (mg/dL)	0.78 (0.17)	0.71 (0.19)
AST (U/L)	26.2 (11.70)	25.9 (16.29)
ALT (U/L)	28.2 (21.91)	25.3 (21.79)
Total chol. (mg/dL)	214.5 (23.55)	214.6 (30.81)
LDL-C (mg/dL)	149.6 (15.98)	155.0 (14.10)
Triglyseride (TG) (mg/dL)	149.5 (69.40)	148.1 (71.71)

week of treatment, whereas placebo did not. Meanwhile, effect of NC120 on triglyceride was small and not significant (**Figure 2**).



**Figure 2.** Effects of NC120 on serum levels of Total cholesterol, LDL-cholesterol, and triglyceride on D-0, D-7, and D-28. (\*:  $p < 0.05$  vs D-0).

**Table 2** shows the data on adverse events during this study. There was no subject undergoing serious adverse event, while non-serious adverse events were experienced by almost same number of patients receiving NC120 (28%) or placebo (29.1%).

## Safety Analysis

**Table 2.** List of adverse events and adverse drug reactions related to study product.

Adverse Event	NC120 (n = 25)	Placebo (n = 24)
Polyuria	0	1
Gastric pains	1	1
Sleepy	2	1
Itching	3	1
Nausea	1	1
Constipation	0	1
Numbness	0	1
Serious adverse event	0	0
Total	7 (28.0)	7 (29.1)

## DISCUSSION

NC120 is a herbal product containing combination of Red Yeast Rice (RYR) extract 375 mg (comparable to 0.32 mg lovastatin), guggulipid extract 110 mg (11 mg Guggulsterones), and chromium picolinate 50 mg.<sup>6</sup> It represents an alternative lipid lowering agent for those are intolerant to statin drugs, either due to myalgia or liver dysfunction. The results of this study showed that NC120 started to lower total cholesterol and LDL-cholesterol significantly since day-7 of treatment. Continuation of the treatment until day-28, further decreased the lipid level, although not significantly different from day-7. It seems that optimal effect has already been achieved within one or two weeks of treatment. This effect is comparable to statin which begin to decrease LDL within two weeks. Red Yeast Rice in NC120 contains monakalin K which is comparable to 0.32 mg of lovastatin. Since the lovastatin content is small, it may contribute albeit small, to the lipid lowering action of RYR.

Becker et al.<sup>10</sup> reported that RYR extracts was effective in reducing blood cholesterol without increasing myalgia and creatine phosphokinase (CPK) in statin intolerant patients.<sup>9</sup> This group reported a significant decrease in blood cholesterol at week 12 of treatment, whereas in our study, the decrease of blood cholesterol was observed much earlier. Explanation of this difference was not clearly known, but some differences are found between our study and

that of Becker's. Our study was conducted on naïve patient while the study of Becker was done on patients who have failed statin therapy due to myalgia side effect. Dietary restriction was implicated in the study of Becker, while the diet of the patients in our study remained as usual. In addition, NC120 also contains guggulipid which was reported to have lipid lowering effect.<sup>10</sup>

Another clinical trials reported that red yeast rice product should contain substantial amount of monakalin K to have significant lipid lowering effect. While some red yeast rice products on the market contain very little of monakalin K.<sup>11</sup> Each capsule of NC120 contains monakalin K comparable to 0.32 g lovastatin. This amount is indeed very small compared to therapeutic dose of lovastatin. It can be assumed that mechanisms other than HMG-CoA reductase inhibition, may have participated in the effect of NC120. This assumption is supported by the fact that many red yeast rice products also contain very small of monakalin K, yet show significant effect on blood cholesterol.<sup>11</sup> One of the aims of using herbal products is to avoid adverse effects such as myalgia and liver dysfunction as commonly encountered with statin drugs. In our study, no patients showed these adverse effects. We did not measure the creatine phosphokinase (CPK), but no subject complaining of myalgia, nor elevation of liver enzymes during 4 weeks of treatments. This finding was supported by the study of Becker et al,<sup>10</sup> that no increase of CPK after treatment with red yeast rice product. This confirms the safety profile of NC120 and that this herbal drug is suitable for those who are intolerant to statin drugs.

Other compositions of NC120 are guggulipid and chromium picolinate. Guggulipid is a resin of the Commiphora mukul tree and well known as guggulsterone. It has been used since more than 2000 years in Ayurvedic medicine to heal many kinds of diseases. The stereoisomers E- and Z-guggulsterone have been identified as the active agents in this resin. With sequestration effect on bile acid, guggulsterone is assumed to inhibit lipid emulsification in the intestine, and thus, block lipid absorption. Clinical study has shown that guggulipid 2 x 50 mg/day significantly lowered blood cholesterol

compared to placebo.<sup>12</sup> Another study reported a decrease of total cholesterol level by 13% and triglyceride level by 12% after 12 weeks of treatment.<sup>13</sup> In our study, NC120 contains 110 mg of guggulipid, and the dose used was 2 capsules twice daily. It means that the dose of guggulipid in our study is more than four times of the previous study.<sup>13</sup> This might explain why the effect on cholesterol can be observed much earlier in our study.

Chromium picolinate is a chemical substance that frequently used for diabetic patients. It has some metabolic effects on carbohydrate and lipid metabolism, as well as other beneficial effect on hormonal disorder, including polycystic ovary syndrome (PCOS).<sup>14</sup>

We did not observe significant effect of NC120 on triglyceride level. On the contrary, a greater decrease of triglyceride was observed in placebo group compared to NC120 group, although the difference was not statistically significant. Explanation of this discrepancy is not known, but the possible arbitrary changes could not be ruled out. Therefore, it may be concluded that the mechanism of action of NC120 in lowering total cholesterol and LDL-cholesterol was a mixture of inhibition of HMG-CoA reductase (a small part) and mostly by blocking lipid absorption by guggulesterone.

Chromium picolinate (CrPic) is another active component found in NC120. This substance is frequently used in many food supplements owing to its various effects including antioxidant, some positive effects in carbohydrate and lipid metabolism.<sup>15</sup> Some animal studies reported its effects in lipid metabolism. Its mechanisms in improving lipid profile is not clear. But, it is assumed to derived from its stimulatory effect on 5-AMP kinase, and subsequently suppresses sterol regulatory element binding protein (SREBP-1). In addition, CrPic also has inhibitory effect on acetyl Carboxylase, expected to decrease the activity of malony-CoA, an enzyme involved in cholesterol synthesis.<sup>15</sup>

During this study, 7 out of 25 patients (28%) in NC120 group and 7 out of 24 patients (29.1%) in placebo group reported some subjective adverse events, including gastric pain, nausea,

itching, and sleepy. It can be said that the percentage of adverse events is quite identical in both groups. No influence of these adverse events on the continuation of the treatment. Typical side effect of statin group in the form of myalgia and myopathy was not found during the treatment with NC120. Laboratory parameters of organ function, including peripheral blood count, serum transaminase, and serum creatinine were not different between NC120 and placebo group. It can be concluded that NC120 has a good safety profile.

A pilot study with sample size of 30 patients in each group was planned at the beginning of the study. However, after recruiting 163 patients, most of the subjects had LDL level below inclusion criteria after run-in period of 2 weeks. Indeed, the recruitment of subjects was very slow, therefore an interim analysis was performed during the study in order to obtain some data for calculating sample size needed to have 80% of study power. It turned out that the minimum sample size needed for each group is only 25. Thus, this study was terminated after reaching that number of subjects.

## CONCLUSION

This study showed that NC120 is effective in reducing blood cholesterol (total-cholesterol and LDL-cholesterol) since the first week of treatment, without significant effects on triglyceride. This drug seems to have a good safety profile with the incidence of adverse effect comparable to placebo. Based on these results, NC120 could be considered as an alternative for statin-intolerant patients. However, considering that the actual use would be for a much longer time, more data is needed to assure the safety for longtime usage.

## ACKNOWLEDGMENTS

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