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The Effects of Noni (*Morinda citrifolia* L.) Fruit Juice on Cholesterol Levels: A Mechanistic Investigation and An Open Label Pilot Study

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ABSTRACT

The traditional usage of noni fruit did not include any claims for lowering cholesterol levels in humans. However, recently a commercial noni fruit juice blend, Tahitian Noni Original® Bioactive (TNOB),was shown in a double blind, and placebo control clinical trial to significantly lower cholesterol levels in current smokers. But, its effect on cholesterol levels of nonsmokers with normal cholesterol levels, and its mechanisms of action, has not been fully elucidated. The current study evaluates the effects of various noni preparations (TNOB, NFJC (noni fruit juice concentrates), NFJME (noni fruit juice methanol extract)) on HMG-CoA Reductase and $ACAT_{hepatic/intestine}$ enzymes *in vitro*. Further, TNOB was evaluated for its potential cholesterol-lowering effects in 10 non-smoking subjects with normal to mild cholesterol levels. TNOB and NFJC both inhibited HMG-CoA Reductase, and ACAT enzymes concentration-dependently *in-vitro,* and NFJC has a <1.0 mg/mL IC_{50} on HMG-CoA Reductase enzymes. NFJME, the active fraction from the noni fruit juice, in 100µg/mL, inhibited HMG-CoA reductase by 81%. TNOB showed a trend towards lowering total cholesterol and LDL levels while increasing HDL levels in nonsmokers. Noni fruit juice has the potential to lower cholesterol levels in nonsmokers perhaps via its inhibitory effects on HMG-CoA reductase and ACAT enzymes as its possible mechanism of action. However, a larger clinical trial is warranted to assess its effects in non-smokers with higher cholesterol levels above 220 mg/dL to evaluate the nature of this cholesterol-lowering trend seen in this pilot study.

INTRODUCTION

Morinda citrifolia L (Noni) has been used in Tonga, Tahiti and throughout all of Polynesia for over 2000 years, and is reputed to have a repertoire of health benefits. Traditionally, noni fruit was fermented and the juice was used to treat various human ailments, including but not limited to, high blood pressure (*toto ma'olunga*), kanisā (cancer), *suka* (diabetes), *langa e hokotanga hui* (gout), *nounou e mānava* (asthma), *tale* (coughs), *mamahi e monga* (sore throat), respiratory infections, *kulokula* (inflammation), *langa hui* (arthritis), *mamahi e te'enifo* (sore gums), *kona* (fish poisoning), *lavea* (cuts) and *lavea loloto* (deep wounds and cuts) (Palu, 2004). Noni fruit juice has also been found to contain various amounts of vitamins, minerals, and other bioactive compounds, including iridoids, that contribute to its potential disease-preventive properties and other health promoting effects (Wang *et al*., 2002; Palu *et al*., 2010; Deng *et al*., 2011).

The known benefits of noni fruit juice are just beginning to immerge as modern research techniques are employed, such as enzyme and ligand binding studies, *in-vivo* studies, and human clinical studies. But its effect on cholesterol levels in

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humans has not been investigated prior to the advent of Morinda Inc., in 1996, perhaps due in part to the absence of traditional usage of noni on lowering cholesterol by traditional healers in Polynesia and elsewhere. However, recently, Wang and colleagues (2006) reported in their clinical trial which used the commercial noni fruit juice blend (TNOB) in current smokers, to significantly lowered triglyceride and LDL while it raised HDL levels. But its potential cholesterol-lowering effect has not been investigated in non-smokers and noni's potential cholesterol-lowering mechanisms have not been fully elucidated.

Potential cholesterol-lowering effects from any medicinal plants or pharmaceutical drugs have been shown to have inhibitory effects on the HMG-CoA Reductase enzymes (Williams, 2002; Tobert, 2003). HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase enzyme is very well established as a rate limiting enzyme involved in the biosynthesis of cholesterol in humans. As such, it has become a primary target for researchers from the pharmaceutical industry and medicinal plants scientist for any compounds that may have inhibitory effects on this enzyme. In fact, cholesterol-lowering drugs, collectively known as statins, are inhibitors of the enzyme HMG-CoA reductase. Inhibition of this enzyme leads to lower production of cholesterol biosynthesis in humans which ultimately leads to a reduction in cardiovascular health risks (Williams, 2002).

Interestingly, medicinal plants including garlic have been used for centuries due to its versatile health benefits, including but not limited to, its cancer-protective and cardiovascular-protective effects, but the scientific support were minimal at best until recently. Its anti-hypercholesterolemic effects and its mechanisms were elucidated to include depression of hepatic activities of lipogenic and cholesterogenic enzymes such as malic enzyme, fatty acids synthase, glucose-6 phosphate dehydrogenase and HMG-CoA reductase. Furthermore, garlic was also shown in a randomized, double-blind placebo controlled clinical trial to lower cholesterol levels in 30 men with plasma cholesterol concentration between 220 and 285 mg/dL (Yeh & Liu, 2001).

In addition to inhibitory effects of pharmaceutical drugs and medicinal plants on HMG-CoA Reductase enzymes, as a way of controlling cholesterol levels, the acyl-CoA:cholesterol acyltransferase, commonly known as ACAT, is the enzyme responsible for esterification of intra-cellular free cholesterol to cholesterol esters leading to promotion of storage of lipids in various tissues in the body (Brewer, 2000; Buhman *et al*., 2001). While ACAT enzymes are divided into $ACAT_1$ and $ACAT_2$, their functions also differ from one another. $ACAT_1$ appears to help maintain free cholesterol balance while $ACAT_2$ is involved in cholesterol absorption in the intestine, transportation of chylomicrons, and providing cholesterol esters to the liver for the production of VLDL. Therefore it is desirable that in order to lower cholesterol levels in hypercholesterolemic subjects, the ACAT enzymes must be suppressed with either pharmaceutical drugs or medicinal plants. Hence, some researchers even suggest that HMG-CoA reductase and ACAT enzymes must be suppressed concomitantly to bring high cholesterol levels closer to baseline, and further reduce the risk for cardiovascular diseases (Lada *et al*., 2007; Burnett *et al*., 1999; Lee *et al*., 2001; Sliskovic & White, 1991).

Serum cholesterol levels, triglycerides, homocysteine and LDLs have been reported to be lowered while HDL increases by ingestion of a commercial noni fruit juice, TNOB, in a double blind, placebo control human clinical trial involving 38 current smokers. But, there were no significant changes in the placebo group; however, significant changes occurred in the TNOB group. In fact, total cholesterol andtriglyceride levels were lowered by 7-22% and 10-54%, respectively. Further, homocysteine and LDL levels were lowered by 21% and 6-10%, respectively. In contrast, the HDL levels were increased by 16% in the TNOB group compared to the placebo group (Wang *et al*., 2006). TNOB cholesterol-lowering effects were shown in the clinical trial involving current smokers but its cholesterol-lowering effects in nonsmoking subjects has not been studied, and the cholesterol-lowering mechanisms have not been fully elucidated. To this end, a series of *in-vitro* bioassays were employed to evaluate the inhibitory effects ofTNOB, NFJC (noni fruit juice concentrates), and NFJME (a methanol fraction of noni fruit juice) on HMG-CoA Reductase and $ACAT_{hepatic/intestine}$ enzymes to elucidate its possible mechanism of actions. Further, an open label, pilot human clinical trial was also set up to evaluate TNOB cholesterol-lowering effects in ten, nonsmoking subjects with cholesterol levels ranging from 134 to 229 mg/dL.

MATERIALS & METHODS

Noni samples

Commercial noni fruit juice products, TNOB, and a concentrate of noni fruit juice (NFJC), were obtained from Tropical Resources Inc., (737 East 1180 South American Fork, Utah, USA). These noni products are made exclusively from noni fruits grown in French Polynesia. Noni fractions from our internal bioassay-guided fractionation project were extracted as follows: Two kilograms of freeze-dried powder of *M. citrifolia* puree (lot #52410) was percolated with 20 L of methanol to afford MeOH extract solution. The solution was concentrated to a syrup, under pressure using a rotary evaporator. A small portion of the syrup was taken and dried to result in 2 g of the MeOH extract of the noni fruit powder. The remaining of the syrup was added with 3 L of H_2O, and then partitioned sequentially against petroleum ether (3 L x 4) and EtOAc (3 L x 3), to afford petroleum ether (41.7 g) and EtOAc (47.7 g) partitions yielding the noni fruit juice methanol extracts (NFJME).

Effects of TNOB, NFJC and NFJME on HMG-CoA reductase enzymes

The effects of TNOB, NFJC and NFJME on HMG-CoA Reductase enzyme activity were evaluated using the method

described previously (Heller & Gould, 1975; Kubo & Strott, 1987). Briefly, the reaction mixture included 1, 5, and 10 mg/mL TNOB and NFJC, and also 100 µg/mL of NFJME, in duplicates, and a 2.5 µM [^{14}C] HMG-CoA, in 1% DMSO, and incubated with incubation buffer consisting of 100 mM KH_2PO_4, pH 7.5, 20 mM G-6-P, 2.5 mM NADP, 10 mM EDTA, 5 mM DTT, 1.4 U G-6-DH. The reaction mixture was further incubated at 37^{o}C for 15 min. The reaction was quantitated using [^{14}C] Mevalonate and Lovastatin was used as a reference compound. Significant criteria were set at ≥ 50% of stimulation or inhibition.

Effects of TNOB and NFJC on ACAT enzymes (intestine & hepatic)

The ACAT (hepatic & intestine) enzymes activity was evaluated using the method described previously (Largis *et al*., 1989; Sliskovic *et al*., 1991). Briefly, the reaction mixture included 1, 5, and 10 mg/mL of TNOB and NFJC, in duplicates, an 18µM [^{14}C] Palmitol CoA (intestinal) and 12.7 µM [^{14}C] Palmitol CoA for hepatic in 1% DMSO. The mixture was then incubated with the incubation buffer consisting of 0.2 M Potassium Phosphate, pH 7.4, 105 mg/mL BSA at 37^{o}C for 15 min. The reactions were quantitated using [^{14}C] cholesterol ester by column chromatography and Lovastatin was used as a reference compound. Significant criteria were set at ≥ 50% of stimulation or inhibition.

TNOB potential cholesterol-lowering evaluation in non-smokers

TNOB was evaluated for its cholesterol-lowering potential in 10 non-smoking subjects (age 40+) who were considered to have normal and borderline high cholesterol levels, but were not currently taking prescribed cholesterol-lowering medication, drinking alcohol and smoking cigarettes. Participants were required to read, understand, and sign informed consent forms. They were required to fast 4 hours prior to being pre-tested and before post-tested at the end of the trial. Participants blood LDL, HDL, and total cholesterol was measured before and after the trial under the supervision of staff of BYU-Hawaii Health Center. Each participant drank 2 ounces of TNOB in the morning without diluting it or mixing it with any other liquids, and in the evening, 30 minutes before meals, consecutively for 30 days. They were also told not to change their eating habits and lifestyles during the trial. Participants were contacted every week through email to make sure they were drinking the proper amounts of TNOB, and to ensure that no complications existed. The pilot study was conducted in conformity with Ethical Principles for Medical Research Involving Human Subjects as described in the Declaration of Helsinki, and in OCR HIPAA Privacy.

Analysis of the Data

Descriptive statistics, such as the mean ± standard deviation (SD), were calculated for the participants' cholesterol biomarkers such as LDL, HDL and total cholesterol levels (TC) and the total cholesterol and HDL ratios (TC/HDL) before and after the trial. The pre- and post-trial data were analyzed statistically using Student's *t*-test to assess the significance of any changes in the cholesterol biomarkers at the $P<0.05$ level of confidence.

RESULTS

To evaluate the inhibitory effects of noni on HMG-CoA Reductase enzymes, noni samples in various concentrations, were incubated with the enzymes and enzyme inhibition was quantified using EIA. TNOB and NFJC were shown to inhibit HMG-CoA Reductase enzymes concentration dependently. TNOB, in 1, 5, and 10 mg/mL concentrations, inhibited HMG-CoA Reductase enzymes by 50, 81 and 83%, respectively (Fig. 1) while NFJC, in the same concentrations, inhibited the same enzymes by 58, 94 and 96%, respectively with <1.0 mg/mL IC_{50} (Fig. 2). NFJME, in 100 µg/mL, inhibited HMG-CoA Reductase enzymes by 81%.

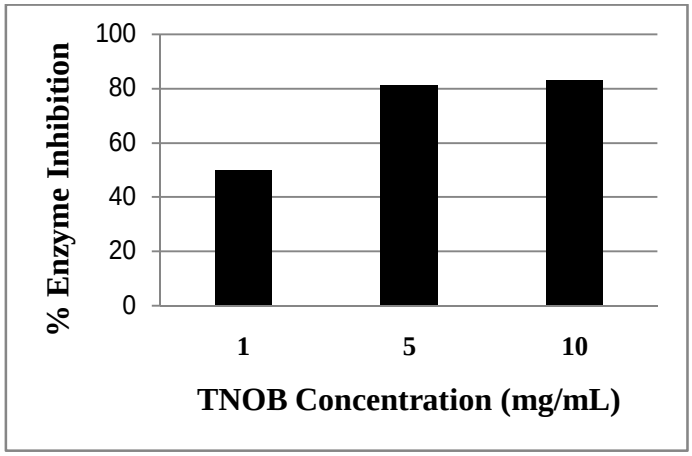

Fig. 1: Average percent inhibitory effects of TNOB, in various concentrations, in duplicates, on HMG-CoA Reductase enzymes *in-vitro*.

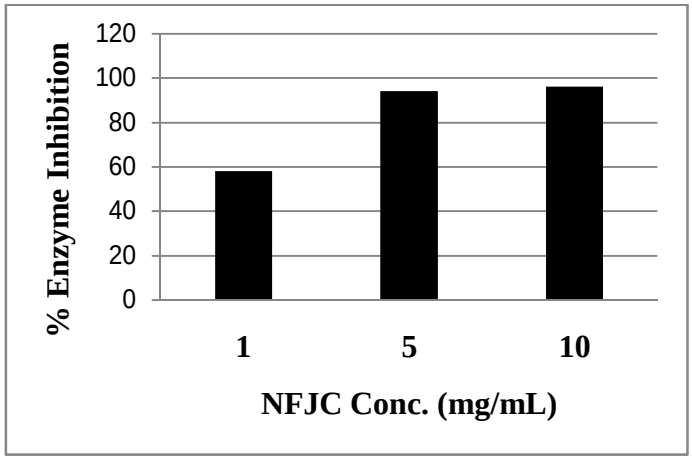

Fig. 2: Average percent inhibitory effects of NFJC, in various concentrations, in duplicates, on HMG-CoA Reductase enzymes *in-vitro* with IC_{50} = <1.0 mg/mL.

Since both ACAT (hepatic) and ACAT (intestine) enzymes normal function includes cholesterol homeostasis, and

over-active ACAT enzymes are known to contribute to atherosclerosis, noni effects on ACAT enzyme activities were examined. TNOB and NFJC inhibit both ACAT (hepatic& intestine) enzymes, concentration dependently, but were lower than their inhibitory effects on HMG-CoA Reductase enzymes. Concentrations of 1 and 5 mg/mL of TNOB inhibited ACAT (hepatic) enzymes by 5 and 17%, respectively, while at the same concentrations, TNOB inhibited ACAT (intestine) enzymes by 9 and 31%, respectively. NFJC, in 1 and 5 mg/mL inhibited ACAT (hepatic) enzymes by 75 and 94%, respectively, while in the same concentrations, NFJC inhibited ACAT (intestine) by 68 and 90%, respectively.

Table 1: Pre-trial levels* (mean ± SD) of cholesterol, HDL, LDL and ratio of total cholesterol and HDL in non-smoking subjects before the trial (p<0.99).

Cholesterol Levels				
Subjects	**Total Cholesterol (TC)**	**HDL**	**LDL**	**TC/HDL Ratio**
1	164	41	105	3.9
2	229	62	144	3.7
3	134	25	69	5.3
4	200	40	120	5.0
5	212	43	150	5.0
6	225	42	144	5.4
7	147	35	89	4.2
8	219	39	152	5.6
9	162	41	102	3.9
10	152	31	74	4.9
Totals	1844	399	1149	46.9
Average	184.4	39.9	114.9	4.7

*TC: 184.4±36.1; HDL: 39.90±9.61; LDL: 114.9±31.7; TC/HDL ratio: 4.7±0.7

Cholesterol lowering effects of noni was evaluated in non-smoking subjects having desirable (<200 mg/dL) and borderline high cholesterol levels (200-239 mg/dL). Table 1 shows the pre-trial levels of total cholesterol, HDL, and LDL levels, and the ratio of total cholesterol and HDL levels while Table 2 shows the post-trial levels. The average of each category such as the total cholesterol, LDL, and TC/HDL ratio of before and after the trial all falls within the appropriate range except HDL, which is slightly lower.

Table 2: Post-trial levels* (mean ± SD) of total cholesterol (TC), HDL, LDL and ratio of total cholesterol and HDL in non-smoking subjects taking 4 ounces of TNOB for 30 days (p<0.99).

Cholesterol Levels				
Subjects	**Total Cholesterol (TC)**	**HDL**	**LDL**	**TC/HDL Ratio**
1	150	39	96	3.8
2	197	49	131	4.0
3	148	24	82	6.2
4	212	46	140	4.6
5	206	43	129	4.8
6	228	42	155	5.4
7	160	50	82	3.2
8	241	37	158	6.5
9	161	40	101	3.9
10	121	32	67	3.7
Totals	1824	402	1141	46.1
Average	182.4	40.2	114.1	4.6

*TC: 182.4±39.6; HDL: 40.2±7.89; LDL: 114.1±32.6; TC/HDL ratio: 4.6±1.11

The total cholesterol decreased by 2.0 (pre-trial: 184.4±36.1; post-trial: 182.4±39.6); HDL increased by 0.3 (pre-trial: 39.90±9.61; post-trial: 40.2±7.89); LDL decreased by 0.8 (pre-trial: 114.9±31.7; post-trial: 114.1±32.6); and TC/HDL ratio decreased by 0.1 (pre-trial: 4.7±0.7; post-trial: 4.6±1.11) after 30 days. Even though the changes in the total cholesterol, HDL, and LDL levels, and the TC/HDL ratios in the post-trial were not statistically significant (p<0.9981) at the 95% level of confidence, there is a trend towards decreasing levels of total cholesterol and LDL levels, and TC/HDL ratio after 30 days. However, there is also a trend for increasing HDL levels.

DISCUSSION

The discovery of statins, which have the ability to lower blood cholesterol levels, fueled much excitement among those sufferings from hypercholesterolemia, and hypercholesterolemia-related diseases. Statins have now been successfully used for decades in the treatment of hypercholesterolemia, but sometimes some of the patients experienced side effects, such as severe myopathy, and rhabdomyolysis, and creatine phosphokinase elevation to name just a few(Tokinaga *et al.*, 2006; Sinzinger *et al.*, 2002). The mechanism for the statins cholesterol-lowering effect has been described in the literature and is reported to inhibit the HMG-CoA Reductase enzyme, which is involved in the rate limiting steps of cholesterol biosynthesis in humans (Stancu & Sima, 2001; Maron *et al.*, 2000; Cordle *et al.*, 2005).

ACAT is an important part of the membrane proteins that are localized in the endoplasmic reticulum which catalyzes the formation of cholesterol esters from cholesterol and fatty acyl coenzyme A. Cholesterol esters are then stored in lipid droplets in the cytoplasm of the cell. This process is tightly regulated and it is crucial to maintaining proper cholesterol levels in humans to avoid cardiovascular diseases (Leon *et al.*, 2005). However, evidences from other studies reveal that mice lacking $ACAT_2$, on a low cholesterol regular commercial diet, had plasma cholesterol concentrations similar to those of wild type mice. But when the $ACAT_2$-deficient mice were fed a high fat and high cholesterol diet, they maintained normal cholesterol levels and were resistant to gallstone formation compared to wild-type mice, which experienced more than twofold increases in cholesterol, and concomitantly developed gallstone (Buhman *et al.*, 2000; Chen, 2001).

We were able to show that TNOB and NFJC have inhibitory effects on HMG-CoA Reductase and ACAT enzymes. However, NFJC inhibitory effects on HMG-CoA Reductase enzymes was more pronounced, with <1.0 mg/mL IC_{50}, than the inhibition of HMG-CoA Reductase enzymes by TNOB at the 1, 5, and 10 mg/mL concentrations. NFJC is a concentrate made from noni fruit juice, and it inhibitory effects on HMG-CoA Reductase demonstrated that there are compounds or a compound, present in nonifruit that has the potential to not only inhibit HMG-CoA

Reductase and ACAT enzymes *in-vitro* but perhaps in humans as well as reported by Wang and colleagues (2006). The potential existence of a compound or compounds in the noni fruit juice was later confirmed when we evaluated the inhibitory effects of NFJME on HMG-CoA Reductase. NFJME, in 100 µg/mL concentration, inhibited HMG-CoA Reductase enzymes by 81%, which is essentially the same amount of inhibition observed under 5 mg/mL concentration of TNOB. But the NFJME inhibition of HMG-CoA Reductase enzymes was less than the inhibition of NFJC (94%) on HMG-CoA Reductase, at the 5, and 10 mg/mL concentrations. However, the inhibition of NFJC at the 10 mg/mL concentration was not significantly different from that of the 5 mg/mL concentration. Therefore, we speculate that perhaps there are more HMG-CoA Reductase inhibitory compounds present in the noni fruit juice concentrates that compete for the active site of the HMG-CoA Reductase enzymes, and at higher concentrations, the enzymes reach its saturation point. Hence, NFJC concentrations beyond 5 mg/mL do not add any more inhibition of the enzymes that will be significantly different from its saturation point. As such, further research into enzymes saturation capacity with noni fruit juice is warranted.

The results from the *in-vitro* bioassays show that both noni samples, TNOB and NFJC, inhibited both HMG-CoA Reductase and ACAT (hepatic & intestine) enzymes, concentration dependently, and NFJME contains active compounds against HMG-CoA Reductase enzymes. These enzymes are also known to be involved in the biosynthesis, homeostasis, and cholesterol trafficking in humans. Interestingly, Kamiya and colleagues (2004) showed that some of the chemical constituents of the noni fruit juice (3, 3'-bisdemethylpinoresinol, americanol A, americanin A, americanoic acid A, morindolin, and isoprincepin) inhibited copper-induced LDL oxidation, obtained from the MeOH extract and the EtOAc-soluble phase which showed 88 and 96% inhibition, respectively. The inhibitory effects of noni fruit juice on HMG-CoA Reductase, and the ACAT enzymes (intestinal and hepatic) obtained from this study, together with the inhibiting effect on copper-induced LDL oxidation, may explain, at least in part, the cholesterol lowering effects observed in the clinical trial of current smokers drinking TNOB reported by Wang and colleagues (2006).

Additionally, the results from this trial, though not significant, showing trends towards lowering cholesterol and LDL levels, and increasing HDL level. It was also interesting to see that majority of the participants with cholesterol levels in the normal range remains in the normal range. Further, there were 5 people, at the starting of the trial, with cholesterol levels ≥ 200 mg/dL which was reduced to only 4 people after the trial. Perhaps, the shorter period of time for this trial, and the inclusion of the subjects with cholesterol levels in the normal range, and all participants not modifying their diets during the trial affected the significance of the results after the trial. Therefore, a longer trial, at least from 3-6 months, with nonsmoking participants, having higher cholesterol levels (≥240 mg/dL) will allow us to see the actual effects of TNOB on cholesterol levels. Additionally, a longer trial may also help answer whether the trends seen in a shorter trial is actually realized. That is, if TNOB trend for lowering cholesterol levels after just one month of use continues to lower cholesterol levels after 3 and 6 months. In conclusion, to our knowledge, our laboratory is the first to elucidate that the inhibitory effect of noni on HMG-CoA Reductase and ACAT enzymes is a possible mechanism which explains the cholesterol-lowering effects of noni fruit juice. Base on our *in-vitro* and human pilot study results, and results reported by Wang and colleagues (2006), and Kamiya and colleagues (2004), a longer human clinical trial is warranted to assess the efficacy and dosage of the noni fruit juice blend, TNOB, on hypercholesterolemic nonsmoking subjects with cholesterol levels above 220 mg/dL.

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Conflict of Interest

Authors 'Afa K. Palu and Brett J. West are employees of Morinda Bioactives.

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