



Letter to the Editor

Pterostilbene raises low density lipoprotein cholesterol in people



Keywords:

Pterostilbene
Low density lipoprotein cholesterol
Sirtuin 1
Nicotinamide riboside
Polyphenol

Resveratrol and pterostilbene are polyphenolic compounds found in fruits and nuts. Though resveratrol does not depend on sirtuin 1 for its metabolic effects [1,2] and pterostilbene has not been shown to bind to sirtuin 1, Elysium Health combines nicotinamide riboside (NR) [3] with pterostilbene with the expressed purpose of increasing sirtuin 1 activity by a combined mechanism [4]. The literature indicates that sirtuin 1 activators would be expected to improve lipid management [5,6]. However, as summarized in Table 1, daily administration of NR plus pterostilbene produced a dose-dependent and clinically statistically significant increase in total cholesterol driven entirely by increased low density lipoprotein cholesterol (LDL-C) [4]. The authors did not release their primary data for independent assessment of significance and did not disclose results previously reported for pterostilbene [7] that are wholly consistent with the study's finding of what is clearly a clinically meaningful increase in LDL-C. While the authors cite this study to point out the earlier observation that pterostilbene reduced blood pressure, they neglected to cite clinically meaningful increases in LDL-C for treatment groups receiving 100 mg or 250 mg daily pterostilbene for 6–8 weeks (Table 1) as well as significantly decreased high density lipoprotein cholesterol in subjects who were not taking statins [7]. These data are inconsistent with pterostilbene as a sirtuin 1 activator and raise important questions about the safety of pterostilbene supplementation considering the importance of controlling LDL-C to cardiovascular health [8,9]. Significantly, clinical studies of NR alone (without pterostilbene) at higher doses than tested in the Elysium Health study established safety and showed no increase in LDL-C [10,11].

Table 1
Pterostilbene elevates LDL-C.

Pterostilbene dose (mg/day)	Placebo-corrected increase in LDL-C (mg/dl)	P-value
100 (7)	20.0	0.006
250 (7)	19.7	0.007
50 with 250 mg NR (4)	5.4	≤0.05
100 with 500 mg NR (4)	14.7	≤0.05

Conflict of interest

CB developed intellectual property exclusively licensed and developed by ChromaDex for nutritional and therapeutic uses of NR.

References

- [1] Pacholec M, Bleasdale JE, Chrnyk B, Cunningham D, Flynn D, Garofalo RS, et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. *J Biol Chem* 2010;285(11):8340–51. <https://doi.org/10.1074/jbc.M109.088682>.
- [2] Park SJ, Ahmad F, Philp A, Baar K, Williams T, Luo H, et al. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell* 2012;148(3):421–33. <https://doi.org/10.1016/j.cell.2012.01.017>. S0092-8674(12)00030-X.
- [3] Bieganowski P, Brenner C. Discoveries of nicotinamide riboside as a nutrient and conserved NRK genes establish a preiss-handler independent route to NAD+ in fungi and humans. *Cell* 2004;117(4):495–502. [https://doi.org/10.1016/S0092-8674\(04\)00416-7](https://doi.org/10.1016/S0092-8674(04)00416-7).
- [4] Dellinger RW, Santos SR, Morris M, Evans M, Alminana D, Guarente L, et al. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD(+) levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging Mech Dis* 2017;3:17. <https://doi.org/10.1038/s41514-017-0016-9>.
- [5] Purushotham A, Schug TT, Xu Q, Surapureddi S, Guo X, Li X. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. *Cell Metab* 2009;9(4):327–38. <https://doi.org/10.1016/j.cmet.2009.02.006>.
- [6] Hong S, Moreno-Navarrete JM, Wei X, Kikukawa Y, Tzamelis I, Prasad D, et al. Nicotinamide N-methyltransferase regulates hepatic nutrient metabolism through Sirt1 protein stabilization. *Nat Med* 2015;21(8):887–94. <https://doi.org/10.1038/nm.3882>.
- [7] Riche DM, Riche KD, Blackshear CT, McEwen CL, Sherman JJ, Wofford MR, et al. Pterostilbene on metabolic parameters: a randomized, double-blind, and placebo-controlled trial. *Evid Based Complement Alternat Med* 2014;2014:459165. <https://doi.org/10.1155/2014/459165>.
- [8] Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American college of cardiology/American heart association task force on practice guidelines. *J Am Coll Cardiol* 2014;63(25 Pt B):2935–59. <https://doi.org/10.1016/j.jacc.2013.11.005>.
- [9] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63(25 Pt B):2889–934. <https://doi.org/10.1016/j.jacc.2013.11.002>.
- [10] Martens CR, Denman BA, Mazzo MR, Armstrong ML, Reisdorph N, McQueen MB, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults. *Nat Commun* 2018;9(1):1286. <https://doi.org/10.1038/s41467-018-03421-7>.
- [11] Døllnerup OL, Christensen B, Svart M, Schmidt MS, Sulek K, Ringgaard S, et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity and lipid-mobilizing effects. *Am J Clin Nutr* 2018;108(2):343. <https://doi.org/10.1093/ajcn/nqy13>.

Charles Brenner*
Department of Biochemistry, University of Iowa, Iowa City, USA
Amy C. Boileau
ChromaDex, Inc, Irvine, USA

* Corresponding author.
E-mail address: charles-brenner@uiowa.edu (C. Brenner).

28 September 2018