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Nutrigenomics: Using Sulforaphane Consumption as a Mechanism to Prevent Cardiovascular Disease through Epigenetic Regulation

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Broccoli saves lives: How sulforaphane can prevent cardiovascular disease through epigenetic regulation

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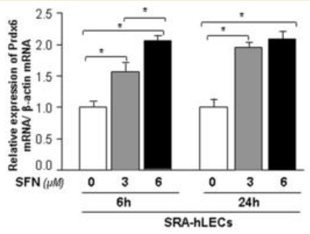
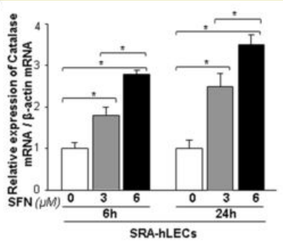
Introduction

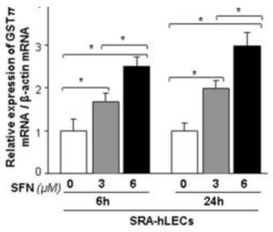
Cardiovascular disease is the leading cause of death in the United States. Diet composition and reduced expression of Nrf2,a transcription factor that binds with the antioxidant response element (ARE) to control a battery of antioxidant genes and phase II enzymes, are both possible factors contributing to cardiovascular disease. Hypertension is known as a ”silent killer” because its symptoms often go undetected, but it can cause dysfunctions like cardiac hypertrophy, an abnormal enlargement of the heart muscle, and eventually lead to cardiovascular disease. Nutrigenomics is an emerging field that investigates how macronutrients, micronutrients, and bioreactive chemicals directly and indirectly affect gene expression. Research in this field has shown that phytochemicals in cruciferous vegetables have great potential in preventing cardiovascular disease. As vitamin supplementation grows in scope and popularity, it is becoming common to replace vegetable consumption with multivitamins. The purpose of this research was to investigate how sulforaphane, an isothiocyanate found in its greatest quantities in broccoli, prevents cardiovascular disease through epigenetic regulation in order to promote the understanding that vitamin supplementation does not adequately replace the health benefits of phytonutrients found in vegetables. In order to investigate sulforaphane’s ability to prevent cardiovascular disease through epigenetic regulation, I studied journal articles that focused on experiments involving sulforaphane-induced activation of Nrf2, up-regulation of phase II enzymes, reductions in blood pressure, and elimination of cardiac dysfunctions. I also analyzed the effects of different preparations of broccoli on the yield of sulforaphane.

Antioxidant genes and enzymes





Kubo, Chhuncchа, Singh, Sasaki, and Singh (2017) studied SRA-hLECs. Above are graphs showing up-regulation of antioxidant genes Prdx6 and Catalase after sulforaphane treatment. To the right is a graph showing up-regulation of glutathione-S-transferase, a phase II enzyme.



- **Zhang, Su, Khor, Shu, and Kong (2013)** conducted a study on prostate TRAMP C1 cells. Researchers treated cells with sulforaphane for 5 days. Their results are shown in the table below:

Relative levels	Control	1 μM SFN	2.5 μM SFN
Nrf2 protein	1.00	1.38	1.40
NQO1	1.00	4.77	6.04

- **Wu et al. (2004)** studied spontaneously hypertensive stroke-prone rats. The rats were treated with 200 mg of broccoli sprouts high in glucoraphanin. The results are shown below:

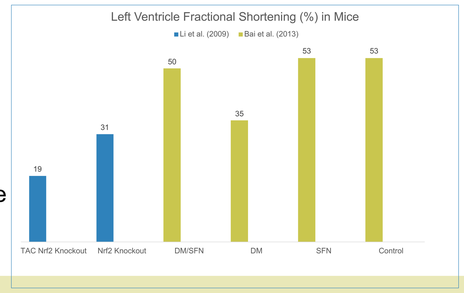
Relative enzyme levels	Control	5 .5 μM SFN
GSH	1.00	1.63
GPx	1.00	1.75
GRed	1.00	1.75

Killing the silent killer and resulting cardiac dysfunctions

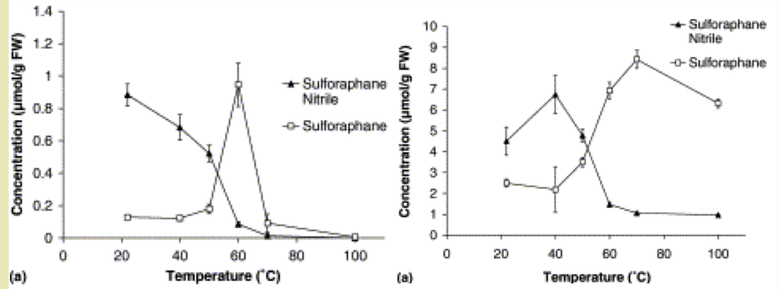
Mean Blood Pressure	3 months	6 months
Control	86.14	88.27
SFN	82.82	84.73
DM	97.42	103.53
DM/SFN	87.81	90.60

.**Bai et al. (2013)** observed that sulforaphane significantly reduced blood pressure (above) and eliminated cardiac dysfunctions such as increased interventricular septal thickness, increased left ventricle posterior wall thickness, and decreased fractional shortening (below) in diabetic mice (DM) 8-10 weeks in age.

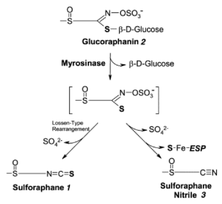
Li et al. (2009) found that Nrf2 activation prevented cardiac dysfunctions including decreased left ventricle fractional shortening (right) and cardiac hypertrophy in mice with transverse aortic constriction (TAC).



Preparation is key



- (above) **Matusheski, Juvik, and Jeffrey (2004)** found that broccoli florets (left, heated for 5 minutes) are significantly more sensitive to heat than broccoli sprouts (right, heated for 10 minutes).



- **Wu et al. (2004**) found that air-drying broccoli sprouts resulted in little to no hydrolysis of glucoraphanin, while freezing and thawing broccoli sprouts caused hydrolysis to occur, leaving no detectable glucoraphanin behind.

Conclusions

- Sulforaphane-induced activation of Nrf2 results in up-regulation of antioxidant genes including Prdx6, Catalase, and NQO1, and up-regulation of phase II enzymes such as glutathione-S-transferase, glutathione peroxidase, and glutathione reductase.
- Sulforaphane-induced activation of Nrf2 results in reduced blood pressure and elimination of cardiac dysfunctions such as cardiac hypertrophy and decreased fractional shortening.
- There is more research to be done on the ideal preparation of broccoli to maximize health benefits, but mild heating and little exposure to water during cooking of broccoli will maximize sulforaphane yield during consumption.

References

- Applewhite, J. S. (2009). Food and Farm Eastern Broccoli [Photograph]. Arlington, VA.
- Bai, Y., Cui, W., Xin, Y., Miao, X., Barati, M. T., Zhang, C., . . . Cai, L. (2013). Prevention by sulforaphane of diabetic cardiomyopathy is associated with up-regulation of Nrf2 expression and transcription activation. Journal of Molecular and Cellular Cardiology, 57, 82-95. doi:10.1016/j.yjmcc.2013.01.008
- Kubo, E., Chhunchha, B., Singh, P., Sasaki, H., & Singh, D. P. (2017). Sulforaphane reactivates cellular antioxidant defense by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress. *Scientific Reports (Nature Publisher Group)*, *7*, 1-17. doi: 10.1038/s41598-017-14520-8
- Li, J. S., Ichikawa, T. L., Villacorta, L., Janicki, J., Brower, G., Yamamoto, M., & Cui, T. (2009). Nrf2 protects against maladaptive cardiac responses to hemodynamic stress. Arteriosclerosis, Thrombosis, and Vascular Biology, 29(11), 1843-1850. doi:10.1161/ATVBAHA.109.189480
- Matusheski, N. J., Juvik, J. A., & Jeffery, E. H. (2004). Heating decreases epithiospecifier protein activity and increases sulforaphane formation in broccoli. *Phytochemistry*,*65*(9), 1273-1281. doi:10.1016/j.phytochem.2004.04.013
- Popov. A. [Blood pressure]. Retrieved from https://www.sciencealert.com/experts-change-what-high-blood-pressure-hypertension-is
- Wu, L., Noyan Ashraf, M. H., Facci, M., Wang, R., Paterson, P. G., Ferrie, A., & Juurlink, B. H. J. (2004). Dietary approach to attenuate oxidative stress, hypertension, and inflammation in the cardiovascular system. Proceedings of the National Academy of Sciences, 101(18), 7094–7099. doi:10.1073/pnas.0402004101
- Zhang, C., Su, Z., Khor, T. O., Shu, L., & Kong, A. T. (2013). Sulforaphane enhances Nrf2 expression in prostate cancer TRAMP C1 cells through epigenetic regulation. Biochemical Pharmacology, 85(9), 1398-1404. doi:10.1016/j.bcp.2013.02.010

Acknowledgements

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