

The Age of Nutraceuticals: Exploring New Therapeutic Targets

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In the modern era, cardiovascular disease prevention still represents a difficult clinical challenge. Despite the impressive innovations in both diagnostic options and therapeutic interventions observed over the last decades, which have been leading to a substantial reduction of in-hospital mortality due to acute cardiovascular and cerebrovascular events, it remains a high burden of out-of-hospital morbidity, which is currently sustained and increased by the large proportions of high-risk patients who are survivors after acute myocardial infarction, stroke and congestive heart failure [1–3]. This has obvious and relevant consequences, both from a therapeutic point of view, as well as from a socio-economic point of view, and heavily affects the sustainability of the health care systems in various Countries, worldwide.

Several reasons can be advocated for explaining the persistently high burden of cardiovascular and cerebrovascular diseases [4–7]. Among these, the relatively poor adherence to conventional therapeutic strategies in high risk patients, the mounting prevalence of major conventional risk factors, such as smoking, hypertension, hypercholesterolemia, obesity and diabetes in the general population, as well as the growing incidence of novel and unconventional risk factors, mostly including sedentary, working and personal stressors, unbalanced diet (i.e. junk

food), atherogenic dyslipidaemia, metabolic syndrome, hyperuricemia, environmental pollution and atmospheric variations in apparently healthy individuals, all are items that might be involved in determining the susceptibility to major cardiovascular and cerebrovascular accidents.

Several pharmacological agents can be used to effectively reduce this risk, although several studies suggested that these drugs are affected by relatively low adherence and persistence over time and that they do not work, if not associated with virtuous life-style and healthy diet. However, diets are often rich in uric acid-raising components, such as purines, proteins and sugars, thus leading to a progressive and marked increase in serum uric acid concentrations. This condition has demonstrated to have potentially relevant clinical consequences on major cardiovascular and cerebrovascular outcomes. On the other hand, Mediterranean diet has been viewed for long time as a valid support for effective prevention of cardiovascular diseases, also in view of its positive effect of serum uric acid concentration. Unfortunately, dietary changes are often not recommended by prescribing physicians and/or recommended but characterized by poor adherence and even worst persistence to the prescribed diet by patients.

In the latest few years, the search and the potential clinical applications of nutraceuticals have been actively pursued and have been often successful. The introduction of natural compounds for management of several clinical conditions, including cardiovascular diseases, has been generally well perceived by asymptomatic high-risk patients, and their use has displayed an impressive growth in the general population. As an example, the application of nutraceuticals for the management of several metabolic disorders, such as hypercholesterolemia or lipid abnormalities, is currently having a very favourable impact. As a consequence, physicians have

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shifted their prescriptions from conventional drugs (i.e. statins) to nutraceuticals, especially in the presence of mild hyperlipidemia [8–10]. This therapeutic approach is often based on and supported by preferences and requests expressed by patients with respect to conventional lipid lowering therapies, even in the case of well-documented drugs, most of all, for the fear of unfavourable side effects. This behaviour may not be shared and conceptually supported in many cases. However, at the same time, it has an intrinsic advantage, because it makes the patient more aware, compliant and committed to take care of a certain cardiovascular risk factor, by associating more virtuous and healthy life-style measures with the regular use of a nutraceutical approach which may permit to achieve levels closer to or within normality.

High levels of uric acid are currently viewed not only as a metabolic abnormality leading to chronic hyperuricemia without or with gout, but also as an additional potential cardiovascular risk factor, predisposing to major cardiovascular events [11, 12]. This view has a solid epidemiological background and evidence, and thus it is currently analysed to seek whether its normalization by the pharmacological approach available leads to lesser cardiovascular risk and disease [13].

In this issue of High Blood Pressure and Cardiovascular Prevention, a proof-of-concept pilot study by Rozza and co-workers [14] introduces the novel observation that a nutraceutical compound, Zinutrik, containing a fixed combination of kaempferol, baicalin, caffeine and rutin, is able to reduce uric acid levels in asymptomatic hyperuricemic patients. This double-blind, placebo-controlled, randomized pilot study (PICONZ-UA) also explores, though on a relatively small sample and over a short-term observation, the influence of this compound on the Framingham risk score [15], showing a global improvement and suggesting a promising, positive influence, even only within the short-time frame of the study observation.

Obviously, this novel approach may reveal very helpful in a clinical context, such as asymptomatic hyperuricemia in which life-style and dietary approach often fail due to poor adherence and lack of confidence of physicians to put on conventional drug treatment asymptomatic patients. Beside the significant reduction of blood levels of uric acid clearly supported by the results obtained, the study shows intriguing results on lipid profile and Framingham risk score [15], which, as suggested by authors, may be due to the properties of kaempferol, a polyphenol which can block NADPH oxidase and thus interfere with the oxidative process and of baicalin, a concentrated extract of the dried root of *scutellaria baicalensis*, which displays scavenging action on radical oxygen species. Altogether, Zinutrik may be able to counteract the pro-oxidant promoting activity of elevated uric acid levels.

Of course, larger and longer observations may be required to define the full potential of this new nutraceutical fixed combination with interesting properties. However, at this stage, this pilot study opens a new field of therapeutic application for nutraceuticals and a new exciting season for this area of investigation and clinical use.

Compliance with Ethical Standards

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References

1. Abrahamsson P, Dobson J, Granger CB, McMurray JJ, Michelson EL, Pfeffer M, et al. Impact of hospitalization for acute coronary events on subsequent mortality in patients with chronic heart failure. *Eur Heart J*. 2009;30(3):338–45.
2. Shah RU, Tsai V, Klein L, Heidenreich PA. Characteristics and outcomes of very elderly patients after first hospitalization for heart failure. *Circ Heart Fail*. 2011;4(3):301–7.
3. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116(13):1482–7.
4. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet*. 2011;377(9765):557–67.
5. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet*. 2011;377(9765):578–86.
6. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*. 2011;378(9785):31–40.
7. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet*. 2011;377(9765):568–77.
8. Izzo R, de Simone G, Giudice R, Chinali M, Trimarco V, De Luca N, et al. Effects of nutraceuticals on prevalence of metabolic syndrome and on calculated Framingham Risk Score in individuals with dyslipidemia. *J Hypertens*. 2010;28(7):1482–7.

9. Jung MH, Seong PN, Kim MH, Myong NH, Chang MJ. Effect of green tea extract microencapsulation on hypertriglyceridemia and cardiovascular tissues in high fructose-fed rats. *Nutrition research and practice*. 2013;7(5):366–72.
10. Trimarco V, Izzo R, Stabile E, Rozza F, Santoro M, Manzi MV, et al. Effects of a new combination of nutraceuticals with *Morus alba* on lipid profile, insulin sensitivity and endothelial function in dyslipidemic subjects. A cross-over, randomized, double-blind trial. *High Blood Press Cardiovasc Prev*. 2015;22(2):149–54.
11. Silbernagel G, Hoffmann MM, Grammer TB, Boehm BO, Marz W. Uric acid is predictive of cardiovascular mortality and sudden cardiac death in subjects referred for coronary angiography. *Nutr Metab Cardiovasc Dis*. 2013;23(1):46–52.
12. Kleber ME, Delgado G, Grammer TB, Silbernagel G, Huang J, Kramer BK, et al. Uric acid and cardiovascular events: a Mendelian randomization study. *J Am Soc Nephrol*. 2015;26(11):2831–8.
13. Savarese G, Ferri C, Trimarco B, Rosano G, DelleGrottaglie S, Losco T, et al. Changes in serum uric acid levels and cardiovascular events: a meta-analysis. *Nutr Metab Cardiovasc Dis*. 2013;23(8):707–14.
14. Rozza I, Trimarco V, Izzo R, Grassi D, Ferri C. Effects of a novel fixed combination of nutraceuticals on serum uric acid concentrations and the lipid profile in asymptomatic hyperuricemic patients. Results from the PICONZ-UA study. *High Blood Press Cardiovasc Prev* 2016;23(4). doi:[10.1007/s40292-016-0168-x](https://doi.org/10.1007/s40292-016-0168-x).
15. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Group CHDRP. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2):180–7.