

# Nutraceuticals in cardio-metabolic therapy

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ABSTRACT

Cardiovascular diseases are the leading cause of death in the Western world and the leading cause of death, hospitalization and disability among people with type 2 diabetes mellitus. The aim of this paper is to discuss which nutraceuticals could be helpful in controlling factors contributing to high cardiovascular risk, such as type 2 diabetes, hypertension and dyslipidaemia.

## Keywords

Cardiovascular diseases  
Nutraceuticals  
Prevention

Cardiovascular diseases are the leading cause of death in the Western world and the leading cause of death, hospitalization and disability among people with type 2 diabetes mellitus [1]. The incidence of cardiovascular disease in patients with diabetes is more than double that in those without diabetes. Similarly, the mortality rate after a first myocardial infarction in patients with diabetes is much higher than that in those without diabetes [2,3].

Factors contributing to the high cardiovascular risk in patients with diabetes include:

- Risk factors such as hypertension and dyslipidaemia: insulin resistance, typical of diabetes, leads to reduced absorption and utilization of fatty acids in the muscles. Visceral adipose tissue also increases lipolysis and releases a greater quantity of fatty acids. These two factors cause a rise in circulating free fatty acids, resulting in increased production of VLDL in the liver.

- Increased atherosclerotic disease (macro- and microangiopathy): insulin resistance and hyperinsulinism lead to activation of pro-inflammatory cytokines, resulting in endothelial dysfunction responsible for atherosclerosis (diabetic macroangiopathy) which causes chronic heart disease and peripheral artery disease. Moreover, hyperglycaemia increases oxidative stress and promotes the formation of glycosylation end products and diacylglycerol. These three factors are implicated in atherosclerosis of small vessels (diabetic microangiopathy), resulting in the onset of diabetic retinopathy, diabetic nephropathy and diabetic foot.
- A pro-thrombotic state with increased platelet reactivity and consequent increased vulnerability and susceptibility to atherosclerotic plaque rupture: hyperglycaemia, insulin resistance and obesity lead to increased production of inflammatory factors and fibrinogen. Activation of coagulation, inhibition of fibrinolysis and increased platelet reactivity cause hyperaggregability. Patients with diabetes and cardiovascular disease have an excess of thromboxane A<sub>2</sub> which has a potent vasoconstrictor effect and simultaneously induces platelets to aggregate [4].
- Dysfunction of myocardial muscle cells (diabetic cardiomyopathy) in patients with diabetes: energy metabolism in myocytes is impaired, with reduced glucose utilization, the utilization of fatty acids as the main source of energy, an increase in oxygen use and lower contractile efficiency. The increased oxidative stress and reduced nitric oxide production lead to increased apoptosis with loss of myocytes, an increase in proteins of the extracellular matrix and myocardial fibrosis.

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Patients with diabetes and at risk of cardiovascular disease should be strongly encouraged to change their lifestyle, with the aim of improving their glycaemic control, blood pressure and lipid profile. Suitable drug therapies are commercially available, but patients often prefer to take natural remedies. Consequently, nutraceuticals have been increasingly used in recent years to treat patients. Nutraceuticals are substances of natural origin with pharmacological properties and are designed to be good adjuvants, in conjunction with diet and drug treatment, and to improve health status. Different nutraceuticals with various characteristics, including antioxidant, lipid-lowering, hypoglycaemic and anti-obesity properties, are on the market.

Of particular interest are the nutraceuticals with cardio-metabolic properties, including L-carnitine, berberine, omega-3 polyunsaturated fatty acids, fermented red rice and alpha lipoic acid (Table 1).

L-carnitine is a natural compound found in the plasma and tissue of mammals, and is distributed mainly in skeletal and cardiac muscle. Sources of L-carnitine include meat and milk products, but it is also synthesized from lysine and methionine. L-carnitine is involved in the transportation of long chain fatty acids across the mitochondrial membrane into the matrix, has a role in the processes of  $\beta$ -oxidation and has effects on the oxidation of glucose in tissues. Clinical studies have shown that supplementation with L-carnitine promotes insulin sensitivity and has a lipid-lowering action [5–9].

*Berberis aristata* and in particular its extract, berberine, is of particular interest and has been marketed in combination with *Silybum marianum*, a potential inhibitor of P-glycoprotein, with the aim of increasing its bioavailability. The combination of *B. aristata*/*S. marianum*, based on 588 mg titrated to 85% of *B. aristata* extract berberine (equal to 500 mg of berberine) and 105 mg of extract of *S. marianum* standardized to 65% by flavanolignanes, has been shown to reduce glycated haemoglobin, basal insulin, HOMA-IR, total cholesterol, LDL cholesterol and triglyceride levels in

patients with type 2 diabetes with suboptimal glycaemic control [10]. A further study evaluated the effect of this combination on lipid profile, insulin resistance and the levels of some adipocytokines in a sample of overweight dyslipidaemic patients. Supplementation with this nutraceutical combination for 3 months in a randomized trial demonstrated a decrease in fasting insulin and HOMA-IR, and an improvement in lipid profile [11,12]. The combination of *B. aristata* and *S. marianum* has also been shown to be effective in improving the lipid profile in combination with statins in patients unable to tolerate high statin doses [13].

Omega-3 fatty acids are long-chain polyunsaturated fatty acids, components of the cell membranes of organs and tissues. Even at moderate concentrations, they are able to modulate complex biological processes, influencing the progression of the affecting disease and the functionality of the cardiovascular, nervous and immune systems. Omega-3 polyunsaturated fats have demonstrated a positive effect by lowering triglycerides and, in secondary prevention patients, an anti-arrhythmic action [14].

Red yeast rice is derived from common rice (*Oryza sativa*) fermented using various strains of *Monascus purpureus*. During fermentation, the yeast is enriched with monacolins, a group of substances known for their lipid-lowering ability. A cause–effect relationship has been demonstrated between the consumption of monacolin K derived from red yeast rice and the maintenance of normal levels of LDL cholesterol [14].

Alpha lipoic acid is used to treat diabetic neuropathy in combination with symptomatic treatment and physical therapy. Alpha lipoic acid has an anti-oxidant effect and is the metabolic component of some enzymatic reactions involved in glucose metabolism. A recently published study [15] showed that alpha lipoic acid delivered in a food supplement is effective in decreasing high sensitivity C-reactive protein compared to baseline and to placebo in type 2 diabetic patients. The food supplement increased superoxide dismutase and glutathione peroxidase, and decreased malondialdehyde, all anti-oxidative stress markers.

Taking everything into account, nutraceuticals should be considered drug coadjuvants and not drug alternatives: for example, nutraceuticals with lipid-lowering effects can be helpful in obtaining a satisfactory lipid profile in patients intolerant to high doses of statins. Similarly, nutraceuticals with hypoglycaemic properties cannot replace conventional anti-diabetic drugs but may be useful as an addition to standard therapy to improve insulin resistance and glycaemic control. Although nutraceuticals are naturally derived,

Nutraceutical	Effect
L-carnitine	Promotes insulin sensitivity and has a lipid-lowering effect
Berberine	Improves lipid profile and has a hypoglycaemic effect
Omega-3 polyunsaturated fatty acids	Lowers triglycerides
Fermented red rice	Improves lipid profile
Alpha lipoic acid	Improves symptoms of diabetic neuropathy, and improves oxidative stress markers

**Table 1** - Nutraceuticals with cardio-metabolic properties

not everyone can take them and they can be dangerous, so they should be used only under the direction of a physician and in combination with a balanced diet [14].

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