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IM - COMMENTARY

Silybin and metabolic disorders

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Mediterranean diet represents a fundamental strategy in the prevention of cardiovascular and metabolic disorders as demonstrated by observational and interventional trials [1]. Among the most represented elements of the Mediterranean diet are polyphenols that display protective effects on cardiometabolic disorders by counteracting oxidative stress that represent a key point of the preventive strategy in this setting. Hence, oxidative stress seems to be involved in both cardiovascular and metabolic disorders [2]. Indeed, atherosclerotic disease is associated with increased level of oxidative stress [3] as well as metabolic disorders such as non-alcoholic fatty liver disease (NAFLD) [4] and diabetes [5] (Fig. 1).

Amid the several natural elements proposed to be protective in these contexts is the flavolignan silybin [7]. The effect of silybin is reported on by Sciacqua and colleagues [6] in this issue of the Journal.

Silybin is the major active constituent of silymarin, and it represents about 50–70% of the silymarin extract. Similar to the other flavolignans, limiting factors for the use of silybin are its low solubility in water, low bioavailability, and poor intestinal absorption [7]. To counteract this aspect, different more soluble derivatives of silybin have been synthesized. In particular, when conjugated to vitamin E and phospholipids, silybin seems to significantly improve its bioavailability. Moreover, this combination also displays increased antioxidant and antifibrotic activity [7].

In liver cells, as well as in other types of cells, the common effects of silybin may be summarized as follows: (1) antioxidant; (2) direct or indirect (through the antioxidant capability) modulator of inflammation and fibrogenesis; and (3) indirect or direct modulator of some intrahepatic metabolic pathways [7] (Fig. 1).

Silybin acts as an antioxidant because it inhibits radical formation, binds some radical species (scavenger), interferes with lipid peroxidation of membranes (and, therefore, modulates membrane permeability), and increases the intracellular content of scavengers [8]. Silybin inhibits the formation of oxidative species such as superoxide anion radicals and of nitric oxide, decreases the content of malondialdehyde, and totally abolishes the decrease of antioxidants such as glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase [7]. These results, which are dose dependent, have been documented in animal and human models of cardio-metabolic diseases [7].

Silybin also displays other metabolic effects; for instance, it interferes with some mechanisms of action of insulin. In fact, it modulates the uptake of glucose in adipocytes by blocking the insulin-dependent glucose transporter 4. Several studies investigated this issue in human models. Thus, in a double-blind, randomized trial in patients with poorly controlled non-insulin-dependent diabetes mellitus and alcoholic liver disease [9], and in a randomized, double-blind, placebo-controlled trial in patients with type II diabetes [10], silybin significantly affects plasma levels of glucose and triglycerides, with a trend toward lower hemoglobin A1c levels.

The silybin–vitamin E–phospholipid complex was previously tested in different metabolic settings such as patients with NAFLD demonstrating its ability in reducing insulin resistance evaluated by the HOMA test after a 6-month treatment [11]. The effect of this complex on hypertensive patients with reduced glycemic control was investigated by Sciacqua and colleagues [6]. Hypertensive patients with normal glucose tolerance (NGT) but 1-h post load plasma glucose ≥ 155 mg/dl (1-h high), during the oral glucose tolerance test (OGTT), show higher insulin resistance and multiple target organ damage, and this represents an interesting model of metabolic disorder. The authors demonstrate that after 6 months of silybin

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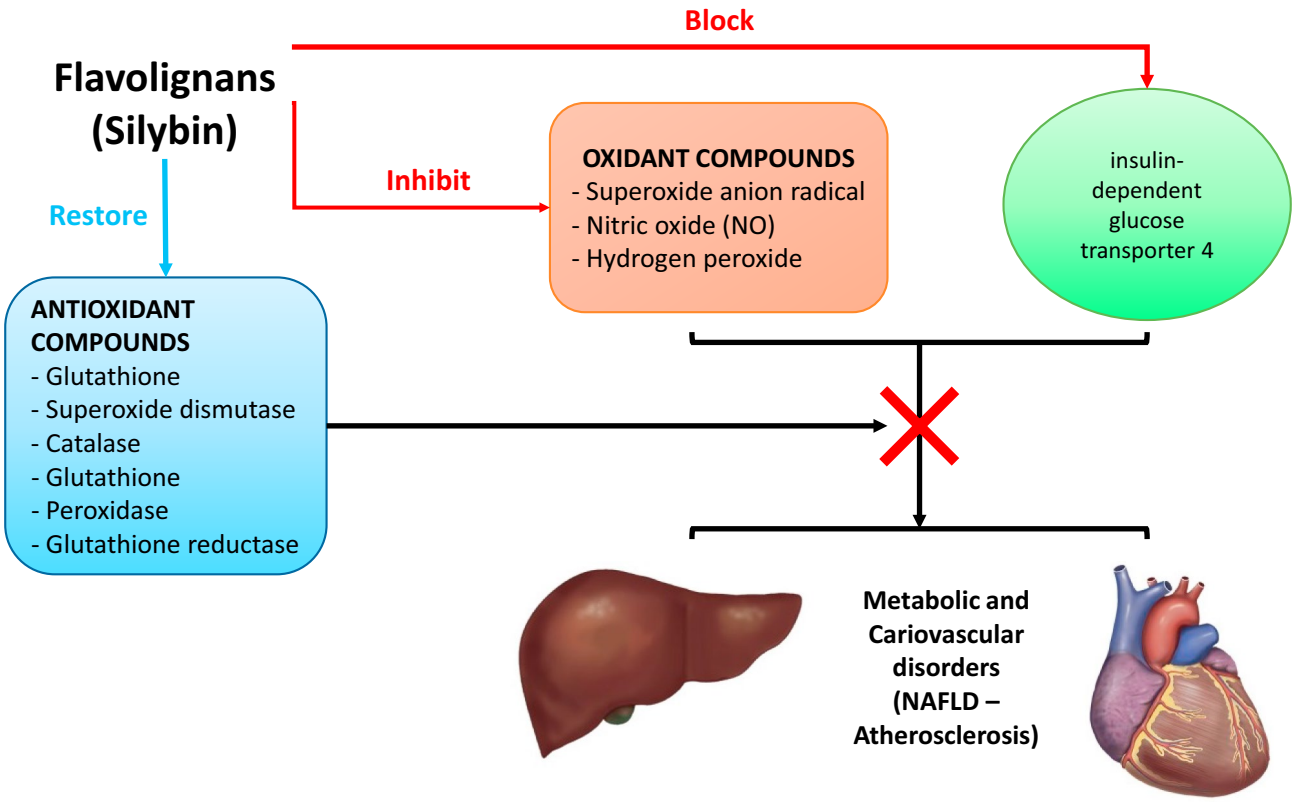

Fig. 1 Schematic representation of silybin on cardiometabolic diseases

intake, there is a significant improvement in metabolic profile. The glucose response during OGTT is significantly improved. Moreover, silybin intake is associated with a significant reduction of both clinical and central systolic blood pressure, with improvement in clinical and central pulse pressure, and reduction of arterial stiffness parameters. This is of particular interest because it was previously demonstrated that antihypertensive drugs are able to affect oxidative parameters [12], but the effect of polyphenols such as silybin in this setting has not been investigated until now. Similarly, other polyphenols were tested on arterial stiffness demonstrating their ability in modulating arterial relaxation, but the data on silybin are still poor. Hence, we are waiting for clinical randomized prospective trials to confirm the intriguing data here reported by Sciacqua and colleagues.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement on human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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