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Milk thistle to treat non-alcoholic fatty liver disease: dream or reality?

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"Milk thistle is one of the most successful examples of developing a modern therapy from traditional medicine … Based on the data currently available, we believe that milk thistle is a medicinal plant that represents a concrete reality for non-alcoholic fatty liver disease treatment…"

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. The prevalence of NAFLD in the western countries is around 25% in the general population, and it is estimated that 2–3% present an active disease with inflammation (non-alcoholic steatohepatitis–NASH), which may progress to advanced fibrosis, liver cirrhosis and hepatocarcinoma [1]. The incidence of NAFLD is rising rapidly because of the ongoing type 2 diabetes and obesity epidemic burden [2]. The mechanism involved in the occurrence of fatty liver and in the progression to a more serious disease is unclear and is probably due to a metabolic profile expressed in a context of genetic predisposition. In this way, a two-step hypothesis has been proposed. The first step induces liver fat accumulation (steatosis), which is still reversible, and the second step prompts steatosis progression to steatohepatitis (NASH) [3,4]. At present, insulin resistance, oxidative stress, cytokines and obesity are identified as the major factors involved in NAFLD/NASH pathogenesis. These factors can promote intra-hepatic fat accumulation and lipotoxicity and develop inflammation, oxidative stress, apoptosis and fibrogenesis that determine the progression of the disease. With regard to therapy, the approach to NAFLD is based on lifestyle intervention. Accordingly, regular physical activity, special diets and weight reduction have widely been used and tested in several studies. However, there is no consensus concerning pharmacological treatment [5,6].

Silybum marianum, commonly known as milk thistle (MT), a member of the *Asteraceae/Compositae* family, is an annual or biennial herb native of the Mediterranean and North African regions and is used in the treatment of liver diseases for millennia. In Roman times, Pliny the Elder (A.D. 77), reported that MT was 'excellent for carrying off bile'. The active complex of MT is a lipophilic extract from plant seeds and it is composed of isomer flavonolignans (i.e., silibinin, isosilibin, silidianin and silichristine), collectively known as silymarin. Silymarin comprises at least 70% of the standardized MT. Silibinin is the major isomer and the most active component and represents about 60–70%, followed by silichristin (20%) and silidianin (10%) [7]. Although being used in a clinical practice worldwide, the therapeutic efficacy of MT has been questioned for years. Silymarin reduces lipid peroxidation and free radical production and has an anti-fibrotic agent by inducing the apoptosis of hepatic stellate cells, or inducing degradation of collagen deposits [8,9]. Its therapeutic efficacy and its influence on liver-related mortality have been reported for alcoholic, hepatitis B and C virus liver diseases [10]. Preclinical evidence reports the action of

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silibinin on glucose and lipid metabolism in an experimental NASH model, by the inhibition of NF-κB controlled transduction cascade in liver cells [11]. The bioavailability of silibinin is low and it can be enhanced by adding solubilizing substances to the extract, as the complexation with phosphatidylcholine or β-cyclodextrin and possibly by the choice of the capsule material [7].

Hepatoprotective effects of MT

MT is one of the most investigated plants with the known mechanisms of the action for the treatment of liver diseases. Some studies have suggested that the active extract of MT possesses anti-oxidant, anti-inflammatory and anti-fibrotic properties and that it stimulates protein biosynthesis and liver cells regeneration. Hepatoprotective effects of silymarin could be summarized in four points: activity against lipid peroxidation as a result of free radical scavenging and the ability to increase the cellular content of glutathione, efficacy to increase the membrane stability and to regulate membrane permeability in the presence of xenobiotic damage, ability to regulate nuclear expression by means of a steroid-like effect and inhibition of transformation of stellate hepatocytes into myofibroblasts, which induce deposition of collagen fibres leading to the liver injury progression [8–12].

The anti-inflammatory action is also related to its interaction with multiple cytokine-induced signaling pathways to downregulate inducible nitric-oxide synthase (iNOS) expression and to the inhibition of cyclooxygenase (COX)-2 expression. Finally, silymarin inhibits the activation of the protein kinases and of a c-jun N-terminal kinase and promotes liver cell regeneration by stimulating nucleolar polymerase A and by increasing the ribosomal protein synthesis [13].

MT in NAFLD treatment

Some well-designed studies have reported that silymarin can exert beneficial effects in NAFLD. The data indicate that silymarin appears to be effective to reduce the biochemical, inflammatory and ultrasonic indices of liver steatosis. Velussi *et al.* reported that the silymarin treatment (12 months, 600 mg silymarin/day) was associated with a reduction of insulin resistance and a significant decrease in fasting insulin levels [14]. This data suggest a direct activity of silymarin on the endogenous and exogenous insulin. Hajaghamohammadi *et al.,* in a randomized clinical trial, evaluated the efficacy of silymarin in NAFLD patients (140 mg of silymarin/day for 2 months) compared to metformin, pioglitazone [15]. The reduction in the transaminases levels in the silymarin group was significantly more evident than that in other groups, mainly than in the metformin groups. The decrease in the transaminases levels was confirmed by another Iranian prospective and randomized study where silymarin was compared to vitamin E [16]. A pilot study by Loguercio *et al.* reported that a new silybin-vitamin E complex (silybin + vitamin E + phospholipids at a dose of four pills/day for 6 months), significantly improved plasma levels of liver enzymes, insulin resistance and echographic score of liver steatosis in the NAFLD patients. The composition of a pill was of 94 mg silybin, 194 mg phophatidilcholine and 90 mg vitamin E [17]. More recently, the same study group made a placebo-controlled, double-blind, Phase III, randomized clinical trial and assessed the efficacy of the same silybin-vitamin E complex (two pills/day for 1 year), with the improvement in liver enzymes, insulin resistance and liver histology of NAFLD [18].

Mitochondria play a key role in the hepatocyte metabolism, being the site of β-oxidation and oxidative phosphorylation. The oxidative stress in NASH is closely related to mitochondrial dysfunction. During the NASH progression, an oversupply of free fatty acids induces an increase of mitochondrial H_2O_2 production which in turn oxidizes mitochondrial membranes and regulates the activity of the uncoupling protein-2 and carnitine palmitoyl transferase-1. In this context, Serviddio *et al.,* evaluated the effect of silybin-phospholipids complex on the liver redox balance and mitochondrial function in a dietary model of NASH, and found that this association was effective in mitochondrial membrane stabilization, oxidative stress inhibition and preservation of hepatic mitochondrial bioenergetics [19].

However, the standardization of silymarin in its various formulations and effective dosages is still lacking. In addition, the relevant problem of most clinical trials on this topic has been the definition of the end-points, such as the progression of fibrosis or the reduction of transaminase levels. Such pitfalls may lead to miss the important treatment effects. Well-designed, double-blind, placebo-controlled studies are still required.

Conclusion & future perspective

NAFLD, in its different stages is the most common chronic liver disease worldwide. Pathogenic mechanisms of the NAFLD progression include a series of consecutive pathogenetic steps. Therapeutic NAFLD approach is currently based on lifestyle changes, while there is no consensus concerning an effective pharmacological treatment [2]. MT is one of the most successful examples of developing a modern therapy from traditional medicine. Several pharmacological studies have reported that silymarin and silibinin exert several hepatoprotective actions [7]. In particular, in the NAFLD patients, the action on insulin resistance, lipid peroxidation and glutathione levels restoration may explain its efficacy in liver steatosis improvement and fibrosis regression [20]. Based on the data currently available, we believe that MT is a medicinal plant that represents a concrete reality for NAFLD treatment, but larger clinical trials and new evidence-based medicine studies are necessary to confirm its short- and long-term efficacy.

Financial & competing interests disclosure

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