# Extract from *Silybum marianum* as a Nutraceutical: a Double-blind Placebo-controlled Study in Healthy Young Men

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**Abstract**

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In a randomized, double-blind, placebo-controlled study, the effect of an extract from *Silybum marianum* seeds (ESM, milk thistle extract) on lipid and liver parameters and the antioxidant capacity of serum was investigated in 29 healthy men aged 18–32 years. They received either 858 mg of ESM (531 mg silymarin complex calculated on pure silibinin), or placebo, daily for the period of 60 days. No side effects were found. A routine biochemical analysis of the serum was performed as a measure of lipid and liver metabolism. Positive trend towards decreased serum cholesterol level and HDL-cholesterol increase was observed in the ESM group as compared to the placebo group. The serum antioxidant capacity was significantly higher in the ESM group. The results suggest the use of ESM as a dietary supplement for hypercholesterolemia.

**Keywords:** *Silybum marianum*; silymarin complex; double-blind; randomised placebo-controlled study; cholesterol; HDL; antioxidant status; nutraceutical

Epidemiological studies suggest that an increased intake of some phytochemicals, e.g. flavonoids, phenolic acids, carotenoids, phytosterols, etc., reduces the risk of coronary heart disease (HERTOG *et al.* 1993), stomach carcinoma (DORANT *et al.* 1996) and hypercholesterolemia (MIETTINEN *et al.* 1995). Saint Mary's Milk thistle (*Silybum marianum* Gaertn. or *Carduus marianus* L., Compositae), known as a medicinal herb for almost two millennia, exhibits a physiological benefit to liver functions and provides protection against some liver diseases (SCHUPPAN *et al.* 1999). Standardized extracts from *S. marianum* seeds (ESM, milk thistle extract, Cardui mariae fructus extractum siccum) are mixtures of chemically defined flavonolignans and flavonoids (the silymarin complex, approx. 70–80%) and a chemically undefined polymeric fraction (polymeric and oxidised polyphenolic compounds, 30–20%) (ŠIMÁNEK *et al.* 2000). The mixture of flavonolignans was named silymarin (WAGNER *et al.* 1968), its constituents being silibinin, isosilibinin, silidianin and silicristin. Silibinin, the main component of the silymarin complex, is a mixture of two diastereomers having different pharmacokinetic profiles (KŘEN *et al.* 1997) in approximate proportion of 1:1 (MORAZZONI & BOMBARDELLI 1995). The principal active component of ESM is silibinin. Its antioxidant activity prevented lipid peroxidation and preserved the lipid profile of hepatocyte membranes in rats treated with an iron-enriched diet (PIETRANGELO *et al.* 1995). Silibinin has been shown to inhibit the proinflammatory leukotriene $B_4$ in rat Kupffer cells (DEHMLOW *et al.* 1996) and the oxidation of human low-density lipoproteins (ŠKOTTOVÁ *et al.* 1999). Silibinin and silicristin showed remarkable stimulatory effects on African green monkey kidney cells (SONNENBICHLER *et al.* 1999). Silymarin retarded collagen accumulation in chronic bile duct-ligated rats (BIOGK *et al.* 1997). Inhibition of dietary induced hypercholesterolemia was ob-

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served in rats fed a high cholesterol diet supplemented with ESM; however, silibinin was not effective (KREČMAN *et al.* 1998). The polymeric fraction of ESM was probably responsible for this effect. On the other hand, currant oil induced oxidisability of rat LDL was suppressed by silibinin-phosphatidylcholine complex (ŠKOTTOVÁ *et al.* 2000). Clinical trials demonstrated that the pharmacological efficacy of ESM was either controversial, or exhibited suboptimal pharmacological effects (FLORA *et al.* 1998).

Two types of products containing ESM are available on the market: (i) phytopreparations (MARTINDALE 1995) and (ii) established nutraceuticals (http://www.doctors-nutrition.com/milkthistle.htm). Most preparations containing ESM and registered as hepatoprotective drugs still pose a problem because of the imprecise documentation of individual components of the silymarin complex (ŠIMÁNEK *et al.* 2000). The typical dose for phytopreparations or nutraceuticals is 300 to 900 mg of ESM (i.e. 210 to 630 mg silymarin complex), taken daily in three portions for eight weeks. There were no known side effects or contraindications, and this extract was safe for use during pregnancy and lactation.

Although the pharmacological effects of ESM were demonstrated in both *in vitro* and *in vivo* studies, as mentioned above, no clinical study with *S. marianum* extract taken as a dietary supplement was available. The aim of this study was to investigate whether the high daily dose 858 mg of ESM (531 mg of silymarin complex) could improve liver function in healthy young men, especially lipid metabolism and the antioxidant capacity of blood.

## MATERIAL AND METHODS

***Volunteers and Study Schedule***: Twenty-nine healthy men aged 18–32 years were randomised to the active-treatment group (17 men, aged 20.65 ± 0.88 years, BMI [body mass index] 22.61 ± 0.91, W/H ratio [waist-to-hip ratio] 0.81 ± 0.01) and the placebo group (12 men, aged 20.75 ± 0.69 years, BMI 21.69 ± 0.78, W/H ratio 0.79 ± 0.01). No significant differences in age and BMI (at 99% of LSD, $p < 0.01$) were found between the two groups. At the 95% level LSD a significance at $p < 0.05$ was found in W/H ratio between the treatment and placebo group. The volunteers were non-smokers, non-drinkers and did not take any medication. The extract of *Silybum marianum* or placebo was administered in a single dose of 286 mg three times a day with meals for a period of 60 days.

***Ethical Approval***: Volunteers were informed about the potential effects of ESM and of its safety aspects, and each consented to participating in the study. During the study the volunteers were under the control of the University Hospital Lipid Centre with the recommendation for diet. The Medical Ethical Committee of the Faculty Hospital, Olomouc (Czech Republic), approved the protocol.

***Characteristics of ESM and PlaceboTablets***: The tablet contained 286 mg of Cardui mariae fructus extractum siccum (177 mg silymarin complex of the following composition: silibinin 44.5%, isosilibinin 5%, silidianin 1.4%, silicristin 10.9% and taxifolin 2.5%; lot 211194, Galena Pharmaceutical Company, Opava, Czech Republic), microcrystallic cellulose (74 mg), polyvidone 25 (5 mg), Crosspovidine XL (5 mg), silicium dioxide (5 mg), magnesium stearate (5 mg). The placebo tablet consisted of lactose (300 mg), hydrogenated soy oil (95 mg), and magnesium stearate (5 mg). The ESM and placebo tablets were coated with the same suspension containing hydroxypropylmethylcellulose, polyethylene glycol (PEG 6000), titanium dioxide and magnesium stearate.

***Blood Samples***: The venous blood was collected at the beginning of the study to provide baseline followed by the first EMS or placebo treatment. Further collections were made after the first and second month of study between 7.30 a.m. and 9.00 a.m. after overnight fasting. Serum was separated by centrifugation at 2000 g for l0 min at +4°C. The routine biochemical analyses were performed on the day of serum separation. Serum samples for special analyses (lipid peroxidation, total thiol groups and total antioxidant capacity) were stored at –80°C in separated aliquots, usually for less than l month.

***Serum Determinations***: Cholesterol, triacylglycerols (TAG), LDL and HDL-cholesterol, apolipoproteins A-I and B, glucose, uric acid, bilirubin, liver enzymes (ALT, AST, GMT, ALP and cholinesterase) were measured on an automated analyser HITACHI 9l7 (Boehringer Mannheim, Germany). Chemicals were purchased from Sigma – Aldrich (Prague), kits from Roche (Switzerland). Precinorm L and Precipath L (Certificate QCS l998, Roche) were used for quality control.

***Assessment of Serum Total Antioxidant Capacity***: The serum antioxidant capacity was measured using a Potentiostat Galvanostat Model 273, EG&G (Princeton Applied Research, USA) cyclic voltammetry apparatus. A three-electrode system was used throughout the study. The working electrode: glassy carbon disk (Laboratory Instruments, Czech Republic) 2 mm in diameter; the auxiliary electrode: platinum wire, and calomel saturated electrode as the reference electrode were used. The glassy carbon electrode was polished before each measurement. Serum measurements (0.3 ml) were carried out in phosphate buffered saline, pH 7.4 (1.5 ml) at a scan rate of 200 mV/s. All cyclic voltammograms were performed in the range (–4) –(0.8) V. Each sample was analysed twice.

***Lipid peroxidation***: Lipid peroxidation products in serum were assessed by the reaction with thiobarbituric acid as thiobarbituric acid reactive substances (TBARS) and expressed as the concentration of malondialdehyde (BUEGE & AUST 1978).

***Protein Thiol Groups and Glutathione***: Determination of the total thiol level (T-SH) in the serum was estimated

according to HU (1994) using 2,2-dithiobisnitrobenzoic acid (DTNB).

***Determination of Silibinin Diastereomers A and B in Plasma***: To assess bioavailability of our ESM preparation, one volunteer of the ESM group was randomly selected on day 30. The volunteer refrained from taking xanthine containing beverages and foods such as coffee, tea and chocolate 24 h before plasma collection and fasted from the evening before blood sampling. The experiment was started at 7.00 a.m. immediately after oral administration of the EMS tablet (286 mg ESM). The blood was collected at 0.5, 1 and 2 h. Total silibinin concentration reached 184 ± 12 ng/ml at 2.0 h (approx. proportion of diastereomers 1:1) and free silibinin concentration reached 83 ± 8 ng/ml (approx. proportion of free diastereomers 3:1). The plasma levels of total silibinin (both diastereomers of free and conjugated silibinin after enzymatic cleavage by mixture of β-glucuronidase/arylsulphatase from *Helix pomatia*) and free silibinin (both diastereomers) were determined by HPLC method with $C_{18}$ SPE preseparation (KOSINA & BARTEK 2000). Silibinin, 98% HPLC purity, mixture of diastereomers A and B (1:1), Galena Pharmaceuticals Co., Ltd., (Opava, Czech Republic) was used as a standard. Concentrations of analysed components were expressed in ng/ml of plasma. Values are expressed as the mean ± SD of three analyses. Plasma concentrations of total and free diastereomers of silibinin are shown in Fig. 1.

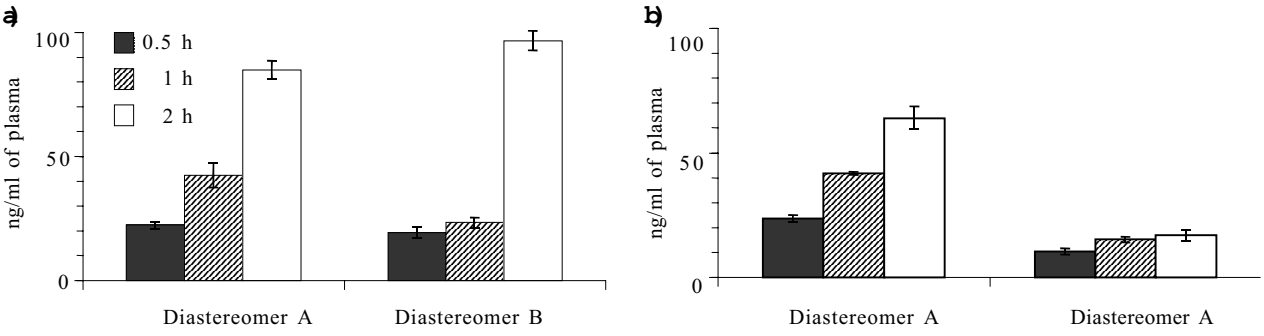
***Statistical Analysis***: Age, BMI and W/H ratio were evaluated using Statgraphics 6.0 ANOVA. Biochemical parameters were evaluated using the statistical program SPSS 8.0. Data are expressed as the mean ± SD. For the statistical evaluation of voltammetry, the least square method was used by approximation of discrete data using algebraic polynomial. Calculations were performed using the MATLAB 5.2 software.

## RESULTS AND DISCUSSION

In this study, we measured the efficacy of high dosage of ESM versus placebo by biochemical parameters in serum of healthy young men (Table 1). Twenty-nine study participants were randomly divided into two groups of 17 and 12, and were administered 858 mg/day of ESM (531 mg silymarin complex), or placebo, respectively for a period of 60 days. There were no withdrawals, and no participant fell ill or was taking any other medication for the duration of the experiment. There were no reports of side effects. Three blood samples were collected from each participant, in the morning of the 1st, 30th and 60th day. The biochemical parameters are summarized in Table 1 as the means and standard deviations of the difference (%) of individual values obtained from the 1st and 3rd blood sample of ESM and placebo groups.

A trend of increase in the HDL-cholesterol (+3.4), ApoA1 (+5.1), and decrease of the total cholesterol (–3.5) and LDL-cholesterol (–4.4) was found in the ESM group when compared with the placebo group. Even though none of these trends reached statistical significance, the effect of ESM on the equilibrium of lipid metabolism in the volunteer group may be considered as a positive effect. Although changes in parameters monitoring liver damage were statistically insignificant in both groups (Table 1), they support the inclusion of EMS as a nutraceutical with a prophylactic effect on liver functions.

The blood antioxidant status of study participants was monitored by evaluating the lipoperoxidation parameters – total thiols and thiobarbituric acid reactive substances and by the cyclic voltammetry (CV). The CV was conveniently used and validated for the quantification of low molecular weight antioxidants (LMWA) (KOHEN *et al.* 2000). LMWA play a major role in protecting biological systems against reactive oxygen-derived species and reflect the antioxidant capacity of the system. The values of the biological oxidation potential $E_a$ (V), which relates to the nature of LMWA, and the intensity of the anodic current wave $I_a$ (A.10$^{-8}$), which relates to the concentration of LMWA in serum, are given in Table 1. Differences in lipoperoxidation damage parameters between the ESM group and the placebo group were statistically insignificant. On the other hand, the CV parameter $I_a$ showed that a long term administration of ESM led to a statistically




1. Concentrations of total (a) and free (b) diastereomers of silibinin in the plasma of a single volunteer after oral administration of 286 mg ESM (177 mg silymarin complex) at 0.5, 1.0, and 2.0 hrs

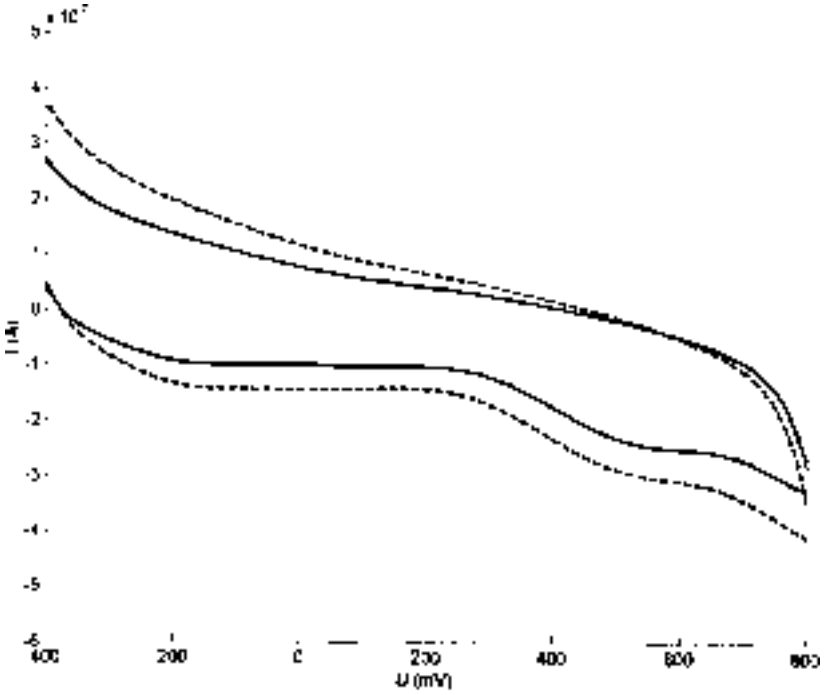
I. Statistical evaluation of the effects of *S. marianum* extract (ESM) on lipid and liver metabolism and serum antioxidant capacity in healthy volunteers

| Metabolic parameter | Treatment | Mean ± S.D. | | Statistical parameters of difference (1st–3rd) | | |
|---|---|---|---|---|---|---|
| | | 1st | 3rd | mean ± S.D. | mean (%) | trends (%) |
| Total cholesterol (mM) | ESM | 4.38 ± 0.58 | 4.43 ± 0.76 | + 0.07 ± 0.46 | + 1.4 | –3.5 |
| | Placebo | 4.39 ± 0.86 | 4.61 ± 0.79 | + 0.23 ± 0.55 | + 4.9 | |
| TAG (mM) | ESM | 1.17 ± 0.65 | 1.18 ± 0.59 | + 0.05 ± 0.37 | + 4.6 | –0.1 |
| | Placebo | 1.06 ± 0.60 | 1.11 ± 0.44 | + 0.05 ± 0.50 | + 4.7 | |
| LDL-cholesterol (mM) | ESM | 2.56 ± 0.45 | 2.61 ± 0.59 | + 0.06 ± 0.43 | + 2.3 | –4.4 |
| | Placebo | 2.58 ± 0.74 | 2.76 ± 0.69 | + 0.19 ± 0.35 | + 6.7 | |
| HDL-cholesterol (mM) | ESM | 1.63 ± 0.22 | 1.50 ± 0.26 | –0.13 ± 0.13 | –8.2 | +3.4 |
| | Placebo | 1.67 ± 0.30 | 1.47 ± 0.34 | –0.19 ± 0.21 | –11.6 | |
| ApoA1 (g/l) | ESM | 1.34 ± 0.10 | 1.34 ± 0.13 | –0.01 ± 0.11 | + 0.7 | + 5.1 |
| | Placebo | 1.35 ± 0.15 | 1.29 ± 0.18 | –0.06 ± 0.12 | –4.4 | |
| ApoB (g/l) | ESM | 0.75 ± 0.15 | 0.76 ± 0.14 | + 0.01 ± 0.09 | + 1.1 | –3.3 |
| | Placebo | 0.75 ± 0.17 | 0.79 ± 0.18 | + 0.03 ± 0.09 | + 4.4 | |
| Glucose (mM) | ESM | 5.10 ± 0.37 | 5.20 ± 0.38 | + 0.11 ± 0.36 | + 2.1 | + 2.0 |
| | Placebo | 4.94 ± 0.41 | 4.95 ± 0.60 | + 0.003 ± 0.62 | + 0.1 | |
| Uric acid (μM) | ESM | 384.70 ± 96.20 | 357.20 ± 64.30 | –8.00 ± 34.65 | –2.2 | –4.4 |
| | Placebo | 364.70 ± 66.90 | 373.00 ± 45.10 | + 8.33 ± 51.58 | + 2.2 | |
| ALT (μkat/l) | ESM | 0.33 ± 0.18 | 0.34 ± 0.12 | + 0.01 ± 0.11 | + 2.7 | –7.1 |
| | Placebo | 0.39 ± 0.14 | 0.43 ± 0.24 | + 0.04 ± 0.14 | + 9.8 | |
| AST (μkat/l) | ESM | 0.42 ± 0.24 | 0.37 ± 0.12 | –0.04 ± 0.13 | –9.3 | –2.9 |
| | Placebo | 0.39 ± 0.18 | 0.37 ± 0.12 | –0.03 ± 0.05 | –6.4 | |
| GMT (μkat/l) | ESM | 0.26 ± 0.06 | 0.28 ± 0.07 | + 0.02 ± 0.05 | + 6.8 | –5.9 |
| | Placebo | 0.36 ± 0.17 | 0.41 ± 0.17 | + 0.05 ± 0.11 | + 12.7 | |
| CHS (μkat/l) | ESM | 130.90 ± 22.10 | 132.60 ± 22.30 | + 0.36 ± 9.05 | + 0.3 | + 2.3 |
| | Placebo | 143.20 ± 34.90 | 140.40 ± 33.30 | –2.80 ± 6.96 | –2.0 | |
| AP (μkat/l) | ESM | 1.52 ± 0.60 | 1.60 ± 0.59 | + 0.08 ± 0.31 | + 5.3 | –6.0 |
| | Placebo | 1.20 ± 0.25 | 1.35 ± 0.29 | + 0.15 ± 0.23 | + 11.3 | |
| Bilirubin (μM) | ESM | 16.91 ± 7.16 | 15.06 ± 9.59 | –1.23 ± 8.38 | –7.3 | –4.4 |
| | Placebo | 18.00 ± 7.55 | 17.48 ± 7.04 | –0.52 ± 7.75 | –2.9 | |
| Total thiols (mM) | ESM | 0.51 ± 0.04 | 0.72 ± 0.13 | + 0.22 ± 0.15 | + 30.4 | + 1.8 |
| | Placebo | 0.51 ± 0.05 | 0.72 ± 0.13 | + 0.21 ± 0.14 | + 28.6 | |
| TBARS (μM) | ESM | 4.62 ± 0.62 | 4.78 ± 0.65 | + 0.18 ± 0.65 | + 4.0 | –2.9 |
| | Placebo | 4.88 ± 0.50 | 5.22 ± 0.59 | + 0.34 ± 0.76 | + 6.9 | |
| $E_a$ (V) | ESM | 0.53 ± 0.04 | 0.56 ± 0.02 | + 0.03 ± 0.06 | + 5.5 | –2.7 |
| | Placebo | 0.54 ± 0.02 | 0.58 ± 0.02 | + 0.05 ± 0.02 | + 8.3 | |
| $I_a$* (A.$10^{-8}$) | ESM | 14.34 ± 1.60 | 15.51 ± 3.40 | + 1.25 ± 2.41 | + 8.1 | + 10.0* |
| | Placebo | 14.96 ± 2.71 | 14.67 ± 2.031 | –0.28 ± 2.32 | 1.9 | |

* significance ($p < 0.05$)

significant increase of LMWA in blood of the ESM group when compared both between samples 1 and 2 (the absolute effect of ESM) and between the ESM and the placebo group. The computer-simulated voltammogram in the ESM group at the beginning and at the end of the experiment showed an increase in the intensity of the anodic current wave ($I_a$) and in the anodic wave area (Fig. 2).

In this study side effects as a response to ESM treatment were not observed. The parameters monitored were lipid and liver metabolism where no statistically significant changes were noted. Although insignificant, the improvement in two parameters of lipid metabolism – levels of cholesterol and HDL cholesterol – may be considered beneficial. The statistically significant improvement in the antioxidant status of blood in the ESM group confirmed that some of the *S. marianum* active components might contribute to the protection against oxidative damage. We conclude that the ESM as nutraceutical might be promising for a wide range of patients.




2. Computer-simulated voltammograms of LMWA in the ESM volunteers serum on the 1st (solid line) and 60th day (dashed line)

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**Abbreviations**

| | |
|---|---|
| ESM | extract from *Silybum marianum* seeds |
| SM | silymarin |
| TAG | triacylglycerols |
| HDL-cholesterol | high-density lipoprotein cholesterol |
| LDL-cholesterol | low-density lipoprotein cholesterol |
| ApoA1 | apolipoprotein A1 |
| ApoB | apolipoprotein B |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| GMT | γ-glutamyl transferase |
| CHS | cholinesterase |
| AP | alkaline phosphatase |
| TBARS | thiobarbituric acid reactive substances |
| $E_a$ | anodic potential (cyclic voltammetry) |
| $I_a$ | intensity of anodic current wave (cyclic voltammetry) |
| SD | standard deviation |
| BMI | body mass index |
| W/H | ratio waist-to-hip ratio |

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**Souhrn**

ŠIMÁNEK V., ŠKOTTOVÁ N., BARTEK J., PSOTOVÁ J., KOSINA P., BALEJOVÁ L., ULRICHOVÁ J. (2001): **Extrakt ze** *Silybum marianum* **jako potravní doplněk: dvojitě slepá, placebem kontrolovaná studie u zdravých mladých mužů**. Czech J. Food Sci., **19**: 106–110.

V randomizované, dvojitě slepé, placebem kontrolované pilotní studii byly hodnoceny účinky extraktu ze semen *Silybum marianum* na lipidové, jaterní parametry a antioxidační kapacitu krve u 29 zdravých mužů ve věku 18–32 let. Dobrovolníci brali denní dávku 858 mg extraktu (531 mg silymarinového komplexu standardizovaného na silibinin) nebo placebo po dobu 60 dnů. V průběhu studie nebyly zaznamenány žádné vedlejší účinky. Parametry lipidového a jaterního metabolismu byly hodnoceny v séru rutinními biochemickými metodami. U skupiny užívající rostlinný extrakt byly nalezeny pozitivní trendy ve snížení sérového cholesterolu, zvýšení hladiny HDL-cholesterolu současně se statisticky významně zvýšenou antioxidační kapacitou krve. Výsledky studie podporují používání extraktu ze *S. marianum* jako složky potravního doplňku v prevenci hypercholesterolemie.

**Klíčová slova**: *Silybum marianum*; silymarinový komplex; pilotní studie; serum; cholesterol; HDL; antioxidační kapacita

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