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ORIGINAL CONTRIBUTION

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Carob pulp preparation rich in insoluble fibre lowers total and LDL cholesterol in hypercholesterolemic patients

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Summary *Background* Recently, insoluble fibre from carob pulp has been found to affect blood lipids in animals in a similar manner as soluble dietary fibre. *Aim of the study* To investigate whether a carob pulp preparation containing high amounts of insoluble fibre has a beneficial effect on serum cholesterol in humans. *Methods* Volunteers ($n = 58$) with hypercholesterolemia were recruited to participate in a randomised, double-blind, placebo-controlled and parallel arm clinical study with a 6 week intervention phase. All participants consumed daily both, bread (two servings) and a fruitbar (one serving) either with ($n = 29$) or without ($n = 29$) a total amount of 15 g/d of a carob pulp preparation (carob fibre). Serum concentrations of total, LDL and HDL cholesterol and triglycerides were assessed at baseline and after week 4 and 6. *Results* The consumption of carob fibre reduced LDL cholesterol by 10.5 ± 2.2 % ($p = 0.010$). The LDL:HDL cholesterol ratio was marginally decreased by 7.9 ± 2.2 % in the carob fibre group compared to the placebo group ($p = 0.058$). Carob fibre consumption also lowered triglycerides in females by 11.3 ± 4.5 % ($p = 0.030$). Lipid lowering effects were more pronounced in females than in males. *Conclusion* Daily consumption of food products enriched with carob fibre shows beneficial effects on human blood lipid profile and may be effective in prevention and treatment of hypercholesterolemia.

Key words hypercholesterolemia – total cholesterol – LDL – HDL – dietary fibre – insoluble fibre – carob – functional food

Introduction

Hypercholesterolemia is one of the major risk factors of cardiovascular diseases. Although diet alone may not produce a sufficient long-term response on blood lipids, effective nutritional interventions in prevention and treatment of hypercholesterolemia are of major importance [1, 2].

A multitude of publications have reported cholesterol-lowering effects of several dietary interventions [3–5]. As adjunctive therapy to a diet low in fat the intake of soluble dietary fibre showed strong evidence in cholesterol-lowering activity [6–12]. Thus, the administration of pectin, guar, psyllium, oat bran and leguminoses has been shown to reduce total and LDL cholesterol in serum in over 80 % of the trials reviewed [6].

Moreover, the focus of dietary fibre research has been extended on the prevention of diabetes mellitus, cardiac infarction and colon carcinoma [13–16]. Especially insoluble fibre has been shown to be effective at preventing induced tumors in rats [17], but little is known about the effect of insoluble fibre on blood lipids. Despite some studies demonstrating improved serum lipids [18] the

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majority of studies failed to find significant effects [8, 19, 20].

The carob tree fruit has a high content of insoluble dietary fibre and polyphenols (tannins) and is supposed to have beneficial effects on human health [21]. In rodent studies carob pod and carob pulp preparations rich in dietary fibre demonstrated a cholesterol-lowering effect and an increased excretion of cholesterol and bile acids [22–24]. In a one-arm clinical pilot study a carob pulp preparation (carob fibre) indicated to be effective in reducing serum total and LDL cholesterol concentrations in human beings [21]. Controlled trials to investigate beneficial effects of carob fibre in humans are lacking.

The present study investigated the effect of a carob fibre, i.e. carob pulp preparation containing high amounts of insoluble fibre, on blood lipids in human volunteers suffering from moderately elevated total serum cholesterol levels during a 6 week intervention phase.

Materials and methods

Study design, subject recruitment and dietary intervention

In the present randomised, placebo-controlled, double-blind and parallel arm clinical trial the lipid-lowering effect of carob fibre consumption was studied in patients suffering from hypercholesterolemia (5.2–7.8 mmol/L corresponding to 200–299 mg/dL). The study was conducted over a total of 8 weeks divided into a run-in phase of 2 weeks and an intervention period of 6 weeks. The study was approved by the Ethical Committee of the Medical Faculty of the Humboldt University, Berlin, Germany. All patients gave written informed consent.

Volunteers were recruited from the In Balance Centre for Alternative Medicine, Berlin, Germany (n = 58). Exclusion criteria were severe organic and systemic diseases, severe obesity (body mass index > 35 kg/m^2), alcohol or drug abuse, participation in clinical trials within the last 4 weeks, pregnancy as well as use of lipid-lowering drugs and vitamin E containing supplements. Volunteers were between 34 and 70 years of age. Two of the participating 58 volunteers dropped out of the study between baseline and week 4, either by own decision or due to elevated blood glucose level. Both were assigned to the placebo group. According to an intention-to-treat analysis results of their preliminary assessments were taken as final data.

During the run-in phase all participants consumed daily both, bread (two servings) and a fruit-bar (one serving) free of carob fibre (placebo products). After the run-in phase participants were randomly assigned to a carob (n = 29) or a placebo group (n = 29). The carob fibre group consumed 15 g carob fibre, i.e. carob pulp preparation rich in insoluble fibre (Caromax™, Nutrinova, Frankfurt, Germany, composition shown in Table 1) per day as ingredient of 4 slices of bread (a total of 180 g; 2 slices in the morning, 2 slices in the evening) and one fruit-bar (about 40 g) to be eaten at noon. Bread and fruit-bars of the placebo group did not contain any carob fibre. The composition of bread and fruit-bar was in accordance to national food regulations. Carob fibre was analysed using AOAC method 993.19 for soluble fibre, AOAC method 991.42 for insoluble fiber and Folin-Ciocaltheu's method for polyphenols [25]. Both, bread and fruit-bar were well accepted by the participants. The patients were asked to keep to their normal eating habits during the study and to note down daily intake of bread and fruit-bar. No problems concerning compliance were observed.

Dietary assessment and patient history

Dietary intake was assessed by a 3-d food record based on usual household measures at baseline and at treatment weeks 3 and 5 or 6. Nutrient intake was calculated using the German Food and Nutrient Data Base Bundeslebensmittelschlüssel BLS II.2 [26].

Patient histories were used to assess stool consistency as well as frequency of flatulence.

Analytical methods

All participants underwent a haematological examination after overnight fasting at recruitment, at baseline and after weeks 4 and 6. Serum lipid profiles including measurement of total cholesterol, LDL, HDL and triglyceride concentrations were analysed by using commercial kits (Boehringer GmbH, Mannheim, Germany) and Olympus AU 600 and AU2700 (Olympus, Lismeehan,

Table 1 Analysis of the carob pulp preparation (carob fibre) used in this study

constituent (g)	per 100 g	per 15 g
Moisture	5.0	0.75
Carbohydrates (sucrose, glucose, fructose)	5.8	0.87
Protein	5.2	0.78
Total fat	0.2	0.03
Ash	3.36	0.504
Soluble fibre[1]	6.2	0.93
Insoluble fibre[2]	68.4	10.26
Water-soluble polyphenols[3]	2.84	0.426

[1] determined by AOAC method 993.19; includes pectins
[2] determined by AOAC method 991.42; includes cellulose, hemicelluloses, lignin and water-insoluble polyphenols
[3] determined by Folin-Ciocaltheu's method

Ireland). The coefficient of variation (CV) was 3.0 %, 2.7 %, 3.4 %, and 2.6 %, respectively. Serum concentrations of apolipoproteins A-I and B were measured by using immunoprecipitation method (Roche Diagnostics, Basel, Switzerland) and Beckman Immage (Beckman Coulter, Fullerton, California, USA). The CV was 5.8 % (apolipoprotein A-I) and 2.6 % (apolipoprotein B), respectively. Blood glucose was analysed by enzymatic determination (Olympus Diagnostics, Lismeehan, Ireland). The CV was 3.7 %. HbA_1C was analysed by HPLC using Tosoh G7 (Eurogenetics, Tessenderlo, Belgium). The CV is 2.9 %. Insulin was analysed by using commercial kits and Elecsys 2010 immunoassay analyser (Roche Diagnostics, Basel, Switzerland). The CV is 4.9 %. All analyses were conducted at the Medizinisch-Diagnostische Institut, Berlin, Germany.

Statistical analyses

All data are given as mean ± standard deviation (SD) or standard error of the mean (SEM). Log-transformed data, i. e. triglycerides, are given as geometric mean and geometric SD or SEM. Baseline characteristics of study groups were compared by Student's t-test and Pearsons chi-square distribution test. Analysis of variance (ANOVA) with repeated measurement design was used to estimate the effect of treatment during intervention period on blood lipids among groups and to estimate between-subjects effects. All models were based on changes of blood lipids from baseline. All two-way interactions between effects were tested. Based on the results of these preliminary analyses, final models only included gender and an interaction term between treatment and gender as independent factors. P-values are given of time trend effects, time × treatment effects and time × treatment × gender effects. For all analyses the statistical software package for social sciences SPSS 11.0 (SPSS Inc., Chicago, Illinois; USA) was used.

Results

General characteristics

Carob fibre and placebo group were similar in almost all baseline characteristics as shown in Table 2. At baseline energy intake was similar in carob fibre and placebo group (treatment group: 10.0 ± 2.7 MJ/d, placebo group: 10.9 ± 2.7 MJ/d). No significant changes in energy intake were observed during the intervention period (carob fibre group: 10.8 ± 2.8 MJ/d; placebo group 11.7 ± 2.9 MJ/d at week 6). In addition, the study groups showed no differences in the intake of carbohydrates, proteins, fat, unsaturated and saturated fatty acids, and cholesterol at baseline and during the intervention period. No significant changes in anthropometric values such as body mass index and hip circumference were observed. The change in body mass index during the intervention period was 0.1 ± 0.5 kg/m^2 in the carob fibre and 0.1 ± 0.6 kg/m^2 in the placebo group (p = 0.821) and was not significant compared to baseline body mass index (p = 0.181). Concerning the variables for blood glucose, HbA_1C, and insulin, no effect was observed.

Table 2 Baseline characteristics of the study population

Parameter	n	group: carob fibre 29	group: placebo 29	p-value
Sex (f/m)		15/14	18/11	0.426[a]
Age (y)		55 ± 10	53.8 ± 12	0.411
Body mass index (kg/m^2)		25.4 ± 3.1	25.8 ± 3.9	0.755
Blood glucose (mg/dL)		79 ± 20	84 ± 29	0.447
Insulin (µu/mL)		7.0 ± 5.6	6.7 ± 5.1	0.829
HbA_1C		5.0 ± 0.7	5.1 ± 0.7	0.618

Values are given as mean ± SD or percent if not indicated otherwise
[a] Pearson test

Serum cholesterol concentrations and triglycerides

Blood lipids and apolipoprotein levels during the intervention period are shown in Table 3, changes in blood lipids of all participants and separated by gender are shown in Figs. 1 and 2.

Total cholesterol concentrations were affected by treatment (p = 0.001). The consumption of carob fibre led to a reduction of total cholesterol of 2.0 ± 1.8 %. Total cholesterol concentrations increased by 7.5 ± 1.7 % in the placebo group. Thus, the difference between treatment groups was 9.5 %. The lipid lowering effect of carob fibre consumption was most obvious in LDL cholesterol (p = 0.010). LDL cholesterol concentrations were reduced by 10.5 ± 2.2 %, whereas they remained unchanged in the placebo group (0.5 ± 2.8 %). No significant changes were observed in HDL cholesterol during the intervention period and no treatment effect was observed. For LDL:HDL cholesterol ratio a marginal improvement was observed in the carob fibre group compared to the placebo group (p = 0.058). The LDL:HDL ratio decreased by 7.9 ± 2.2 % in the carob fibre group and remained unchanged in the placebo group (0.2 ± 3.1 %). For the total:HDL cholesterol ratio, a marginal treatment effect was observed (p = 0.066) in all participants. Triglyceride concentrations were only slightly decreased by carob fibre treatment (p = 0.068) if gender was disregarded. Generally, the degree of any changes in blood lipid concentrations was not related to baseline values.

Table 3 Serum lipids and apolipoproteins during intervention period in human subjects

	Group						p-value[2]
	Carob fibre (n = 29)			Placebo (n = 29)			
	week 0	week 4	week 6	week 0	week 4	week 6	
Total cholesterol (mg/dL)	268±33	261±30	264±37	259±30	267±36	278±37	0.001
LDL cholesterol (mg/dL)	173±27	169±25	155±29	172±26	177±26	172±30	0.010
HDL cholesterol (mg/dL)	58 ±19	57±17	56±18	57±13	59±15	57±13	0.342
Triglycerides (mg/dL)[1]	188 (109–323)	172 (96–308)	169 (88–328)	134 (93–193)	131 (94–184)	141 (103–195)	0.068
Apo A-I (mg/dL)	170±31	146±23	143±23	169±23	147±20	149±23	0.467
Apo B (mg/dL)	139±24	128±23	138±29	131±20	130±21	145±24	0.001
Total:HDL cholesterol	5.0±1.2	4.9±1.3	5.1±1.4	4.7±0.9	4.7±0.9	5.0±0.9	0.066
LDL:HDL cholesterol	3.3±0.9	3.2±0.9	3.0±0.9	3.2±0.8	3.1±0.8	3.1±0.8	0.058
Apo B:apo A-I	0.86±0.23	0.91±0.23	1.00±0.28	0.79±0.17	0.91±0.20	0.99±0.21	0.040

Values are given as mean ± SD if not indicated otherwise
[1] Values are given as geometric mean and geometric SD
[2] Significance of the trend effect of treatment between groups in change from baseline analysed by ANOVA with repeated measurement design

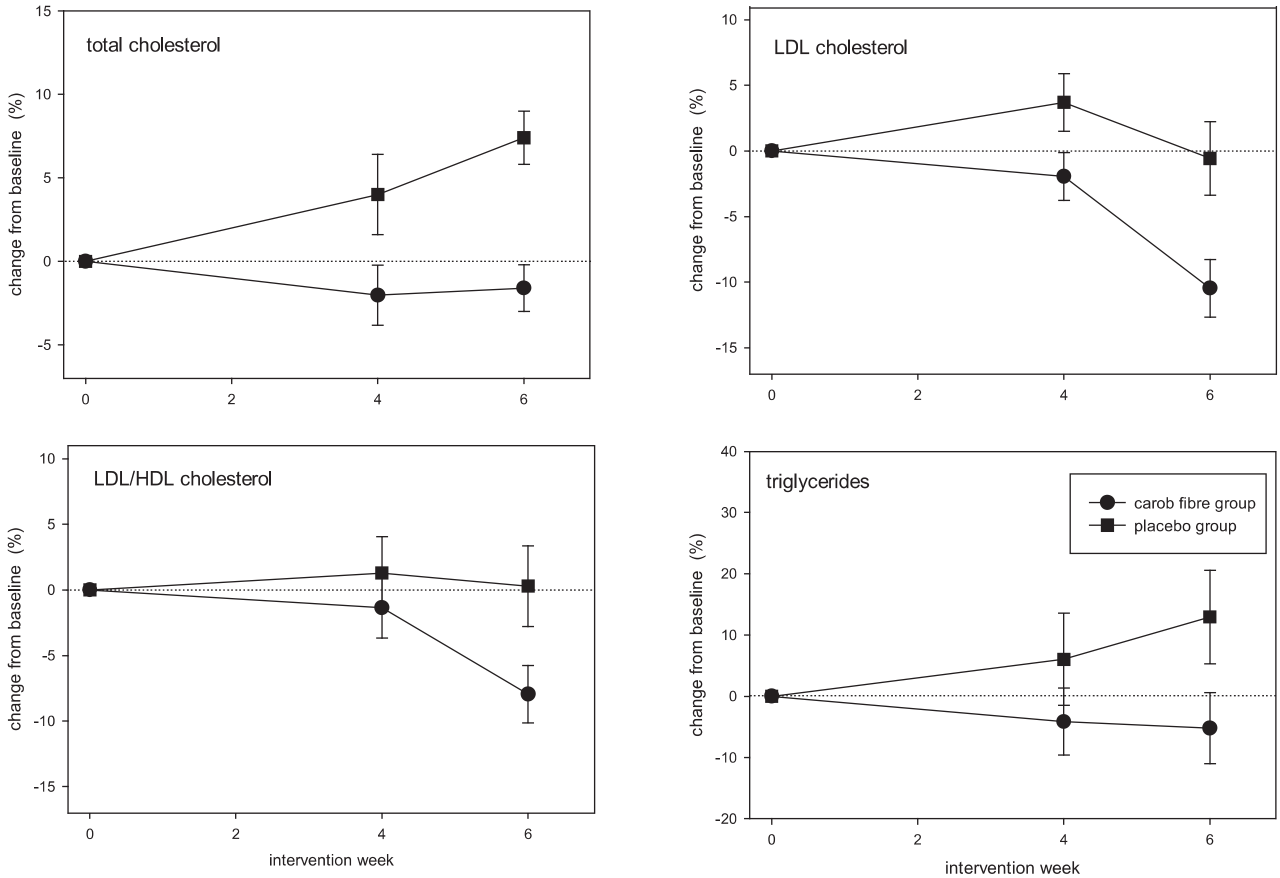

Fig. 1 Blood lipid profiles during the intervention period in patients with moderately elevated cholesterol levels after consumption of carob fibre (n = 29) or placebo (n = 29). Data are mean ± SEM

Changes in apolipoproteins

In all participants apolipoprotein A-I strongly decreased during the intervention period (p = 0.001) but no treatment effect was found. Apolipoprotein B remained unchanged in the carob fibre group but increased in the placebo group (p = 0.001). The difference between treatment groups was 11.9%. Consequently,

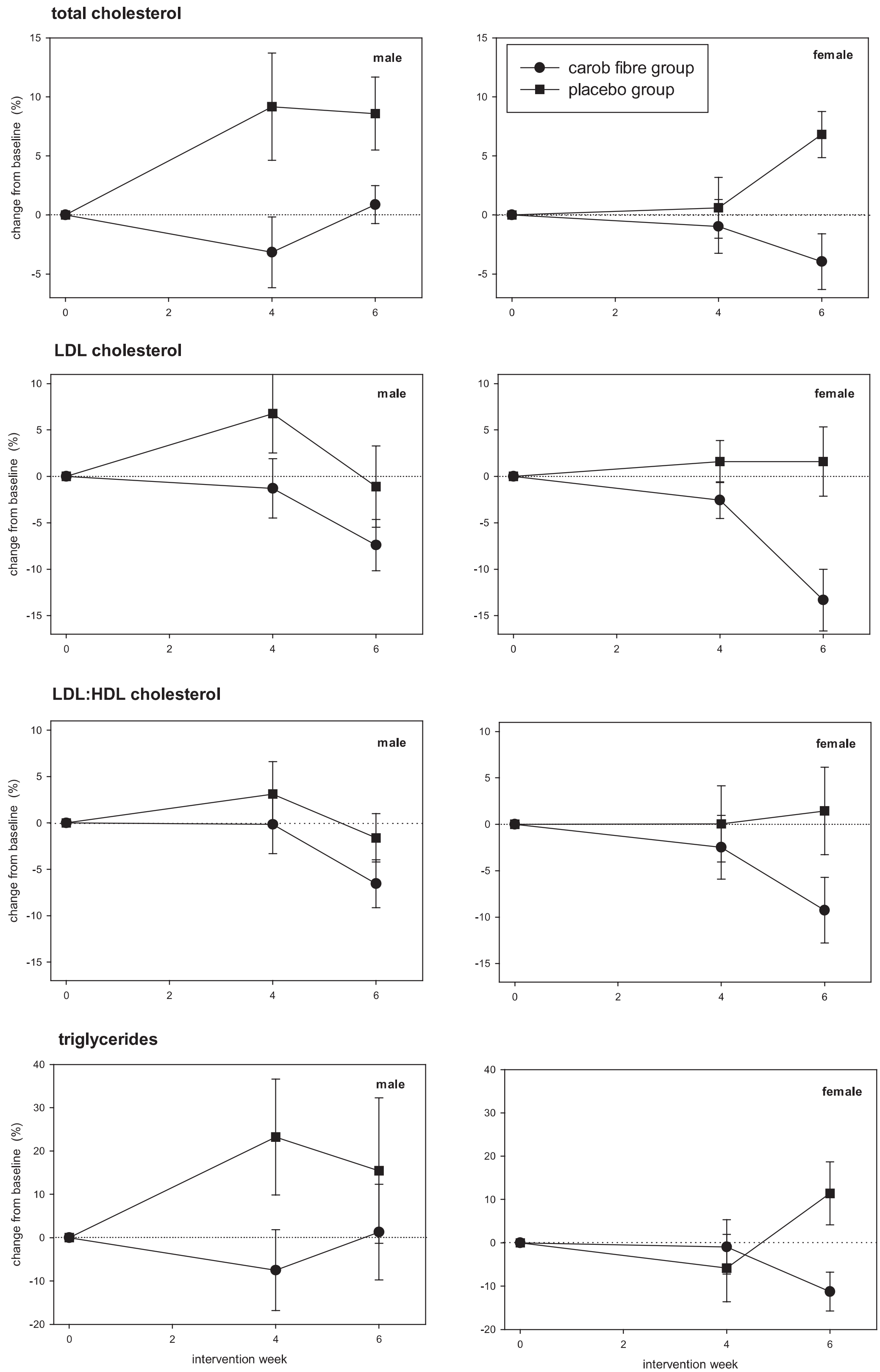

Fig. 2 Blood lipid profiles during the intervention period in males and females with moderately elevated cholesterol levels after consumption of carob fibre (n = 29) or placebo (n = 29). Data are mean ± SEM

apolipoprotein B:A-1 ratio increased stronger in the placebo than in the carob fibre group ($p = 0.040$).

Gender effects on plasma lipid response

Gender effects on plasma lipid response are shown in Fig. 2. The cholesterol-lowering effect of carob fibre was more pronounced in females than in males. In the carob fibre group total cholesterol concentrations decreased by 4% in females compared to 1% in males ($p = 0.044$). The decrease in total cholesterol in male participants of the carob fibre group was more pronounced in week 4 than in week 6 of intervention. In LDL cholesterol response no significant differences were observed between males and females. HDL cholesterol was higher in females than in males ($p = 0.004$) but there was no gender effect on HDL cholesterol response. Despite a lower LDL/HDL cholesterol ratio in females than in males ($p = 0.001$) no gender effect on response was observed. Triglycerides were affected by the different treatment only in females, but not in males, i. e. an interaction between treatment and gender during the intervention period was found ($p = 0.030$).

In all other variables followed over the intervention period no significant alterations and no treatment effect could be found.

Discussion

The present study shows that the intake of carob fibre can reduce LDL and total cholesterol concentrations compared to a control group. These reductions are of clinical relevance [27] and support the findings of a recent pilot study [21].

Elevated levels of blood cholesterol are an important risk factor for cardiovascular diseases [28–30]. Consequently, dietary interventions for lowering blood cholesterol are a major focus in prevention and treatment of cardiovascular diseases [28, 30–33].

Soluble fibre such as oat bran, psyllium, pectin and guar gum have been considered to be effective in treatment of hypercholesterolemia [6, 8, 19, 20, 34–36]. Insoluble fibre like wheat bran seemed to have no direct effect [37]. At present the effect of non-wheat insoluble fibre preparations remains unclear.

In the present study consumption of carob fibre isolated from the pulp of carob pods markedly reduced total cholesterol and LDL. The LDL:HDL ratio marginally decreased in the carob fibre group and was lower compared to the control group. The cholesterol lowering effect of carob fibre was more pronounced in females than in males. Moreover, triglycerides were reduced in females. This might reflect a further activity additional to the beneficial cholesterol-lowering effect of carob fibre, which is comparable to the activity of soluble fibre such as psyllium or pectin [6, 9, 12, 34, 35, 38, 39].

The carob pulp isolate contains high amounts of insoluble fibre and only negligible amounts of soluble fibre. Typical carob fibre components include cellulose, hemicelluloses, and lignin, but also high levels of water-insoluble polyphenols (tannins). Furthermore, water-soluble polyphenols like flavonol glycosides, gallic acid or hydrolysable tannins are important constituents of this mostly insoluble carob preparation [40]. The physiological effects have been demonstrated particularly in animal studies [22–24]. In rats carob fibre demonstrated an increased excretion of cholesterol and bile acids [22] and a reduction in plasma cholesterol levels [23, 24]. The size of the observed effects in rats was even higher than that of psyllium fibre as a representative of soluble fibre [24]. The common opinion needs to be questioned that soluble fibre has a greater potential to alter serum lipid levels than does insoluble fibre [8, 41]. Moreover, the specific composition of the dietary fibre components as well as of fibre-associated bioactive constituents has to be considered in this discussion.

The mechanism how blood cholesterol is influenced seems to be different between soluble and insoluble fibre. Whereas soluble fibre lowers serum cholesterol more by an effect on lipid solubilization, insoluble fibre is able to adsorb bile acids in the chymus as demonstrated in several in vitro and in vivo studies [41–43]. This binding results in an increased faecal loss of bile acids, as they escape the enterohepatic circulation, and thereafter in a higher consumption of endogenous cholesterol for *de novo* cholesterol synthesis. Most investigations support this concept of action [41–43]. Only in a study in rodents a tannin-rich product (Quebracho) enhanced bile acid excretion, but failed to significantly reduce plasma cholesterol [44]. Therefore, it can be assumed that the effect of carob fibre might not be explained by the content of tannin only.

Recent studies in hamsters indicate that the LDL cholesterol-lowering potential of carob fibre is accompanied by a dose-dependent increase in total bile acid excretion. Moreover, a dose-dependent increase in the activity of cholesterol-7α-hydroxylase (Cyp 7 a), the key enzyme in bile acid synthesis, has been observed [45]. The intestinal absorption of dietary cholesterol was not affected in this experiment. This data suggests that the cholesterol-lowering effect of carob fibre is a result of an elevated excretion of bile acids, while dietary cholesterol absorption remains unchanged [45].

In human beings a non-controlled one-arm study showed a remarkable fall of blood total and LDL cholesterol levels after administration of food products containing carob fibre preparations isolated from carob pulp [21]. The results presented here strengthen the perception of carob fibre as exerting a beneficial effect on human health. These effects may be attributed to the high content of lignin and polyphenols, especially tannins, and their ability to adsorb bile acids in the chymus.

In the present study blood lipid response on carob pulp preparation was significantly affected by gender. Lipid-lowering effect of carob pulp consumption was more pronounced in females than in males. These findings confirm observations of other human and animal studies demonstrating that gender and hormonal status have a direct influence on blood lipid response, i. e. that dietary interventions on blood lipids are more effective in women and less effective in men [46–48].

In dietary interventions intended to influence lipoprotein concentrations changes in apolipoproteins A-I and B have not been consistent [20, 39]. In the present study apolipoprotein A-I decreased in both, carob and placebo groups, whereas apolipoprotein B increased only in the placebo group. Other studies investigating soluble fibre with high potential of cholesterol-lowering effects also fail to reduce apolipoprotein A-I and B [9, 39]. Thus, apolipoproteins have been shown to have high individual variability and poor ability in predicting cardiovascular risk [49, 50]. Moreover, nutritional intervention studies may suffer from several unpredictable effects which are difficult to control for [51]. Such influences may disturb results even in carefully designed and conducted studies.

The acceptance, tolerance and compliance of the carob fibre test products by the patients was good. No patient reported increased digestive complaints such as flatulence or constipation. Due to the small sample size and the usually high individual variability of cholesterol response [50] the effects found in the present study need further investigation especially with regard to the mechanisms and the dose-response dependency of the observed cholesterol reduction.

In conclusion, the supplementary intake of carob fibre shows beneficial effects on total and LDL cholesterol levels as well as marginal effects on LDL/HDL cholesterol ratio. Because it is estimated that every 1 % reduction in total cholesterol concentrations will result in a 2–3 % reduction in risk of coronary heart diseases [52] the current results suggest that carob fibre may be effective in dietary treatment of hypercholesterolemia. Further investigations are needed to prove and to investigate the role of carob pulp preparations in primary prevention, for example cholesterol lowering effects in a population with normal blood cholesterol concentrations.

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