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Hypolipidemic effect of Silymarin in Dyslipidaemia of Different Etiologies

Original Article

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Summary:

Fac Med Baghdad 2007; Vol.49, No.4
Received July 2006
Accepted Jun.2007

Background: Many drug and non drug approaches are utilized for the treatment of dyslipidemia; flavonoids, the major constituents of silymarin, have been proved to positively modify lipoproteins in experimentally – induced dyslipidemia.
Objective: This study was designed to evaluate the effect of silymarin, when used alone or in combination with other hypolipidemic agents, on the lipid profile in dyslipidemic patients.
Patients and Methods: Fifty seven patients with dyslipidaemia of various etiologies are involved in this clinical trial. They are randomized into three groups treated with either 400mg / day silymarin (gr. A) or 20 mg / day lovastatin (gr. B) or a combination of 200 mg/day silymarin and 10 mg/day lovastatin (gr. C) for 2 months, only 45 patients complete the study . Serum lipid profile (total cholesterol, triglycerides, LDL-C, VLDL-C and HDL-C) and liver functions indices (SGOT, SGPT, total bilirubin) were evaluated each month during the follow up period.
Results: Treatment with silymarin results in a significant decrease in TC, TG, LDL-C and VLDL-C levels, with a significant elevation in HDL-C levels, without any significant changes in liver function. Meanwhile, adjunct use of silymarin with lovastatin widens the scope of lovastatin-hypolipidemic effect, without increasing in the score of adverse effects, and ameliorating the hepatic damage emerged due to its use.
Conclusions: The results presented in this study indicated that silymarin can be used alone in clinical practice for the treatment of dyslipidemia, and when combined with other hypolipidemic agents like lovastatin, improves therapeutic profile and ameliorate some of its adverse effects.

Introduction:

Dyslipidemia can be defined as an excessive accumulation of one or more of the major lipids transported in the plasma, and is a manifestation of one or more abnormalities of lipid metabolism or transport[(1)]. Dyslipidemia may be manifested as hyper-cholesterolemia or hyper-triglyceridemia or both; and excessive accumulation in the plasma in the form of one or more of lipoprotein classes, can result from defective removal from plasma or excessive endogenous production or both [(2)]. These abnormalities may be primary, or may occur as secondary consequences of other diseases like diabetes mellitus [(3)]. The primary and secondary dyslipidemia are generally characterized by similar laboratory abnormalities [(4)].

The emergence of the role of oxidative stress theory in the pathogenesis of dyslipidemia and related consequences [(5)]

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raises the possibility of using compounds with powerful antioxidant properties, like silymarin, to improve the impaired lipid profile in dyslipidemia. Silymarin is a mixture of flavonolignans isolated from the ripe seeds of the medicinal plant *silybum marianum* (milk thistle) [6].

Multiple biological effects of flavonoids have been described, including anti–inflammatory, antiallergic, antihaemorrhagic, antimutagenic, antineoplastic and hepatoprotective activities. The biological and pharmacological effects of flavonoids in mammals are assumed to result mainly from two properties: modulation the activities of certain enzymes and their antioxidant activity [6]. This study was designed to evaluate the hypolipidemic effects of silymarin in dyslipidemic patients, when used alone or in combination with other hypolipidemic agents like lovastatin.

Patients and Methods:-

This randomized clinical study was carried on 57 patients (25 males and 32 females) with age range of 40- 69 years (54 ± 10) and body weight range of 61-89 kg (76 ± 11), presented with marked dyslipidaemia for more than 2.5 years. The patients were diagnosed with various types of dyslipidaemia and followed by specialist physician and nutrition specialist as out patients for two months at the Specialized Center for Endocrinology and Diabetes (SCED), Al- Rusafa Directorate of Health, Baghdad. They were considered eligible to participate in the study only if diet regulation failed to control their dyslipidaemia. The diagnosis was established by insufficient reduction in LDL-C and TG levels according to the National Cholesterol Education Program (NCEP) reports [7]. They were kept on controlled dietary regimen before and during the study, and their conditions characterized by having elevated total cholesterol > 250 mg/dl and triglycerides > 250 mg/dl. Only 45 patients completed the study, the others were excluded due to either poor compliance with the follow up program or emergence of potential excluding factors. Patients were randomized into three groups and treated as follow: Group A: include 15 patients (8 males and 7 females) treated with 200 mg silymarin twice daily as an oral dosage form (capsule) specially prepared for this purpose for two months .Group B: include 15 patients (7 males and 8 females) treated with 20 mg lovastatin orally, given as a single daily dose at bed time for two months.

Group C: include 15 patients (6 males and 9 females) treated with 200 mg silymarin given as a single daily dose in the morning, and 10 mg lovastatin given as a single daily dose at bed time for two months. Fifteen healthy subjects (5 males and 10 females) were involved and considered as control group for comparison. Biochemical markers required for evaluation were determined at baseline before the initiation of therapy, after one month of treatment and at the end of two months for all patients groups. After over night fasting, blood samples (10 ml) were collected by vein puncture at zero time, after 1 and 2 months of treatment, and transferred into a plain tube and left to clot. Serum was prepared after centrifugation at 3000 rpm for 10 minutes, and kept frozen unless analyzed immediately. Serum cholesterol was estimated according to the method of Richmond (1974) [8], while serum triglyceride levels were determined according to the method of Fossati and Prencipe (1982) [9]. The serum levels of HDL and LDL cholesterol were estimated according to the Burstein *et al* method (1970) [10] and Friedewald *et al* (1972) [11] formula respectively. Serum activities of liver transaminases (SGOT, SGPT) were determined according to Reitman and Frankel method (1957) [12].

Results were expressed as mean ± S.E. or percent of changes. The significance of differences between the mean values was calculated using paired Student's *t*-test. *P*-values less than 0.05 were considered significant.

Results:

Table (1) showed that there is a significant reduction ($P < 0.05$) in the levels of TC and LDL-C after one month (31.9 % and 39.5 % respectively) and two months of treatment with silymarin (45 % and 58.7% respectively) compared with baseline values. The levels of LDL-C were comparable to those of control group after two months of treatment ($P > 0.05$). Regarding TG and VLDL-C, table (1) showed a significant reduction ($P < 0.05$) in

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the levels of these parameters (23% and 28.4% after one and two months of treatment respectively) compared with baseline values. The changes after two months of starting silymarin treatment did not differ significantly ($P > 0.05$) compared to those reported after one month of treatment. Concerning HDL-C levels, table (1) demonstrated that silymarin treatment results in a significant elevation ($P < 0.05$) of this marker after two months of treatment (19.1%) compared to baseline values. The levels of HDL-C were comparable to those of controls at the end of the follow up period ($P > 0.05$). Table (1) showed that there is a significant reduction ($P < 0.05$) in the levels of TC and LDL-C after one month (39.2% and 52.2 % respectively) and two months of treatment with lovastatin (50.1% and 67.6% respectively) compared to baseline values. The levels of these markers were comparable to those of control group at the end of the treatment period ($P > 0.05$).

Regarding TG and VLDL-C levels, table (1) demonstrated that lovastatin did not produce any significant reduction ($P > 0.05$) in the levels of these markers during the follow up period compared to baseline values. Concerning HDL-C, lovastatin significantly elevates ($P < 0.05$) serum levels (5.7 % and 15.7% after one and two months of treatment respectively) compared with baseline values. The levels of HDL-C were comparable to those of control group at the end of the treatment period ($P > 0.05$).

Table (1) showed that there is a significant reduction ($P < 0.05$) in the levels of TC and LDL-C after one month (15.5% and 23.4% respectively) and two months of treatment with this combination (35.3% and 50.7% respectively) compared with baseline values. The levels of LDL-C were comparable to those of control group at the end of the treatment period ($P > 0.05$).

Concerning the effects on TG and VLDL-C levels, table (1) demonstrated that this therapeutic regimen significantly reduces ($P < 0.05$) the levels of these markers at the end of the treatment period (14.8% for both parameters) compared to baseline values. Meanwhile, table (1) showed that this combination results in a significant elevation ($P < 0.05$) in HDL-C levels (11.9% and 31.6% after one and two months of treatment respectively) compared to baseline values. The levels of HDL-C were comparable to those of control group after the end of the treatment period ($P > 0.05$).

Table (2) showed that silymarin does not produce any significant change ($P > 0.05$) in SGOT, SGPT activities or total serum bilirubin levels after the end of treatment period compared to baseline values. All of these liver function indices remain within the normal limits (comparable to control). Lovastatin significantly elevates ($P < 0.05$) the activities of SGOT (37.6% and 73.3%) and SGPT (35.3% and 63.7%) after one and two months of treatment respectively compared with baseline values. Regarding total serum bilirubin, lovastatin did not produce any significant change ($P > 0.05$) in the values of this marker during the treatment period compared to baseline values. Combination of silymarin and lovastatin neither significantly elevates ($P > 0.05$) the activities of SGOT and SGPT nor significantly reduces ($P > 0.05$) the levels of total serum bilirubin during the treatment period compared with those of baseline. All of these liver function indices remain within the normal limits (comparable to control).

Discussion:-

It has been reported previously that silymarin or its polyphenolic fraction modifies the lipoprotein profile in animal model of dyslipidaemia [13]. Therefore, this clinical study was established according to this biological activity and the very well known safety profile of this plant extract. Many pathological conditions, including diabetes mellitus and hypothyroidism were mostly associated with impaired lipid profile;[14] these conditions were considered during patient selection as a clinical model during this study, where all screened patients presented with significantly impaired values of lipid profile compared to controls. Table (1) showed that treatment with silymarin alone (group A) successfully improves the lipid profile markers in dyslipidemic patients during two months of treatment. It has been reported that bioflavonoids and lecithin produced anti–atherosclerotic activity in experimentally –induced atherosclerosis in rabbits, mostly attributed to normalized lipid metabolism [15].

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Administration of silymarin to rats with impaired lipid profile results in significant reduction in TC, LDL-C and VLDL –C levels associated with significant elevation in HDL–C levels, [16] a profile of effects where the results of this study compatible with (table 1). Such observation can be considered as an important indicator for ameliorating atherosclerosis and risk factors for cardiovascular diseases.

Kercman and co-workers (1998) reported that silymarin inhibits development of hypercholesterolemia in rats fed cholesterol – rich diet and compared this finding with that produced by probucol , associated with an increase in HDL-C levels and decrease in the liver contents of cholesterol;[17] while others suggested that silymarin could have a direct effect on cholesterol metabolism in the liver by inhibiting cholesterol biosynthesis. Meanwhile, orally administered silymarin produced mild increase in plasma HDL-C levels without significant changes in total cholesterol levels in the plasma of rats fed standard laboratory diet . However, parenterally administered silymarin failed to reduce plasma total cholesterol, both in rats fed high cholesterol diet or standard laboratory diet, and this may suggest interference with the absorption of dietary cholesterol [18].

Elevation of HDL-C levels in the serum after silymarin treatment (table 1) can be explained by the increase in the production and secretion of apo– AI by the liver, which is considered as the main component of apo – lipoproteins of HDL. [18]

Intracellular esterification of cholesterol, catalyzed by the enzyme acyl–CoA: Cholesterol acyl–transferase (ACAT), is a key pathway involved in several aspects of lipid metabolism including cholesterol absorption, lipoprotein biosynthesis, steroid hormones synthesis and atheroma foam cell formation.[19] Inhibition of ACAT was shown to reduce intestinal absorption of cholesterol in rats [20] and the effects of phenolic compounds from other sources in this respect is very well characterized;[21] silymarin might similarly shows hypocholesterolemic effects through this pathway .Moreover, other suspected mechanism can be suggested through suppression of the enzyme HMG-CoA reductase, where silibinin and taxifolin, major components of silymarin, are found to decrease the synthesis of cholesterol by liver cells *in vitro* through suppression of HMG-CoA reductase.[22] Therefore, silymarin may affect cholesterol levels through a dual mechanism , by acting as trapping resin and/or inhibitor of the rate-limiting step enzyme in cholesterol biosynthesis in the liver , HMG – CoA reductase . In an experimental model of hepatic injury induced by paracetamol in rats, it has been reported that treatment with silymarin improves LDL- binding to the hepatocytes, an important factor in the reduction of plasma LDL-C levels through clearance by hepatocytes [18]. Reduction in serum VLDL –C levels produced by silymarin treatment might not be attributed to decreased formation and secretion in the liver only, but also to a reduction of VLDL secretion in the intestine, [23] a mechanism that also might explain the inhibition of intestinal absorption of cholesterol.

Statins are group of hypolipidemic agents act by competitive inhibition of HMG-CoA reductase , the rate – limiting step in cholesterol biosynthesis, with consequent reduction in LDL-C entry into the circulation.[24] Many studies reported that treatment with lovastatin reduced plasma TC and LDL-C levels with slight increase in HDL-C levels; while the influence on TG and VLDL-C levels seems to be moderate.[25] The data presented in table (1) are found compatible with those reported elsewhere about the effects of lovastatin (group B) . Combination of silymarin and lovastatin (group C) reduced significantly TC and LDL-C and increased HDL-C levels after one month of treatment, while TG and VLDL-C levels were significantly reduced after two months of treatment. Meanwhile, the use of this combination enable reduction the dose of both components (silymarin and lovastatin) with the benefit of producing generalized effects on all components of the lipid profile, with the possibility of lowering the incidence of side effects if any .

It has been reported that there is a strong relationship between hepatic dysfunction and dyslipidemic complications.[26] However , the data presented in table (2) showed no significant differences in the values of liver function markers in all groups compared to control before starting treatment . Concerning the effects on hepatic functions, silymarin is

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very well known as a potent hepatoprotectant , and licensed for clinical use in the treatment of hepatic damage induced by many agents including toxins , drugs and viruses.[27] According to the available experimental evidences, the effect of silymarin on liver tissues can be related to its powerful antioxidant, membrane stabilizing and tissue regenerative activities.[28]

The present study demonstrated that silymarin (group A) non-significantly affecting the activities of SGOT and SGPT and bilirubin levels during treatment period compared to pre- treatment values which are already within the accepted normal ranges (table 2) .

Blocking HMG- CoA reductase by statins may lead to instability of plasma membranes associated with decrease in cholesterol–dependent cytoresistance and leakage of liver enzymes into the circulation.[29] The data presented in table (2) are compatible with the previously reported one, where lovastatin (group B) significantly elevates both SGOT and SGPT activities in the serum after one and two months from initiating treatment compared to baseline values .

Treatment of dyslipidemic patients with combination regimen of lovastatin and silymarin (group C) did not produce any significant elevation in hepatic transaminases activity and bilirubin level in the serum (table 2) . This can be simply explained by the hepatoprotective effect of silymarin against the possible damage produced by lovastatin on the liver; this finding was consistent with those reported elsewhere in this respect. This approach of treatment might have some advantages concerning dose reduction, efficacy and safety over that of using monotherapy or toxic combination in dyslipidaemia. In conclusion, Silymarin can be used alone effectively and safely in the treatment of dyslipidaemia of different etiologies and when combined with lovastatin improves its lipid-lowering profile and prevent its suspected side effects.

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Table 1: Effects of 400 mg/day silymarin, 20 mg/day lovastatin and combination of 200 mg silymarin with 10 mg lovastatin on the lipid profile.

Group	Duration	TC mg/dl	TG mg/dl	LDL mg/dl	VLDL mg/dl	HDL mg/dl
Control n=15	---------	185 ± 3.0	141 ± 2.5	106 ± 5.4	28 ± 0.22	51 ± 1.3
Group A n=15	**Baseline**	390 ± 7.4 ^{a*}	346 ± 13.6 ^{a*}	281 ± 7.99 ^{a*}	69 ± 5.3 ^{a*}	40 ± 1.0 *
	1 month	265 ± 9.2 ^{b*}	266 ± 11.7 ^{b*}	170 ± 6.9 ^{b*}	53 ± 6.4 ^{b*}	42 ± 0.7 ^{a*}
	2 months	215 ± 3.4 ^{c*}	247 ± 10.8 ^{b*}	116 ± 0.6 ^{c}	49 ± 2.5 ^{b*}	48 ± 0.6 ^{b}
Group B n=15	**Baseline**	385 ± 10.0 ^{a*}	269 ± 0.8 ^{a*}	289 ± 6.1 ^{a*}	54 ± 3.6 ^{a*}	42 ± 1.2 ^{a*}
	1 month	234 ± 8.5 ^{b*}	255 ± 0.89 ^{a*}	138 ± 4.81 ^{b*}	51± 0.9 ^{a*}	44 ± 1.0 ^{b*}
	2 months	192 ± 5.7 ^{c}	254 ±1.0 ^{a*}	94 ± 4.7 ^{c}	51 ± 4.4 ^{a*}	48 ± 1.34 ^{c}
Group C n=15	**Baseline**	317 ± 12.1 ^{a*}	270 ± 15.4 ^{a*}	227 ± 0.6 ^{a*}	54 ± 8.3 ^{a*}	36 ± 0.1 ^{a*}
	1 month	268 ± 9.0 ^{b*}	266 ± 12.0 ^{a*}	174 ± 4.7 ^{b*}	53 ± 4.5 ^{a*}	40 ± 0.2 ^{b*}
	2 months	205 ± 7.3 ^{c*}	230 ± 7.6 ^{b*}	112 ± 0.70 ^{c}	46 ± 7.8 ^{b*}	47 ± 1.3 ^{c}

Group A: patients treated with silymarin (400 mg /day);group B: patients treated with lovastatin (20 mg/ day); group C: patients treated with silymarin (200 mg) + lovastatin (10 mg) / day; results were presented as mean ± SE; n= number of subjects; results with non identical superscripts (a, b, c) within the same group were considered significantly different ($P < 0.05$); * = significant difference from control ($P < 0.05$) .

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Table 2: Effects of 400 mg/day silymarin, 20 mg/day lovastatin and combination of 200 mg silymarin with 10 mg lovastatin on the liver functions.

Group	Duration	SGOT U/l	SGPT U/l	T.serum bilirubin mg/dl
Control **n=15**	---------	11.9 ± 1.0	11.0 ± 0.9	1.0 ± 1.1
Group A ***n=15***	Baseline	12.0 ± 1.7 [a]	12.5 ± 1.0 [a]	1.2 ± 0.5 [a]
	1 month	11.9 ± 0.8 [a]	11.8 ± 0.8 [a]	1.1 ± 0.8 [a]
	2 months	11.8 ± 1.3 [a]	11.4 ± 1.3 [a]	1.0 ± 0.7 [a]
Group B ***n=15***	Baseline	11.5 ± 1.1 [a]	10.2 ± 0.8 [a]	1.21 ± 0.3 [a]
	1 month	15.8 ± 0.1 [b*]	13.8 ± 1.0 [b*]	1.22 ± 0.4 [a]
	2 months	19.9 ± 0.1 [c*]	16.7 ± 0.9 [c*]	1.24 ± 0.5 [a]
Group C n=15	Baseline	11.5 ± 0.8 [a]	12.1 ± 1.8 [a]	1.25 ± 0.6 [a]
	1 month	11.6 ± 0.7 [a]	12.5 ± 0.9 [a]	1.23 ± 0.4 [a]
	2 months	11.8 ± 1.8 [a]	12.9 ± 0.2 [a]	1.20 ± 0.3 [a]

Group A: patients treated with silymarin (400 mg /day); group B: patients treated with lovastatin (20 mg/ day); group C: patients treated with silymarin (200 mg) + lovastatin (10 mg) / day; results were presented as mean ± standard error; n= number of subjects; results with non identical superscripts (a, b, c) within the same group were considered significantly different ($P < 0.05$); * = significant difference from control ($P < 0.05$) .

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