Silymarin in type 2 diabetes mellitus: a systematic review and metaanalysis of randomized controlled trials

Luminita Voroneanu¹, Ionut Nistor¹, Raluca Dumea¹, Mugurel Apetrii¹, Adrian Covic¹

¹Nephrology Department, Faculty of Medicine, University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Romania

OBJECTIVES

Type 2 diabetes mellitus (T2DM) is associated with increased risk of cardiovascular disease and nephropathy – now the leading cause of end stage renal disease and dialysis in Europe and United States. Inflammation and oxidative stress plays a pivotal role in the development of diabetic complications.

METHODS

We conducted a systematic review of randomized controlled trials. Electronic databases: Pubmed, Medline, EMBASE, Cochrane Central – Cochrane Controlled Trials Register, AMED (Allied and Complementary Medicine), EBM Reviews – ACP Journal Club, and MD Consult were searched up to June 2015 without language restriction.

Silymarin, an herbal drug with antioxidant and antiinflammatory properties, may improve glycemic control and prevent the progression of the complications.

The aim was to evaluate the benefits and risks of silymarin supplementation to patients with T2DM

Meta-analysis using a random-effect model was done for allcause mortality, diabetes complication, glycemic control, lipids control and treatment-specific side effects.

RESULTS

	Exp	perimental		(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.1.1 HbA1C									
Fallah Huseini 2006	6.78	1.05	25	9.45	2.16	25	18.7%	-2.67 [-3.61, -1.73]	•
Fallahzadeh 2012	-0.18	0.72	28	-0.19	1.2379	28	25.2%	0.01 [-0.52, 0.54]	•
Hussain 2007	7.45	0.8	18	8.71	0.6261	20	26.3%	-1.26 [-1.72, -0.80]	
Velussi 1997	7.2	0.2	30	8	0.3	30	29.8%	-0.80 [-0.93, -0.67]	•
Subtotal (95% Cl)			101			103	100.0%	-1.07 [-1.73, -0.40]	•
1.1.2 fasting glucose									
Fallah Huseini 2006	133	39	25	188	48	26	10.0%	-55.00 [-78.96, -31.04]	<u> </u>
Fallahzadeh 2012	-3.43		28	-11	57.252	28	7.7%	7.57 [-20.57, 35.71]	
					3.6	20	45.0%	-25.56 [-27.47, -23.65]	-
Hussain 2007	167.58	7.34	18						
Hussain 2007 Velussi 1997	167.58 165		18 30			30	37.3%		— — —
Hussain 2007 Velussi 1997 Subtotal (95% Cl)	167.58 165		30 101	193	17	30 10 4	37.3% 100.0 %	-28.00 [-34.09, -21.91] - 26.86 [-35.42, -18.30]	-
Velussi 1997 Subtotal (95% Cl)	165	1	30 101	193	17	104		-28.00 [-34.09, -21.91]	
Velussi 1997 Subtotal (95% CI) Heterogeneity: Tau ^z =	165 41.39; Ch	1 i ^z = 11.67,	30 101 df = 3 (193	17	104		-28.00 [-34.09, -21.91]	
Velussi 1997 Subtotal (95% Cl)	165 41.39; Ch	1 i ^z = 11.67,	30 101 df = 3 (193	17	104		-28.00 [-34.09, -21.91]	

Five random controlled trials (RCTs) with 270 patients with T2DM were included in the study. In low- to moderate-quality evidence, routine silymarin administration was associated with <u>a significant reduction in fasting</u> <u>blood glucose levels</u> (Mean Difference [MD] (-26.86 mg/dl; 95% CI [-35.42, – 18.30]) in four trials - see figure 1; Similarly, compared with placebo, silymarin administration <u>reduced</u> <u>significantly HbA1c levels ([MD] - 1.07; 95 % C.I. [-1.73-0.40])</u>

Test for subgroup differences: Chi² = 34.71, df = 1 ($P \le 0.00001$), I² = 97.1%

Favours [experimental] Favours [control]

-20 -10 0 10 20

Figure 1. Glycemic control outcomes

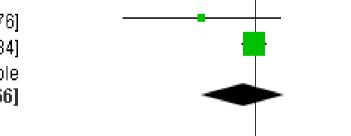
	Experimental			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	. SD		Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.2.1 colesterol total									
Fallah Huseini 2006	198	41	25	215	50	26	26.8%	-17.00 [-42.05, 8.05]	
Fallahzadeh 2012	-22.9	48.9994	28	-12.2	33.268	28	29.5%	-10.70 [-32.64, 11.24]	
Velussi 1997	162	9	30	150	5	30	43.7%	12.00 [8.32, 15.68]	
Subtotal (95% CI)			83			84	100.0%	-2.48 [-23.14, 18.18]	
Heterogeneity: Tau ² = :	251.05; ·	Chi ^z = 8.83	3, df = 2	? (P = 0.	01); I ^z = 77	%			
Test for overall effect: 2	Z = 0.24	(P = 0.81)							
4.0.0 trialiogrida									
1.2.2 trigliceride									
Fallah Huseini 2006	211	136	25	207	93	26	10.7%	4.00 [-60.19, 68.19]	
Fallahzadeh 2012	-10.3	60.3467	28	-6.04	47.8647	28	32.6%	-4.26 [-32.79, 24.27]	
Velussi 1997	154	26	30	128	19	30	56.7%	26.00 [14.48, 37.52]	
Subtotal (95% CI)			83			84	100.0%	13.78 [-9.12, 36.67]	
Heterogeneity: Tau ² = 3	206.10; ·	$Chi^2 = 4.00$	0, df = 2	P = 0.	14); I² = 50	%			
Test for overall effect: 2	Z = 1.18	(P = 0.24)							
1.2.3 hdl colesterol									
Fallah Huseini 2006	61	19	25	85	91	26	21.0%	-24.00 [-59.76, 11.76]	_
Fallahzadeh 2012	0.32	10.5736	28	0.61	8.9488	28	79.0%	-0.29 [-5.42, 4.84]	
	_	_	_	_	_	_			

 Fallahzadeh 2012
 0.32
 10.5736
 28
 0.61
 8.9488
 28
 79.0%
 -0.29 [-5.42, 4.84]

 Velussi 1997
 0
 0
 0
 0
 0
 0
 Not estimable

 Subtotal (95% Cl)
 53
 54
 100.0%
 -5.27 [-24.20, 13.66]

 Heterogeneity: Tau² = 111.19; Chi² = 1.65, df = 1 (P = 0.20); l² = 40%
 10
 10



Favours [experimental] Favours [control]

Test for subgroup differences: $Chi^2 = 1.73$, df = 2 (P = 0.42), $I^2 = 0\%$

Test for overall effect: Z = 0.55 (P = 0.59)

Figure 2. Lipid control outcomes

Three studies reported data on <u>lipid control. No difference</u> was found between the two arms – MD for cholesterol levels was -2.48 mg/dl; 95 % C.I.-23.14-18.18; MD for HDL cholesterol was -5.27 mg/dl; 95 % C.I. -24.20 – 13.66; MD for triglyceride 13.87 mg/dl; 95 % C.I. -9.12 – 36.67 – see figure 2

Only one small study, with a short follow-up reported a reduction of proteinuria in patients with overt nephropathy - mean difference in change in urinary albumincreatinine ratio between the 2 groups was -347 (95% Cl, -690 to -4) mg/g.

Mean values for changes in renal outcomes (serum creatine, eGFR – estimated glomerular filtration rate) were not significantly different between the two groups- only in one small study.

CONCLUSIONS

REFERENCES

Silymarin interventions might improve glycemic control in patients with type 2 DM. Benefits for silymarin on proteinuria and CKD progressions are uncertain.

However, being aware of the low quality of the available evidence and elevated heterogeneity of these studies, no recommendation can be made and further studies are needed.

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