A Meta-Analysis on Sugar Cane Policosanol as Treatment for Hypercholesterolemia*

Frederick Ogbac, M.D.[1], Rolando Quimpo, M.D.[1], Jaime Enrique Hilado, M.D.[1], Rosa Allyn Sy, M. D., FPCP, FPSEM[2], Vimar Luz, M. D., FPCP, FPSN[3], and Sandra Tankeh-Torres, M.D., FPCP, FPCR[4]

Abstract

Background: Sugar cane policosanol is composed of eight high molecular mass aliphatic alcohols that claimed to have a cholesterol lowering effect. It was first introduced in Cuba and was extracted from local sugar cane. Animal trials and earlier human trials have shown it to have a cholesterol lowering effects.However, recent human trials showed contradicting results.

Objective: The objective of this research is to compare the effects of sugar cane policosanol with placebo or non-treatment on the level of total cholesterol and LDL among patients with hypercholesterolemia.

Materials and Methods: MEDLINE search was done using "sugar cane policosanol (MeSH OR free text) AND hypercholesterolemia (MeSH OR free text)" limited to human subjects, male and female gender, all adult 19+ years, meta-analysis, clinical trials, practice guidelines, and randomized controlled trials. Trials included were randomized controlled trial comparing sugar cane policosanol and placebo in patients with hypercholesterolemia. Three independent reviewers assessed and graded the studies using the Cochrane Collaboration Tool. Review Manager 5 was utilized for calculations using mean difference for continuous variables. A subgroup analysis on the amount of policosanol used was done.

Results: A total of 16 studies were identified and three fulfilled the criteria. One study was a crossover study, while the other two were parallel studies. There was no statistically significant difference in the mean end point level of total cholesterol between the placebo group and sugar cane policosanol group (0.19 (0.08, 0.30)). There was also no statistically significant difference in the mean end point level of LDL (0.09 (-0.01, 0.19)). The subgroup group analysis on both 10mg and 20mg policosanol was also consistent in showing no statistically significant difference in the mean end point levels of total cholesterol, (0.18 (0.05, 0.30)) and (0.39 (0.06, 0.72)) respectively. The subgroup analysis on LDL using 10mg and 20mg also showed no statistically significant difference in the mean end point levels, (0.09 (-0.02, 0.20)) and (0.12 (-0.13, 0.037)) respectively.

Conclusion: In conclusion, sugar cane policosanol did not demonstrate any significant difference in the mean end point levels of both total cholesterol and LDL among patients with hypercholesterolemia compared to placebo.

Introduction

Hypercholesterolemia is defined as the presence of elevated levels of cholesterol in the body. Cholesterol is an amphipathic lipid that is present in tissues and plasma. In the plasma, it is transported in lipoproteins. There are four major groups of plasma lipoproteins namely low density lipoproteins (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL), and chylomicrons. LDL, VLDL, and chylomicrons are associated with increased risk of coronary heart disease while HDL is inversely correlated with risk of coronary heart disease. Hypercholesterolemia is diagnosed as presence of total blood cholesterol levels of greater than or equal to 240mg/dL, while hyperlipidemia is diagnosed as presence of LDL cholesterol of greater than or equal to 160mg/dL, both of which after 12 hours of fasting[1]. The prevalence of hypercholesterolemia in the American Adults from 1999 to 2000 was 50.4% of the male population and 50.9% of the female.[2] Currently, the standard of treatment regimen includes diet modification and statins.

In the 1990s, sugar cane policosanol became popular in reducing hypercholesterolemia. It started as a local product of Cuba and had found its way into the American consumers. Policosanol is a mixture of eight high molecular mass aliphatic alcohols namely octacosanol, triacontanol, hexacosanol, tetracosanol, heptacosanol, nonacosanol, dotriantocanol, and tetratriacontanol.[3] The alcohols are extracted, isolated, and purified from plant waxes, specifically sugar cane. It is water insoluble and has a melting point of 70 to 82°C. The recommended dosages to achieve the benefits are 5 to 20mg/day.[4] The side effects are minimal and the most common is weight loss.[5]

The exact mechanism on how policosanol inhibits cholesterol synthesis is still unknown. There are 2 possible ways on studies have shown how policosanol affects the

[1] *Residents-in-Training, Department of Internal Medicine, Ospital ng Makati*

[2] *Department Chair and Section Head, Section of Endocrinology, Department of Internal Medicine, Ospital ng Makati*

[3] *Member, Section of Nephrology, Department of Internal Medicine, Ospital ng Makati*

[4] *Section Head, Section of Rheumatology, Department of Internal Medicine, Ospital ng Makati*

* *This paper was awarded 1st prize in the 2009 Department of Internal Medicine Paper Presentation, Ospital ng Makati (meta-analysis category)*

cholesterol synthesis. The first postulate is that policosanol has a suppression effect on the enzyme HMG-CoA activity thereby limiting its effect.[6] The other postulate is that it increases LDL metabolism thereby decreasing the cholesterol levels.[3]

The earliest published report on the use of sugar cane wax on cholesterol was on 1984. Administration of sugar cane wax on the rat diet resulted on the reduction in serum and liver lipids.[7] By 1994, animal studies in rabbits showed that policosanol reduces total cholesterol levels through a reduction in the LDL-C levels.[8] And in the same year, the cholesterol lowering effect of policosanol was tested on cultured human fibroblast and it inhibited cholesterol synthesis in the earliest step of cholesterol biosynthesis.[9]

Due to the success of sugar cane policosanol in animal trials, a number of clinical trials has been made over the years to prove its antilipidemic effect. The first ever published clinical trial of policosanol in humans was on 1999 by Prat et al. They compared policosanol with Lovastatin and Simvastatin. The results showed a 24% LDL cholesterol reduction in policosanol while only 22% and 15% reduction in Lovastatin and Simvastatin respectively.[10] In 2000, Castano et al investigated the efficacy, safety, and tolerability of policosanol on postmenopausal women with type II hypercholesterolemia. The results showed that policosanol significantly lowered the LDL-C and total cholesterol and significantly raised the levels of HDL-C without any adverse effects.[11] The antilipidemic effect of policosanol was further proven by other studies showing its LDL reduction effect. But in 2006, Greyling et al released a trial with the results contradicting the previously published trials. The trial concluded that intake of 20mg policosanol for 12 weeks had no significant effect on the lipid levels of hypercholesterolemia and heterozygous familial hypercholesterolemia patients.[12] In a study by Berthold et al done on the same year, the results showed no statistically significant difference between policosanol and placebo treatment.[13]

Objective

The objective of this research is to compare the effects of sugar cane policosanol with placebo or non-treatment on the level of total cholesterol and LDL among patients with hypercholesterolemia.

Methodology

Criteria for considering the studies for this review

The type of studies that was included was randomized placebo controlled trial. The trials included, had subjects aging from 18 years old up to 80 years old of either gender with LDL cholesterol levels of above 130mg/dL with no other co-morbidities. Subjects should not have been on any lipid lowering diet prior to their inclusion in the trial. The trials included had a treatment arm of sugar cane policosanol without any other medications, and a control arm of placebo or non-treatment. There were no restrictions on the amount of dosage, frequency, intensity, and duration of treatment. The trials included outcomes measuring the levels of total cholesterol and LDL.

Search methods for the identification of studies

A literature search using the PUBMED database of the National Library of Medicine was done using "sugar cane policosanol (MeSH OR free text) AND hypercholesterolemia (MeSH OR free text)" limited to human subjects, male and female gender, all adult 19+ years, meta-analysis, clinical trials, practice guidelines, and randomized controlled trials. The search was limited to published articles only.

Data Collection and Analysis

Three independent reviewers conducted validity assessment for each of the included studies. Duplicate and irrelevant reports were removed. The full texts of relevant trials were retrieved. Found studies were assessed and included based on the inclusion criteria. Careful appraisal of the methodology quality, adequacy of allocation concealment, blinding, and follow – up rates was undertaken and a quality assessment rating was given for each studies. Disagreements were resolved by consensus among the reviewers. Desired data were extracted from each of the article. Results were entered in Review Manager 5. The Cochrane Collaboration Tool was used to assess the risk of bias in the included studies. Mean difference for continuous variables was computed and forests plots were constructed for each of the outcome. A subgroup outcome analysis was done on the different amount of policosanol used in the studies, namely 10mg and 20 mg for both total and LDL cholesterol.

Results

Description of Studies

A total of sixteen studies were retrieved from the electronic search. Three clinical trials fulfilled the inclusion criteria. The characteristics of each study were outlined in Table 1. All three trials were randomized, double blinded, and placebo controlled. Among the three, the trial Kassis et al had their participant crossover from the treatment group to the control group and vice versa. The other two trials were both parallel studies. All the trials had participants of 18 years old to 80 years old with LDL cholesterol levels of above 130 mg/dL. All the studies used placebo as their control arm with policosanol amounting from 10mg to 80 mg as their treatment arm. All trials included outcomes measuring the levels of total cholesterol and LDL cholesterol. For their outcome, all three studies indicated the mean baseline and end point levels for both total cholesterol and LDL levels. Kassis et al and Berthold et al used mean to describe the percent change in the levels of total cholesterol and LDL from the baseline to the end point. On the other hand, Dublin et al used median.

Among the sixteen studies, thirteen trials did not fulfil the inclusion criteria. The characteristics of each study are

Table I. Characteristics of Included Studies

Study	Method	Participants	Interventions	Outcome	Grade
Policosanol is ineffective in the treatment of hypercholesterolemia: a randomized controlled trial by Dulin et al 2006	Randomized, double blind, placebo controlled study	18 years old and above male and female with LDL of 3.37 to 5.19 mmol/L (130 to 200 mg/dL) and triacylglycerol of <3.39 mmol/L (300mg/dL)	20mg policosanol OD vs. placebo	LDL, total cholesterol, HDL, triacylglycerol	A
Lack of cholesterol-lowering efficacy of Cuban sugar cane policosanols in hypercholesterolemic persons by Kassis et al 2006	Randomized, double blind, placebo controlled, cross-over study	40 to 80 years old male and postmenopausal female with LDL cholesterol of 3.0 to 5.0 mmol/L (138.2 to 230.4 mg/dL), BMI of 23 to 30, and triacylglycerol of < 4.9 mmol/L	10mg policosanol OD vs. placebo	LDL, total cholesterol, HDL, and triacylglycerol	A
Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial by Berthold et al 2006	Randomized, double blind, placebo controlled study	18 to 80 years old male and female with LDL cholesterol of at least 3.88 mmol/L (>150 mg/dL)	10mg, 20mg, 40mg, 80mg policosanol OD vs. placebo	LDL, total cholesterol, VLDL, lipoprotein a, triacylglycerol	A

outlined in Table 2. Out of the sixteen trials, four compared policosanol with a statin or combined it with another medication namely the study done by Cubeddu et al, Castano et al 2005, Castano et al 2003, and Prat et al. Another four trials included subjects who were persistently hypercholesterolemic despite lipid lowering diet namely Francini-Pesenti et al January 2008, Francini-Pesenti et al March 2008, Mirkin et al, and Castano et al 2000. This subject characteristic may have had an effect on the end point results leading to their exclusion in the study. One study compared the effects of 20mg policosanol versus the 40 mg policosanol namely the study done by Castano et al 2001. The study done by Lin et al used wheat germ policosanol instead of sugar cane policosanol. The study done by Greyling et al included subjects with high total cholesterol and no high LDL levels. The study done by Fernandez et al assessed the adverse events of policosanol among its patients and not its lipid lowering effect. And, the study published by Kassis et al in 2009, which measured LDL oxidation, was just a continuation of the study they previously published in 2006.

Effects of Intervention

The best data to use in this study is the mean percentage change in the levels of total cholesterol and LDL. But because one study used median, the next best data was used, which is the mean end point levels of total cholesterol and LDL. A total of 154 participants were given sugar cane policosanol and 157 participants were given placebo. There was a a statistically significant difference in the mean end point levels of total cholesterol when given either sugar cane policosanol or placebo favoring the latter(0.19 (0.08, 0.30)) (figure 1). No statistically significant difference was however observed in the mean end levels of LDL when given either sugar cane policosanol or placebo (0.09 (-0.01, 0.19)) (figure 2). The subgroup analysis on 10mg sugar cane policosanol showed a total of 99 participants, 49 for the sugar cane policosanol group and 50 for the placebo group. The results showed that there was no statistically significant difference in both mean end point levels of total cholesterol (0.18 (0.05, 0.30)) (figure 3), and LDL (0.09 (-0.02, 0.20)) (figure 4) when given 10mg sugar cane policosanol or placebo. The subgroup analysis on 20 mg sugar cane policosanol showed a total of 95 participants, 46 for the sugar cane policosanol group and 49 for the placebo group. This showed a significant difference in the mean end point levels of total cholesterol (0.39 (0.06, 0.72)) favoring placebo (figure 5), and while non in the LDL (0.12 (-0.13, 0.037)) (figure 6).

Discussion

A number of clinical trials had been made in order to show the effectiveness of sugar cane policosanol as a treatment for hypercholesterolemia. However, the studies are not homogenous and therefore excluded from the review. The main difference of the studies was the intervention used in the trial. The majority of trials found in the electronic search compared sugar cane policosanol to a statin, or combined sugar cane policosanol with another drug, which immediately excluded them for the review. The other reason for the low inclusion rate for the review was the type of participant included per study. Some of the trials included subjects that were diet resistant. This could have altered the results because these subjects would immediately need a medical intervention to lower their lipid levels. Because of this, only three studies were included out of sixteen studies found in the electronic research. After plotting the data into Review Manager 5, fixed effect analysis showed a zero to low percentage of heterogeneity among the studies for

Table II. Characteristics of Excluded Studies

Study	Method	Participants	Interventions	Outcome
Sugar cane policosanols do not reduce LDL oxidation in hypercholesterolemic individuals by Kassis et al 2009	Randomized, double blind, placebo controlled, crossover study	Healthy mild hyperchoelsterolemic men and postmenopausal women (no cut-off LDL levels was indicated)	10mg policosanol OD vs. placebo	LDL, total cholesterol, HDL, triglyceride (no value indicated)
Sugar cane policosanol failed to lower plasma cholesterol in primitive, diet resistant hypercholesterolemia: a double blind, controlled study by Francini-Pesenti et al 2008	Randomized, double blind, placebo controlled study	20 to 60 years old male and female with primitive hypercholesterolemia who obtained an LDL-C reduction of lower and -.3 mmol/L after nomocaloric diet treatment, BMI of 18 to 27, and LDL cholesterol of 4 to 5.2 mmol/L	10mg policosanol OD vs. placebo	LDL, total cholesterol, HDL, triglyceride
Effect of sugar cane policosanol on lipid profile in primary hypercholesterolemia by Francini-Pesenti et al 2008	Randomized, double blind, placebo controlled study	20 to 65 years old male and female with LDL higher than 160mg/dL after 3 months on normocaloric diet, BMI of 18 to 27, and LDL cholesterol of 160 to 250 mg/dL	20mg policosanol OD vs. placebo	LDL, total cholesterol, HDL, triglyceride
Comparative lipid-lowering effects of policosanol and atorvastatin: a randomized, parallel, double-blind, placebo-controlled trial by Cubeddu et al 2006	Randomized, parallel, double blind, double-dummy, placebo-controlled study	Male and female with LDL cholesterol of 140 to 189 mg/dL	20 mg policosanol, 10 mg atorvastatin, combination therapy, vs. placebo	LDL, total cholesterol, HDL, triglyceride
Effects of a policosanol supplement in hypercholesterolemic and heterozygous familial hypercholesterolaemic subjects by Greyling 2006	Randomized, double blind, placebo controlled crossover study	21 years old and older men and women with total cholesterol of above 5mmol/L	20mg policosanol OD vs. placebo	LDL, total cholesterol, HDL, triacylglycerol
Effects of addition of policosanol to omega-3 fatty acid therapy on the lipid profile of patients with type II hypercholesterolemia by Castano et al 2005	Randomized double-blind study	type II hypercholesterolemia	omega-3 FA + placebo, omega-3 FA + policosanol 5 mg/day or omega-3 FA + policosanol 10 mg/day	LDL, total cholesterol, HDL
A pharmacological surveillance study of the tolerability of policosanol in the elderly population by Fernandez et al 2004	Randomized controlled trial	Male and female 60 years old and above	5mg, 10mg, 20mg policosanol OD	Presence of adverse events
Wheat germ policosanol failed to lower plasma cholesterol in subjects with normal to mildly elevated cholesterol concentrations by Lin et al 2004	Randomized double-blind, parallel placebo-controlled	49 +/- 11 years old men and women	20 mg wheat germ policosanol OD	LDL, total cholesterol, HDL, triacylglycerol
Comparison of the efficacy and tolerability of policosanol with atorvastatin in elderly patients with type II hypercholesterolemia by Castano et al 2003	randomised, single-blind, parallel-group study	60-80 years old men and women with type II hypercholesterolemia	10mg policosanol OD vs. 10mg atorvastatin OD	LDL, total cholesterol, HDL
Effects of policosanol 20 versus 40 mg/day in the treatment of patients with type II hypercholesterolemia: a 6-month double-blind study by Castano 2001	randomized, double blind study	patients with type II hypercholesterolemia and dyslipidemia associated with noninsulin dependent diabetes mellitus	20mg policosanol OD vs. 40mg policosanol OD	LDL, HDL
Efficacy and tolerability of policosanol in hypercholesterolemic postmenopausal women by Mirkin et al 2001	Randomized, double-blind, multicenter placebo-controlled	Post menopausal women who had elevated serum total cholesterol and low density lipoprotein (LDL)-cholesterol levels despite a 6-week standard lipid-lowering diet	5mg to 10 mg policosanol vs. placebo	LDL, total cholesterol, HDL
Effects of policosanol on postmenopausal women with type II hypercholesterolemia by Castano et al 2000	Randomized, double-blind, placebo-controlled study	Post menopausal women who had elevated serum total cholesterol and low density lipoprotein (LDL)-cholesterol levels despite a 6-week standard lipid-lowering diet	5mg to 10 mg policosanol vs. placebo	LDL, total cholesterol, HDL
Comparative effects of policosanol and two HMG-CoA reductase inhibitors on type II hypercholesterolemia by Prat et al 1999	Randomized double blind study	Patients with a LDL cholesterol over 160 mg/dl	policosanol 10 mg/day, Lovastatin 20 mg/day, Simvastatin 10 mg/day	LDL, HDL

Figure I. mean end point levels of total cholesterol (mmol/L)

Study or Subgroup	policosanol Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berthold 10 mg 2006	7.59	1.71	28	7.17	1.06	29	2.3%	0.42 [-0.32, 1.16]
Berthold 20 mg 2006	7.46	1.06	27	7.17	1.06	29	4.1%	0.29 [-0.27, 0.85]
Berthold 40 mg 2006	7.07	1.01	27	7.17	1.06	29	4.3%	-0.10 [-0.64, 0.44]
Berthold 80 mg 2006	7.28	1.37	32	7.17	1.06	29	3.4%	0.11 [-0.50, 0.72]
Dulin 2006	6.12	0.52	19	5.68	0.76	20	7.6%	0.44 [0.03, 0.85]
Kassis 2006	5.77	0.21	21	5.6	0.21	21	78.3%	0.17 [0.04, 0.30]
Total (95% CI)			**154**			**157**	**100.0%**	**0.19 [0.08, 0.30]**

Heterogeneity: Chi² = 3.20, df = 5 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)

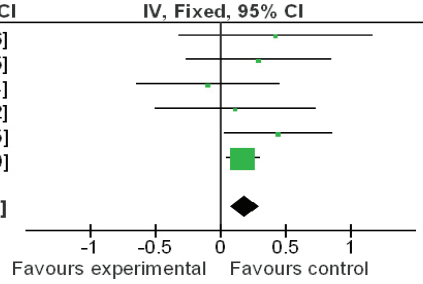


Figure II. mean end point level in LDL (mmol/L)

Study or Subgroup	policosanol Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berthold 10 mg 2006	5.26	1.63	28	4.71	1.08	29	1.8%	0.55 [-0.17, 1.27]
Berthold 20 mg 2006	4.77	0.91	27	4.71	1.08	29	3.3%	0.06 [-0.46, 0.58]
Berthold 40 mg 2006	4.77	0.83	27	4.71	1.08	29	3.6%	0.06 [-0.44, 0.56]
Berthold 80 mg 2006	4.66	1.11	32	4.71	1.08	29	3.0%	-0.05 [-0.60, 0.50]
Dulin 2006	3.73	0.4	19	3.59	0.5	20	11.3%	0.14 [-0.14, 0.42]
Kassis 2006	3.69	0.18	21	3.61	0.18	21	76.9%	0.08 [-0.03, 0.19]
Total (95% CI)			**154**			**157**	**100.0%**	**0.09 [-0.01, 0.19]**

Heterogeneity: Chi² = 1.99, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)

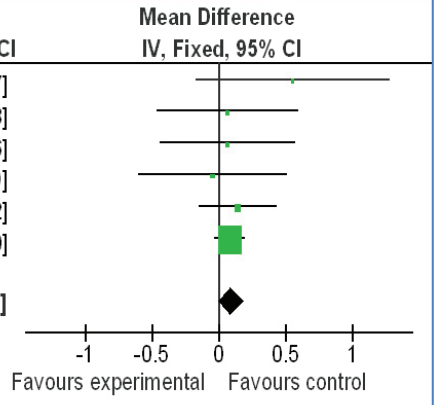


Figure III. mean end point level in total cholesterol (mmol/L), 10mg

Study or Subgroup	policosanol Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berthold 10 mg 2006	7.59	1.71	28	7.17	1.06	29	2.8%	0.42 [-0.32, 1.16]
Kassis 2006	5.77	0.21	21	5.6	0.21	21	97.2%	0.17 [0.04, 0.30]
Total (95% CI)			**49**			**50**	**100.0%**	**0.18 [0.05, 0.30]**

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.77 (P = 0.006)

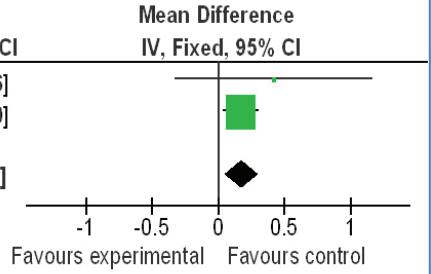


Figure IV. mean end point level in LDL (mmol/L), 10mg

Study or Subgroup	policosanol Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Berthold 10 mg 2006	5.26	1.63	28	4.71	1.08	29	2.2%	0.55 [-0.17, 1.27]
Kassis 2006	3.69	0.18	21	3.61	0.18	21	97.8%	0.08 [-0.03, 0.19]
Total (95% CI)			**49**			**50**	**100.0%**	**0.09 [-0.02, 0.20]**

Heterogeneity: Chi² = 1.60, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.65 (P = 0.10)

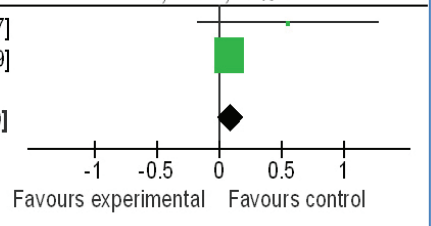


Figure V. mean end point level in total cholesterol (mmol/L), 20mg

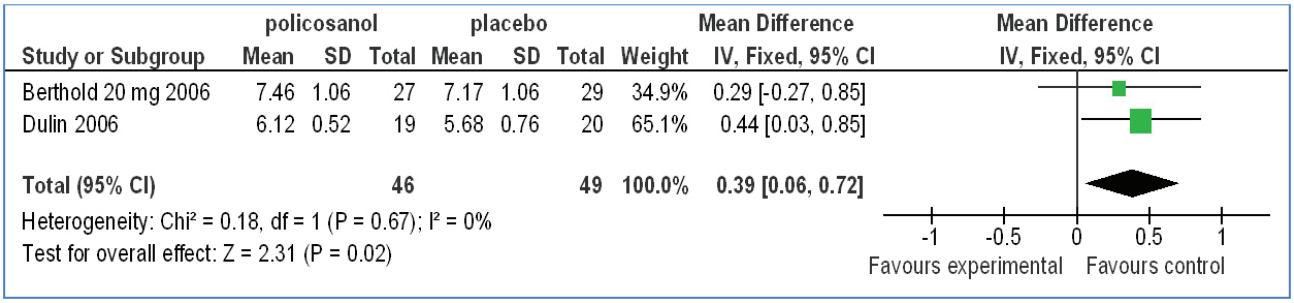
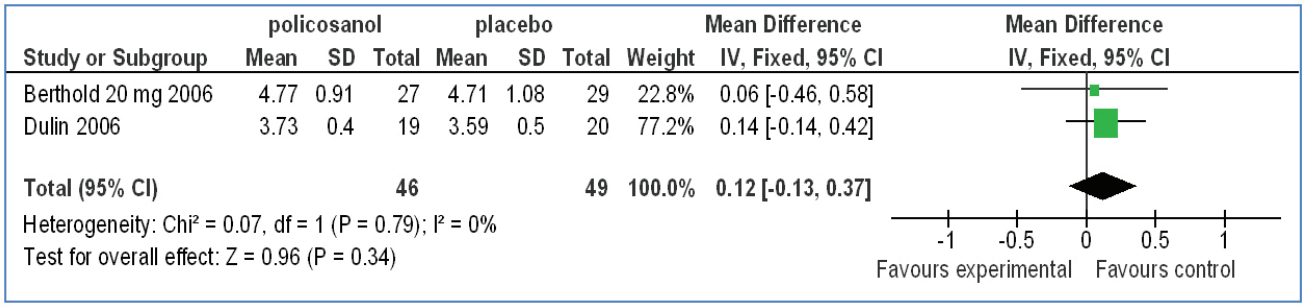


Figure VI. mean end point level in LDL (mmol/L), 20mg



both total cholesterol and LDL levels. Making the studies included almost homogenous to one another. In of the data used, the percent change in the level of total cholesterol and LDL is the best data to be used in this meta-analysis. But because one study used median, other raw data were used in the analysis. The next best raw data available was the mean end point levels of total cholesterol and LDL. Compared to percent change, using the mean endpoint level posseses a risk of a possible bias in the results. One group may have a higher mean baseline level compared to the other thereby affecting the result. But upon review of the studies included, the subjects were well randomized and both treatment and placebo group is homogenous. This solved the risk of a possible bias in the analysis. Another explanation is that if sugar cane policosanol really has an antilipidemic effect, it would have levels of total cholesterol and LDL lower compared to placebo no matter what the baseline levels are. And based from these studies, they are all in agreement that sugar cane policosanol did not show any significant difference in the mean endpoint levels of total cholesterol and LDL compared to placebo even at different doses. The sugar policosanol group even had a higher total cholesterol and LDL mean end point levels compared to placebo.

Conclusion

Sugar cane policosanol did not demonstrate any significant difference in the mean end point levels of total cholesterol and LDL among patients with hypercholesterolemia compared to placebo. There is no evidence on the effect of sugar cane policosanol in terms of lowering total cholesterol and LDL levels. Furthermore, our meta analysis showed no evidence to recommend sugar cane policosanol even as a food supplement with some results favoring non-intervention or placebo. Current trends in the field of medicine gear toward organic means of treatment. However, looking for a promising new organic medication and proving its therapeutic effect may still be a long way. Further research is recommended.

References

1. **NCEP, NHLBI, NIH:** Final Report of the Third Report of the National Cholesterol Program Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Publication, 02-5215,2002.
2. **Ford ES, Mokdad AH, Giles HW, et al:** Serum Total Cholesterol Concentrations and Awareness, Treatment, and Control of Hypercholesterolemia among US Adults: Findings from the National Health and Nutrition Examination Survey, 1999 to 2000. Cir. 107:2185-89,2003.
3. **Menendez R, Arruzazabala L, Mas R, et al:** Cholesterol-Lowering Effect of Policosanol on Rabbits with Hypercholesterolemia Induced by a Wheat Starch-Casein Diet. Br J Nutr. 77(6):923-32,1997.
4. **Janikula M. Policosanol:** A New Treatment for Cardiovascular Disease? Altern Med Rev. 7(3):203-217,2002.
5. **Fernandez L, Mas R, Illnait J, et al. Policosanol:** Results of a Post marketing Surveillance Study of 27,879 Patients. Current Therapeutic Research October. 59(10):717-722,1998.
6. **Menendez R, Amor AM, Rodeiro I, et al.** Policosanol Modulates HMG-CoA Reductase Activity in Cultured Fibroblasts. Arch Med Res. 32(1):8-12,2001.
7. **Sho H, Chinen I, Fukuda N.** Effects of Okinawan Sugar Cane Wax

and Fatty Alcohol on Serum and Liver Lipids in the Rat. Journal of Nutritional Science and Vitaminology (Tokyo). 30(6):553-9,1984.
8. **Arruzazabala ML, Carbajal D, Mas R, et al.** Cholesterol-Lowering Effects of Policosanol in Rabbits. Biological Research. 27(3-4):205-8,1994.
9. **Menendez R, Fernandez SI, Del Rio A, et al.** Policosanol Inhibits Cholesterol Biosynthesis and Enhances Low Density Lipoprotein Processing in Cultured Human Fibroblasts. Biological Research. 27(3-4):199-203,1994.
10. **Prat H, Roman O, Pino E.** Comparative Effect of Policosanol and Two HMG-CoA Reductase Inhibitors on Type II Hypercholesterolemia. Revista medica de Chile. 123(3):286-94,1999.
11. **Castano G, Mas R, Fernandez L, et al.** Effects of Policosanol on Postmenopausal Women with Type II Hypercholesterolemia. Gynecol Endocrinol. 14(3):187-95,2000.
12. **Greyling A, De Witt C, Oosthuizen W, et al.** Effects of a Policosanol Supplement on Serum Lipid Concentrations in Hypercholesterolaemic and Heterozygous Familial Hypercholesterolaemic subjects. Br J Nutr. 95:968-75,2006.
13. **Berthold HK, Unverdorben S, Degenhardt R, et al.** Effect of Policosanol on Lipid Levels among Patients with Hypercholesterolemia or Combined Hyperlipidemia: A Randomized Controlled Trial. JAMA. 295(19):2262-69,2006.
14. **Dulin MF, Hatcher LF, Sasser HC, et al.** Policosanol in Ineffective in the Treatment of Hypercholesterolemia: A Randomized Controlled Trial. Am J Clin Nutr. 84(6):154348,2006.
15. **Kassis AN, Jones PJ.** Lack of Cholesterol-Lowering Efficacy of Cuban Sugar Cane Policosanols in Hyperchoilesterolemic Persons. Am J Clin Nutr. 84(5):1003-8,2006.
16. **Mirkin A, Mas R, Marinto M, et al.** Efficacy and Tolerability of Policosanol in Hypercholesteroilemic Postmenopausal Women. Int J Clin Pharmacol Res. 21(1):31-41,2001.
17. **Castano G, Mas R, Fernandaez L, et al.** Effects of Policosanol 20 versus 40mg/day in the treatment of Patients with Type II Hypercholesterolemia: a 6-month double-blind study. Int Clin Pharmacol Res. 21(1):43-57,2001.
18. **Castano G, Mas R, Fernandez L, et al.** Comparison of the Efficacy and Tolerability of Policosanol with Atorvastatin in elderly patients with Type II Hypercholesterolemia. Drugs Aging. 20(2):153-63,2003.
19. **Lin Y, Rudrum M, van der Wielen RP, et al.** Wheat Germ Policosanol failed to lower Plasma Cholesterol in subjects with normal to mildly elevated Cholesterol Concentrations. Metabolism. 53(10):1309-14,2004.
20. **Fernandez S, Mas R, Gamez R, et al.** A Pharmacological Surveillance Study of the Tolerability of Policosanol in Elderly Population. Am J Geriatr Pharmacother. 2(4):219-29,2004.
21. **Castano G, Fernandez L, Mas R, et al.** Effects of Addition of Policosanol to Omega-3 Fatty Acid Therapy on the Lipid Profile of Patients with Type II Hypercholesterolemia. Drugs R D. 6(4):207-19,2005.
22. **Cubeddu LX, Cubeddu RJ, Heimowitz T, et al.** Comparative Lipid Lowering Effects of Policosanol and Atorvastatin: a Randomized, Parallel, Double-Blind, Placebo-Controlled Trial. Am Heart J. 152(5):982.e1-5,2006.
23. **Francini-Pesenti F, Beltramolli D. Dall'acqua S, et al.** Effect of Sugar Cane Policosanol on Lipid Profile in Primary Hypercholesterolemia. Phytother Res. 22(3):318-22,2008.
24. **Francini-Pesenti F, Brocadello F, Beltramolli D, et al.** Sugar Cane Policosanol Failed to Lower Cholesterol in Primitive, Diet-Resistant Hypercholesterolemia: a Double Blind, controlled study. Complement Ther Med. 16(2):61-5,2008.
25. **Kassis AN, Kubow S, Jones PJ.** Sugar Cane Policosanol do not reduce LDL Oxidation in Hypercholesterolemic Individuals. Lipids. 22(5):391-6,2009.