Complementary Therapies in Medicine 45 (2019) 89–97

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

# Policosanol supplementation significantly improves blood pressure among adults: A systematic review and meta-analysis of randomized controlled trials

Moein Askarpour[a], Ehsan Ghaedi[a,b,*], Neda Roshanravan[c], Amir Hadi[d,e], Hamed Mohammadi[f], Michael E Symonds[g], Maryam Miraghajani[h,g,i,**]

[a] Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[b] Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
[c] Cardiovascular Research Center, Tabriz University of Medical Sciences Tabriz, Iran
[d] Halal Research Center of IRI, FDA, Tehran, Iran
[e] Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[f] Student Research Committee, Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
[g] The Early Life Research Unit, Academic Division of Child Health, Obstetrics and Gynaecology, and Nottingham Digestive Disease Centre and Biomedical Research Centre, The School of Medicine, University of Nottingham, Nottingham, NG7 2UH, UK
[h] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[i] The Early Life Research Unit, Division of Child Health, Obstetrics and Gynaecology, University ofNottingham, Nottingham, UK

ARTICLE INFO

*Keywords:*
Policosanol
Blood pressure
Hypertension
Meta-Analysis

ABSTRACT

*Background and Aims:* Policosanol contains a mixture of concentrated primary aliphatic alcohols extracted from sugar cane wax and is recognized as a cholesterol-lowering drug but previous studies reported that it could be helpful for reducing blood pressure as well. We aimed to systematically review all randomized control trials (RCTs) evaluating the efficacy of policosanol supplementation for lowering high blood pressure.

*Methods and Results:* The following databases were searched up to March 2019: PubMed, Scopus, ISI Web of Science and the Cochrane library. Eligible RCTs were included if they investigate the effects of policosanol supplementation on systolic (SBP) and diastolic (DBP) blood pressure. Pooled effect size was measured using random effect model (DerSimmonon method). A total of nineteen studies with twenty-four arms were considered. Pooled effect size showed that SBP (WMD: −3.423 mmHg, 95% CI: −5.315, −1.531; $p < 0.001$) and DBP (WMD: −1.468 mmHg 95% CI: −2.632, −0.304, p = 0.013). decrease significantly after policosanol supplementation with significant heterogeneity among included studies ($I^2$ = 78.5% and 78.9% for SBP and DBP respectively). All subgroups showed a significant effect of policosanol supplementation except patients with mixed dyslipidemia for SBP and DBP and overweight subjects for DBP.

*Conclusion:* Policosanol could lower SBP and DBP significantly; future long term studies are required to confirm these findings in the general population.

## 1. Introduction

High blood pressure is part of a clinical syndrome that results from multifaceted etiologies and can contribute to the development of complex cardiovascular disorders in hypertensive patients including coronary artery diseases, angina and myocardial infarction.[1] Lowering blood pressure in people with hypertension has been shown to be an effective means of reducing cardiovascular morbidity and mortality,[2] and is therefore of clinical interest.[3–5] Several food and plant bioactives, reported to be important for preventing cardiovascular risk factors, such as hypercholesterolemia, hypertension, etc. They act maybe through beneficial impacts on human vascular health and endothelial

* Corresponding author at: Department of Cellular and Molecular Nutrition, School of Nutrition Sciences and Dietetics, Tehran University of Medical Sciences, Poorsina Street, Enghelab Avenue, PO Box: 14155-6446, Tehran, Iran.
** Corresponding author at: Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The Early Life Research Unit, Academic Division of Child Health, Obstetrics and Gynaecology, and Nottingham Digestive Disease Centre and Biomedical Research Centre, The School of Medicine, University of Nottingham, Nottingham, NG7 2UH, UK.
*E-mail addresses:* ehsanghaedi073@yahoo.com (E. Ghaedi), maryam.sadatmiraghajani@nottingham.ac.uk (M. Miraghajani).

https://doi.org/10.1016/j.ctim.2019.05.023
Received 6 May 2019; Received in revised form 17 May 2019; Accepted 21 May 2019
Available online 23 May 2019

**Table 1**
Cochrane Risk of Bias of included studies.

| Study | Ref | Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other potential threats to validity |
|---|---|---|---|---|---|---|---|---|
| Castano et al. (Cuba, 2001) | (7) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 2001) | (9) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 2002) | (8) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 2003) | (3) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 2005) | (6) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 2006) | (4) | U | U | L | L | L | U | U |
| Castano et al. (Cuba, 1995) | (5) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 1995) | (10) | U | L | L | L | L | U | U |
| Castano et al. (Cuba, 1996) | (11) | U | L | L | L | L | U | U |
| Cho et al. (South Korea, 2018) | (18) | L | L | L | L | L | L | U |
| Crespo et al. (Cuba, 1997) | (15) | U | L | L | L | L | U | U |
| Kim et al. (South Korea, 2018) | (17) | L | L | L | L | L | L | U |
| Marcello et al. (Argentina, 2000) | (1) | U | L | L | L | L | L | U |
| Mas et al. (Cuba, 1999) | (14) | U | L | L | L | L | U | U |
| Mas et al. (Cuba, 2001) | (16) | U | L | L | L | L | U | U |
| Park et al. (South Korea, 2019) | (19) | L | L | L | L | L | L | U |
| Pons et al. (Cuba, 1994) | (12) | U | L | L | L | L | U | U |
| Wang et al. (China, 2017) | (2) | L | U | H | H | L | U | U |
| Zardoya et al. (Cuba, 1996) | (13) | U | L | L | L | L | U | U |

L, low risk of bias; H, high risk of bias; U, unknown risk of bias.

function.[6,7]

Herbal medicines have been one of the most popular alternative and complementary therapies, with a history of practice for thousands of years.[8,9] They are currently becoming more popular as individuals seek out natural and safe remedies from natural sources.[8,9] Policosanol has attracted much attention in this area.[10] Policosanol composed of a mixture of concentrated primary aliphatic primary alcohols purified firstly from sugar cane wax.[10] Policosanol inhibits glycation and oxidation which are associated with atrial stiffness resulting in hypertension.[11,12] Furthermore, policosanol could be helpful for reducing hypertension by promoting normal arterial endothelial cell function, whilst inhibiting platelet aggregation and thrombosis.[10]

Recent studies showed that policosanol supplementation improve peripheral SBP and DBP, and also mean arterial pressure (MAP). [13] However, several studies have investigated the effects of policosanol on high blood pressure, given the controversial results in this field,[11,12,14–28] the efficacy of policosanol needs establishing before it is recommended. The current meta-analyses were to systematically review the scientific data for randomized control trials (RCTs) evaluating the efficacy of policosanol supplements on systolic (SBP) and diastolic (DBP) blood pressure among adults.

## 2. Methods

### 2.1. Search strategy

This study was designed using guidelines known as Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[29] The following databases were systematically searched up to March 2019 with no limitation in time and language to identify relevant published literature: ISI web of Science, PubMed, Scopus and Cochrane library. In our search strategy, the medical subject headings (MeSH) and non-MeSH terms were used by the following keywords “policosanol” OR “Sugarcane policosanol” OR “Octacosanol” OR “Sugar Cane Policosanol” OR “Saccharum Policosanol” OR “Sorghum Policosanol” AND "Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "randomly" OR "placebo" OR "assignment" OR randomized controlled trial OR randomized clinical trial OR RCT OR blinded OR double blind OR double blinded OR "trial" OR 'controlled clinical trial' OR Pragmatic Clinical Trial OR 'crossover procedure' OR Cross-Over trial OR Double-Blind Method OR 'equivalence trial' OR 'double blind procedure'.

### 2.2. Study selection

The title and abstract of all articles obtained in the initial search were evaluated independently by two reviewers (M.A. and N.R.). We included all clinical trials that evaluated the effect of policosanol supplementation on blood pressure (systolic and diastolic) in the present meta-analysis. Original studies were included if they met the following criteria [1] performed a randomized-controlled trial (RCT) design [3]; presented sufficient information on blood pressure in both intervention and control groups; and [4] administered policosanol for at least 7 days [5] were in adults (aged more than 18 years old). Studies that supplemented other compounds in combination with policosanol in both intervention and placebo group also were included. The exclusion criteria were [1] using a mixture of policosanol with other substance only in intervention group [2]; uncontrolled trials [3]; duplicate studies with same population [4]; experimental studies like animal and *in vitro* studies; and [5] reviews, letters to editor, editorial articles, or case reports.

### 2.3. Data extraction

The following details were extracted from eligible studies: study information including first author’s name; publication year; research design and duration of intervention; information of enrolled

participants including number of participants; age; dose of policosanol supplement. Also, mean and standard deviation (SD) of systolic and diastolic blood pressure were extracted.

### 2.4. Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria.[30] The quality of each study was assessed by the following items: adequacy of sequence generation, allocation concealment, blinding, dropouts (imperfect outcome data), selective outcome reporting, and other potential causes of bias. Based on the Cochrane Handbook recommendation, a judgment of "yes" considered as low risk of bias, while "no" considered as high risk of bias and "unclear" as blurred or unidentified risk of bias (Table 1).

### 2.5. Statistical analysis

Mean change and SD for SBP and DBP were used to assess the pooled effect size of the interventions using a random effect model (DerSimonian-Laird method). We used the recommended formula ($SD_{change}$ = square root [($SD_{baseline}^2$ + $SD_{final}^2$) − (2 × r × $SD_{baseline}$ × $SD_{final}$)]) to calculate SD of the mean difference in studies that did not report this parameter.[31] The effect sizes are expressed as weighted mean difference (WMD) and 95% CI. The heterogeneity of the studies was assessed using Cochrane's Q and $I^2$ tests.[32] To find the potential sources of between-study heterogeneity, we carried out a pre-planned subgroup analysis based on study duration and participants' health status, dose and baseline BMI of participants. Heterogeneity between subgroups was evaluated using a fixed-effect model. The non-linear potential effects of policosanol dosage (mg/day) and treatment duration (weeks) were investigated using fractional polynominal modeling.[33] To assess whether the results could have been influenced by each study, an influence analysis [34] was performed that omitted each study in turn. We used Begg's rank correlation test, Egger's regression asymmetry test and visual inspection of funnel plots to evaluate publication bias. Statistical analysis was performed using STATA 11.2 software (StataCorp, College Station, Texas, USA).

## 3. Results

### 3.1. Study selection

Out of 837 provided articles in initial search, 135 duplicated studies excluded. After screening for title and abstract evaluation of unduplicated studies: 651 unrelated studies were discarded due to primary evaluation of inclusion criteria: Unrelated title (n = 569), animal study (n = 48), letter, short survey and note (n = 16), review and book section (n = 18). Consequently, 51 studies remained and after the full text was scrutinized a further 32 studies were excluded: 1) performed on adolescent and children (n = 3), 2) publication that evaluate the effect of L-carnitine supplementation with combination of other treatments ($n$ = 8), 3) studies without enough information included ($n$ = 21). Finally, 19 studies met all inclusion criteria. The PRISMA flow diagram of search process is depicted in Fig. 1.

### 3.2. Study characteristics

Characteristics of included studies are summarized in Table 2. In total, 2426 participants were recruited. The studies included were published between 1994 and 2019. The follow-up period ranged between 3 weeks and 54 weeks, and sample size ranged from 9 to 272 participants. All studies were parallel randomized clinical trials. They enrolled subjects with dyslipidemia,[18,27,28] Type II hypercholesterolemia,[14–17,19–22,25,26,35] hypertension,[19,22] diabetes,[23] coronary disease [36] and healthy subjects.[11–13] Most studies were carried out in Cuba,[14–23,25,26,35,36] with three in South Korea,[11–13] one in China,[28] one in Argentina.[27] One study enrolled only females [12] and the rest involved both genders. In addition studies performed in subjects with different baseline BMI, three studies used subjects under 25 kg/m$^2$,[11–13] ten studies over than 25 kg/m$^2$ [14,16–20,27,28,35,36] and six did not report BMI.[15,21–23,25,26]

### 3.3. Meta-analysis findings

The effect of policosanol supplementation on blood pressure is summarized in Fig. 1. Twenty-four arms from nineteen studies including a total of 2289 participants (1163 cases and 1126 controls) reported SBP as an outcome measure. Pooled effect size showed that SBP decreased significantly after policosanol supplementation (WMD: -3.423 mmHg, 95% CI: -5.315, -1.531; $p < 0.001$) with significant heterogeneity among included studies ($I^2$ = 78.5, $P_{heterogeneity} < 0.001$) (Fig. 1).

Overall, twenty-four arms from nineteen trials reported DBP as an outcome measure. Combining effect sizes revealed a significant decreasing effect of policosanol supplementation on DBP (WMD: -1.468 mmHg 95% CI: -2.632, -0.304, p = 0.013). In addition, a between-study heterogeneity was found ($I^2$ = 78.9%; $P_{heterogeneity} < 0.001$) (Fig. 2).

### 3.4. Subgroup analysis

Results of the subgroup analyses are outlined in Table 3. We stratified studies based on baseline BMI of participants, policosanol dosage, trial duration, and type of study population (healthy, mixed dyslipidemia and familial hypercholesterolemia). Subgroups analyses revealed that baseline BMI of participants, policosanol dosage (mg/day), trial duration (week), and type of study population could be potential sources of heterogeneity. Moreover, this showed that policosanol supplementation significantly decreased SBP in both categories of BMI but decreased DBP only in subjects with BMI < 25 kg/m$^2$ (−5.659 mmHg (−6.972, −4.346), $p$ = 0.000 $I^2$ = 89.6%). Furthermore, both doses of policosanol (< 10 mg and ≥ 10 mg per day) decreased SBP significantly but DBP only decreased significantly ≥ 10 mg per day of policosanol (−2.86 mmHg (−3.693, −2.028); p = 0.000). Higher doses of policosanol showed a greater effect on SBP (i.e. −2.906 mmHg compared with −5.88 mmHg for low and high doses, respectively). SBP and DBP decreased following policosanol supplementation in all subgroups, but in healthy subjects and patients with familial hypercholesterolemia with mixed dyslipidemia blood pressure was unaffected.

### 3.5. Sensitivity analysis and publication Bias

Based on findings from sensitivity analysis, pooled effect sizes, obtained for the effect of policosanol supplementation on SBP and DBP did not depend on a specific particular study or group of studies. In fact, although elimination of Pons et al (1994) study changed overall estimate of effect size to −4.07 mmHg (−5.77, −2.37) but remained statistically significant. There was no evidence of publication bias based on visual inspection of funnel plots and also according to results of Begg's test ($P$ = 0.487 and 0.921 for SBP and DBP respectively).

### 3.6. Non-linear dose-responses between dose and duration of policosanol supplementation and outcomes

Following dose-response evaluation, policosanol supplementation did not change SBP or DBP significantly based on treatment duration (*P-nonlinearity* = 0.48 and 0.949 respectively) and dose (*P-nonlinearity* = 0.267 and 0.102 respectively) (Fig. 3).

### 3.7. Meta-regression analysis

Meta-regression using the random-effects model was undertaken to

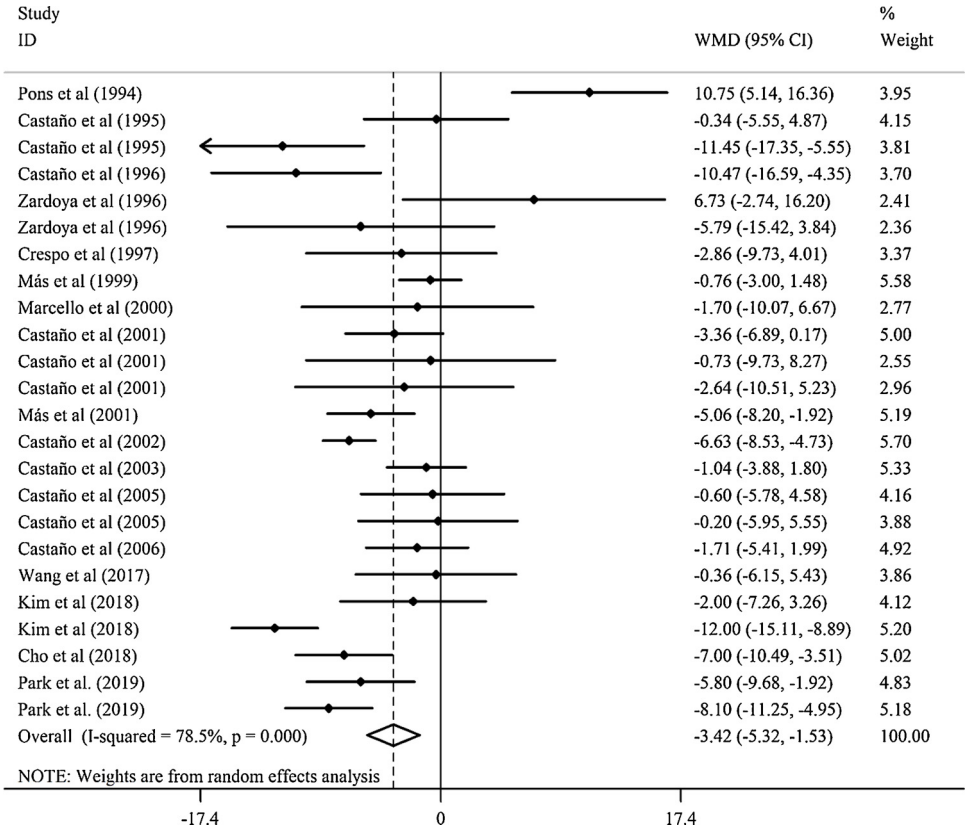


**Fig. 1.** Forest plot of randomized controlled trials investigating the effects of policosanol supplementation on systolic blood pressure.

investigate the potential association between a decrease in bllod pressure and dose of policosanol (mg/day). Meta-regression analysis indicated a linear relationship between dose absolute changes in SBP ($p = 0.049$; beta: $-0.379$) but not DBP ($p = 0.076$; beta: $-0.213$) (Fig. 4).

## 4. Discussion

High blood pressure is one of the most preventable causes of morbidity and mortality worldwide. Consequently, numerous therapeutic strategies have been developed with the objective of preventing hypertension, and the onset of cardiovascular disease, cognitive decline and death including the use of dietary supplement.[37] Policosanol, as a functional food, [38] was reported to have beneficial health effects against in animal models of hypertension and humans.[11,37] Therefore, the purpose of this review is to determine if policosanol supplementation has a beneficial effect on high blood pressure compared with placebo, or other interventions in adults. At present, this is the only meta-analysis in this context. We included 19 RCTs with a total of 2289 participants and a follow-up range 3–54 weeks. This meta-analysis indicated that supplementation with the policosanol significantly decreased both SBP ($-3.423$ mmHg) and DBP (-1.468 mmHg). In addition, meta-regression analysis showed significant effect of increasing dose on lowering effect of policosanol on SBP; future dose escalating trials needed in this context.

As a consequence of significant heterogeneity, we considered the different characteristics for trials and participants as the most likely cause. Subsequent analyses separating trials by subjects' health status and study duration reached a statistical decrease in SBP and DBP for all RCTs with healthy subjects and patients with familial hypercholesterolemia, and with all durations. When we considered BMI $< 25\ kg/m^2$ / BMI $> 25\ kg/m^2$ separately, we identified policosanol significantly decreased SBP in both categories of BMI but decrease DBP only in subjects with BMI $< 25\ kg/m^2$. Similar results were also obtained about doses of policosanol. Both doses of policosanol significantly decreased SBP but DBP could significantly decrease only following more than 10 mg per day policosanol supplementation. There were mixed findings regarding the dose used and BMI. Although the reason for this discrepancy is unclear, variation by hypertension subtype such as isolated systolic hypertension and isolated diastolic hypertension,[39] or resistant hypertension, that is poorly responsive to treatment,[40] and blood pressure variability [39] could modify the treatment response. This discrepancy may also result from other factors such as observer bias, white-coat phenomenon, placebo effects,[41] and age.[37] It is evident that DBP is more commonly elevated among people younger than 50 years. With age, systolic hypertension becomes a more significant problem as a result of progressive stiffening and loss of compliance of larger arteries.[37] Overall our results were in line with a previous review that assessed the beneficial effects of other aliphatic alcohols from sugar cane wax, that reported a protective effect on cardiovascular risk factors.[24] Aliphatic alcohols obtained from beeswax is also effective in reducing the risk of coronary heart disease, and the atherosclerotic process.[42]

Previous studies showed beneficial effects of policosanol on lipid profile [17,18,43]; although others showed that it could not affect lipid profile significantly.[44,45] Therefore, international lipid expert panel emphasized that policosanol must not be administered as a lipid lowering agent in clinical practice until new large-scale trials confirmed its lipid-lowering potential effects.[46] However, it must be noted that recent meta-analysis with 22 RCTs investigated possible lipid lowering effect of policosanol. Results showed that policosanol significantly improve lipid profile except triglyceride.[43] Here we showed that beyond its significant lipid lowering effect it can improve blood pressure as well; but future long-term large scale trials needed to confirm present results.

The exact mechanism of policosanol on the lowering of blood pressure has not been clearly identified. However, the action of

**Table 2**
Characteristics of included studies.

| Author (location, year) | Study design | Population | Sex | Number (Case/ control) | Intervention Mean age (years) | Intervention Mean BMI (Kg/m2) | Duration (Weeks) | Intervention (Intervention group) (Comparison group) |
|---|---|---|---|---|---|---|---|---|
| Castano et al. (Cuba, 2001) | Pararell (double blind) | type II hypercholesterolemia | M/F | 85/81 | 67 | 27.7 | 12 | Policosanol (5 mg/day)Placebo |
| Castano et al. a (Cuba, 2001) | Pararell (double blind) | type II hypercholesterolemia | M/F | 18/19 | 63 | 26.4 | 8 | Policosanol (20 mg/day) Placebo |
| Castano et al. b (Cuba, 2001) | Pararell (double blind) | type II hypercholesterolemia | M/F | 20/19 | 61 | 27.8 | 8 | Policosanol (20 mg/day) Placebo |
| Castano et al. (Cuba, 2002) | Pararell (double blind) | Hypertension and type II hypercholesterolemia | M/F | 272/251 | 66 | 27.5 | 12 | Policosanol (5-10 mg/day) Placebo |
| Castano et al. (Cuba, 2003) | Pararell (double blind) | hypercholesterolemia | M/F | 49/48 | 52 | 25.9 | 8 | Policosanol (5 mg/day) Placebo |
| Castano et al. a (Cuba, 2005) | Pararell (double blind) | type II hypercholesterolemia | M/F | 30/28 | 65 | 25.4 | 8 | Policosanol (5 mg/day) + Omega-3 FA (2g/ day) Omega-3 FA (2g/day) + Placebo |
| Castano et al. b (Cuba, 2005) | Pararell (double blind) | type II hypercholesterolemia | M/F | 28/28 | 65 | 25 | 8 | Policosanol (10 mg/day) + Omega-3 FA (2g/ day) Omega-3 FA (2g/day) + Placebo |
| Castano et al. (Cuba, 2006) | Pararell (double blind) | Dyslipidemia | M/F | 25/26 | 58 | 26.1 | 3 | Policosanol (10 mg/day) + Omega-3 FA (1g/ day) Omega-3 FA (1g/day) + Placebo |
| Castano et al. (Cuba, 1995) | Pararell (double blind) | type II hypercholesterolemia | M/F | 31/33 | 52 | Nr | 54 | Policosanol (10 mg/day) Placebo |
| Castano et al. (Cuba, 1995) | Pararell (double blind) | type II hypercholesterolemia | M/F | 28/31 | 64 | Nr | 54 | Policosanol (10 mg/day) Placebo |
| Castano et al. (Cuba, 1996) | Pararell (double blind) | Hypertensive type II hypercholesterolemia | M/F | 28/28 | 56 | Nr | 54 | Policosanol (10 mg/day) Placebo |
| Cho et al. (South Korea, 2018) | Pararell (double blind) | Healthy Women | F | 31/21 | 31 | 21 | 8 | Policosanol (10 mg/day) Placebo |
| Crespo et al. (Cuba, 1997) | Pararell (double blind) | Diabetic patients | M/F | 10/9 | 58 | Nr | 12 | Policosanol (10 mg/day) Placebo |
| Kim et al. a (South Korea, 2018) | Pararell (double blind) | Healthy participants | M/F | 18/18 | 34 | 23.2 | 24 | Policosanol (10 mg/day) Placebo |
| Kim et al. b (South Korea, 2018) | Pararell (double blind) | healthy participants | M/F | 25/18 | 31 | 23.7 | 24 | Policosanol (20 mg/day) Placebo |
| Marcello et al. (Argentina, 2000) | Pararell (double blind) | combined dyslipidemia | M/F | 14/14 | 55 | 27.7 | 8 | Policosanol (10 mg/day) + Bezafibrafe (400mg/day) Bezafibrafe (400mg/day) |
| Mas et al. (Cuba, 1999) | Pararell (double blind) | type II hypercholesterolemia | M/F | 203/199 | 57 | 28.4 | 12 | Policosanol (5mg/day) Placebo |
| Mas et al. (Cuba, 2001) | Pararell (double blind) | Coronary Disease | M/F | 118/135 | 66 | 26.9 | 54 | Policosanol (5 mg/day) Placebo |
| Park et al. a (South Korea, 2019) | Pararell (double blind) | Healthy participants | M/F | 24/23 | 32.4 | 23 | 12 | Policosanol (10 mg/day) Placebo |
| Park et al. b (South Korea, 2019) | Pararell (double blind) | Healthy participants | M/F | 29/23 | 27.9 | 23.5 | 12 | Policosanol (20 mg/day) Placebo |
| Pons et al. (Cuba, 1994) | Pararell (double blind) | type II hypercholesterolemia | M/F | 25/25 | 61 | Nr | 54 | Policosanol (5mg/day) Placebo |
| Wang et al. (China, 2017) | Pararell (open-label trial) | Dyslipidemia | M/F | 32/31 | 68.7 | 25.4 | 24 | Policosanol (20 mg/day) + Fenofibrate (200 mg/day) Fenofibrate (200 mg/day) |
| Zardoya et al. a (Cuba, 1996) | Pararell (double blind) | type II hypercholesterolemia | M/F | 11/9 | 55 | Nr | 12 | Policosanol (5 mg/day) Placebo |
| Zardoya et al. b (Cuba, 1996) | Pararell (double blind) | type II hypercholesterolemia | M/F | 9/9 | 57 | Nr | 12 | Policosanol (10 mg/day) Placebo |

M, male; F, female; Nr, not reported.

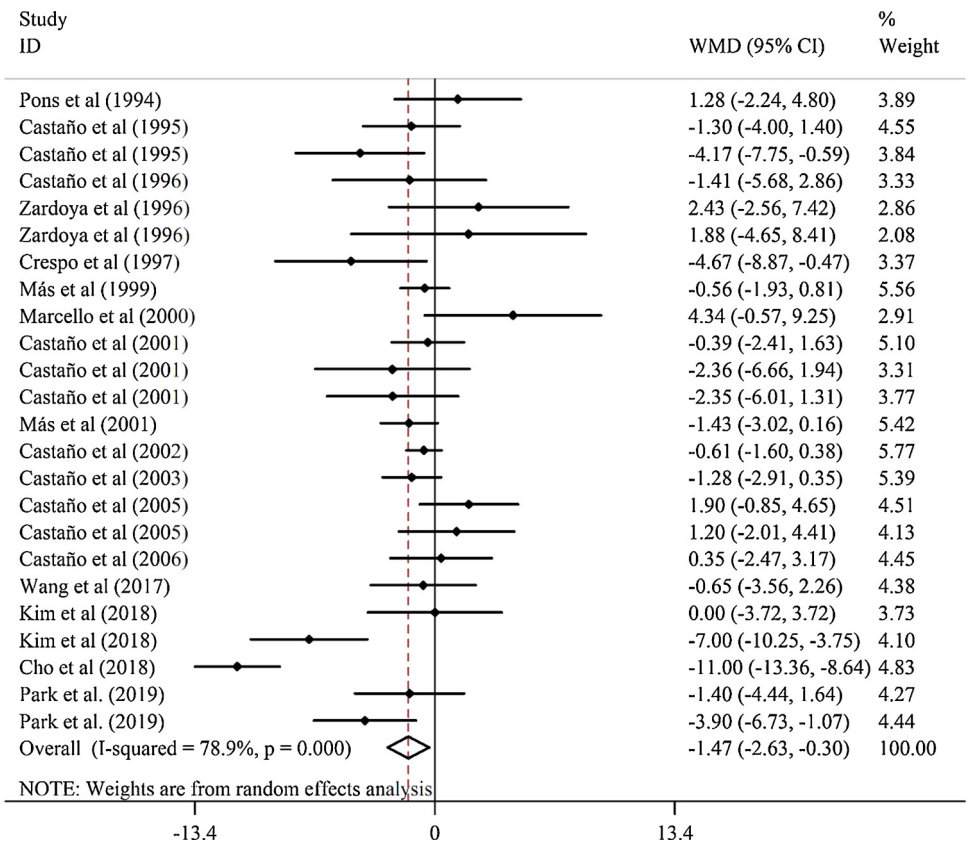


**Fig. 2.** Forest plot of randomized controlled trials investigating the effects of policosanol supplementation on diastolic blood pressure.

**Table 3**
Subgroup analysis to assess the effect of policosanol on systolic and diastolic blood pressure.

| Subgrouped by | No. of trials | WMD(95% CI) | P Value | P for heterogeneity | $I^2$ (%) | P for between subgroup heterogeneity |
|---|---|---|---|---|---|---|
| **SBP** | | | | | | |
| **Total** | **24** | **−3.423 (−5.315, −1.531)** | **0.000** | **0.000** | **78.5** | |
| **Baseline BMI** | | | | | | 0.000 |
| < 25 kg/m$^2$ | 5 | −7.948 (−9.551, −6.344) | 0.000 | 0.012 | 69 | |
| ≥25 kg/m$^2$ | 14 | −3.07 (−4.06, −2.08) | 0.000 | 0.006 | 55.3 | |
| **Dosage** | | | | | | 0.000 |
| < 10 mg | 8 | −2.906 (−3.98, −1.82) | 0.000 | 0.000 | 85.8 | |
| ≥10 mg | 16 | −5.880 (−7.085, −4.676) | 0.000 | 0.000 | 66.6 | |
| **Intervention Duration (Weeks)** | | | | | | 0.000 |
| ≤12 | 15 | −2.961(−4.028, −1.895) | 0.000 | 0.008 | 52.9 | |
| > 12 | 9 | −5.88 (−7.106, −4.66) | 0.000 | 0.000 | 87.7 | |
| **Type of Study Population** | | | | | | 0.000 |
| Healthy | 5 | −7.948 (−9.551, −6.344) | 0.000 | 0.012 | 69 | |
| Familial hypocholesteremia | 16 | −3.07 (−4.02, −2.11) | 0.000 | 0.000 | 77.2 | |
| Mixed dyslipidemia | 3 | −1.465 (−5.380, 2.449) | 0.463 | 0.86 | 0 | |
| **DBP** | | | | | | |
| **Total** | **24** | **−1.468 (−2.632, −0.304)** | **0.013** | **0.000** | **78.9** | |
| **Baseline BMI** | | | | | | 0.000 |
| < 25 kg/m$^2$ | 5 | −5.659 (−6.972, −4.346) | 0.000 | 0.000 | 89.6 | |
| ≥25 kg/m$^2$ | 14 | −0.522 (−1.074, 0.03) | 0.064 | 0.381 | 6.5 | |
| **Dosage** | | | | | | 0.000 |
| < 10 mg | 8 | −0.571 (−1.16, 0.023) | 0.060 | 0.383 | 6.1 | |
| ≥10 mg | 16 | −2.86 (−3.693, −2.028) | 0.000 | 0.000 | 81.8 | |
| **Intervention Duration (Weeks)** | | | | | | 0.715 |
| ≤12 | 15 | −1.503 (−2.174, −0.831) | 0.000 | 0.000 | 84.4 | |
| > 12 | 9 | −1.172 (−1.87, −0.475) | 0.001 | 0.016 | 57.4 | |
| **Type of Study Population** | | | | | | 0.000 |
| Healthy | 5 | −5.659 (−6.972, −4.346) | 0.000 | 0.000 | 89.6 | |
| Familial hypocholesteremia | 16 | −0.661 (−1.19, −0.124) | 0.016 | 0.426 | 2.3 | |
| Mixed dyslipidemia | 3 | −0.746 (−2.89, 1.406) | 0.497 | 0.024 | 73.2 | |

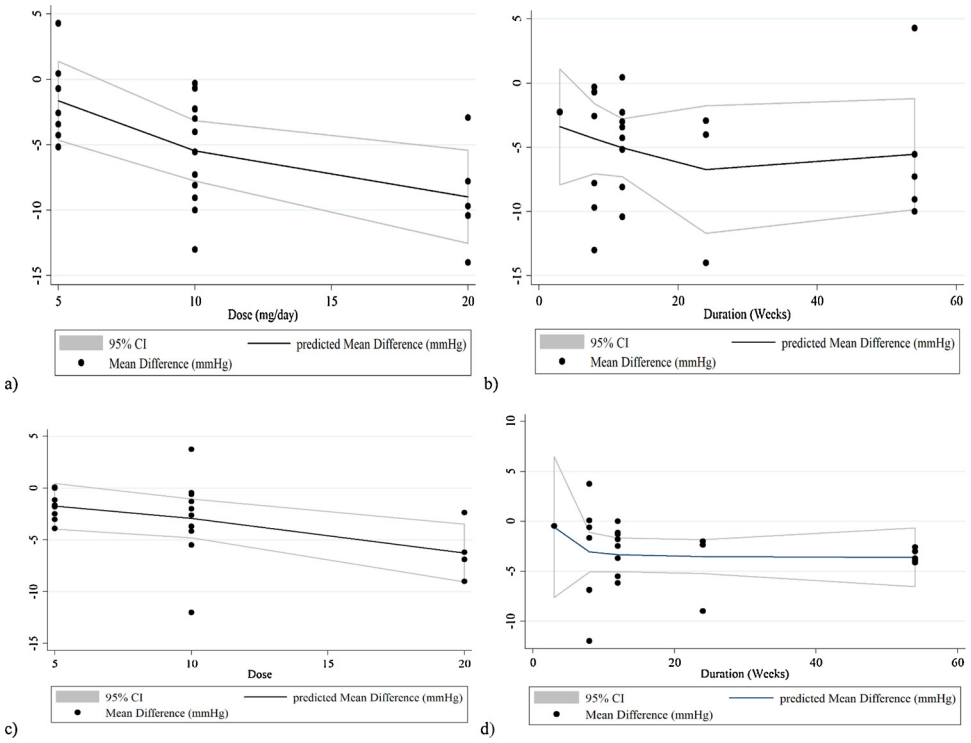


**Fig. 3.** Non-linear dose-response relations between policosanol supplementation and absolute (unstandardized) mean differences. Dose-response relations between policosanol supplementation and absolute mean differences in SBP (mmHg- 19 trials), and DBP (mmHg- 19 trials) based on dose of policosanol (mg/day) and trial duration (week) were depicted. Policosanol supplementation did not change SBP (P-nonlinearity = 0.26), and DBP (P-nonlinearity = 0.102) based on policosanol dose in nonlinear fashion. Policosanol supplementation did not change SBP (P-nonlinearity = 0.48), and DBP (P-nonlinearity = 0.949) based on trial duration (week) in nonlinear fashion. The 95% CI is outlined between lines.

policosanol involves various pathways such as activation of AMP-activated protein kinase (AMPK), [12] that in vascular cells induces vasorelaxation to lower blood pressure.[47] Interestingly, policosanol could inhibit glycation and oxidation which are known to be associated with atrial stiffness resulting in hypertension.[11,12] Since an increased uric acid level is associated with hypertension through increased rennin and decreased nitric oxide, policosanol consumption could reduce serum uric acid and thus prevent hypertension.[48] Furthermore, policosanol could promote arterial endothelial cell function, inhibit platelet aggregation and thrombosis,[10] and lower aldosterone release.[37]

The present meta-analysis had several limitations, with the primary limitation is that heterogeneity still remained, despite sensitivity and subgroup analysis. The effects of confounding variables including, demography, lifestyle, clinical characteristics, and different hypertension subtypes on the efficacy of policosanol remain unclear. Furthermore, most of incudes studies performed by same researcher groups from a single research center. On the other hand, genetic differences could affect the efficacy of policosanol supplements which could not be evaluated.

Moreover, the narrow range of health status of participants and small sample sizes limited our findings. This research had some advantages including subgroup analysis and assessment of baseline BMI of participants, policosanol dosage, trial duration, and type of study population on the overall effect sizes. Moreover, we explored nonlinear dose-response relations and meta-regression analysis. In addition, we tried to minimize any biases in the review process by performing a comprehensive search of the literature and also by conducting and reporting the review by adhering to the PRISMA guidelines.

## 5. Safety

Some studies has approved the policosanol's safety and tolerability in hypercholesterolemic postmenopausal women [49] and in elderly patients at high vascular risk.[50] In addition, recent meta-analysis showed that policosanol was efficacious and well tolerated in dyslipidemia patients with no adverse effects on indicators of hepatic or renal function.[43] Although, mild adverse reactions by policosanol might include digestive symptoms (acidity, constipation, nausea, diarrhea, polyphagia, heartburn or abdominal distension), or in the nervous system (headache, dizziness, nervousness, asthenia, polydipsia, insomnia or somnolence), or cardiovascular system (tachycardia or uncontrolled hypertension), urinary system (nocturia), locomotion (muscle cramps or myalgia), or skin (erythema or dryness), most are transient.[43] It should be mentioned, there are still no available reports with long-term follow-up ensuring the safety of regular consumption of policosanol among patients with hypertension and overall it is considered safe, based on the absence of adverse effects.

## 6. Implications for practice

The current evidence, from randomized trials supports the use of policosanol supplements to adults for improving blood pressure. However, results cannot be generalized to those with other health presentations that were not included in this analysis.

## 7. Implications for research

As we mentioned previously, many factors, such as genetic risk factors,[51] variation by hypertension subtype,[39] age, genetic background,[52] physical activity [53] and type of pharmacological therapy, visceral fat accumulation,[11] sedentary lifestyle could modulate the observed effects. So, well-designed studies assessing policosanol supplements on blood pressure are needed to ascertain the full benefits.

## 8. Conclusion

The results of this meta-analysis showed that policosanol could lower SBP and DBP, with a daily dosage of 5–20 mg/day. Our findings showed that policosanol have a possible positive effects on BP levels. But therapeutic effects have not been proved yet; future long-term large scale studies around the world needed before any confirm conclusion could be drawn.

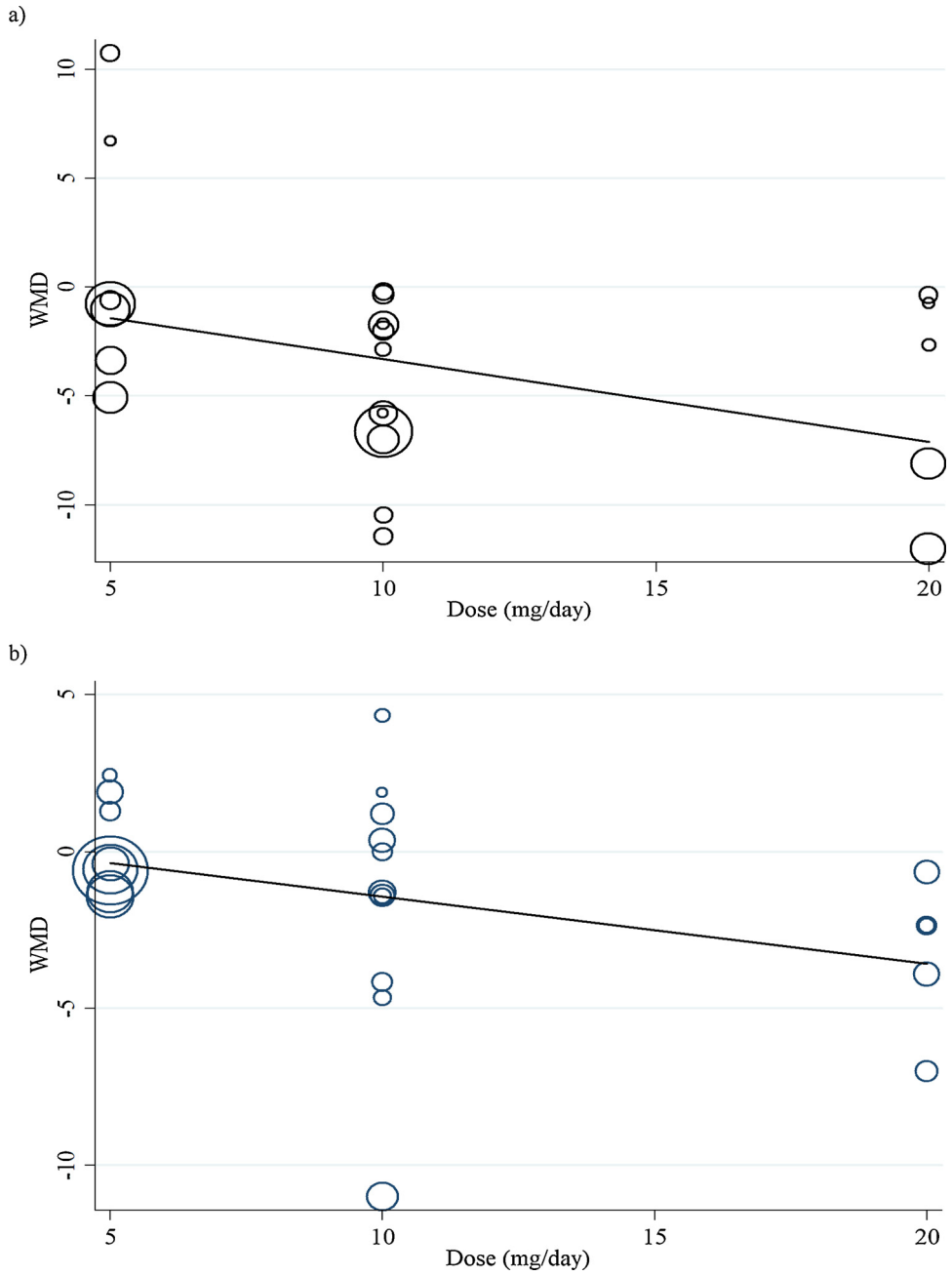


**Fig. 4.** Random-effects meta-regression plots of the association between dose of policosanol (mg/day) and weighted mean difference of (A) SBP (**B**) DBP, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.

## Conflicts of interest

All the authors declared that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.05.023.

## References

1. Lurbe IFE. [2016 - European Society of Hypertension Guidelines for the management of high blood pressure in children and adolescents]. *Anales de pediatria (Barcelona, Spain: 2003)*. 2016;85(4):167–169.
2. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 2017;389(10064):37–55.
3. Ames RP. Hyperlipidemia in hypertension: Causes and prevention. *Am Heart J*. 1991;122(4 Pt 2):1219–1224.
4. Bonaa KH, Thelle DS. Association between blood pressure and serum lipids in a population. The Tromso Study. *Circulation*. 1991;83(4):1305–1314.
5. Lee JS, Chang PY, Zhang Y, Kizer JR, Best LG, Howard BV. Triglyceride and HDL-C dyslipidemia and risks of coronary heart disease and ischemic stroke by glycemic dysregulation status: The strong heart study. *Diabetes Care*. 2017;40(4):529–537.
6. Cicero AF, Fogacci F, Colletti A. Food and plant bioactives for reducing cardiometabolic disease risk: An evidence based approach. *Food Funct*. 2017;8(6):2076–2088.
7. Chrysant SG, Chrysant GS. Herbs used for the treatment of hypertension and their mechanism of action. *Curr Hypertens Rep*. 2017;19(9):77.
8. Moura Mdel G, Lopes LC, Biavatti MW, et al. Brazilian oral herbal medication for osteoarthritis: A systematic review protocol. *Syst Rev*. 2016;5:86.
9. Maiti B, P NB, Singh R. *Recent trends in herbal drugs: A review. 2017*. 2017; 2017 1(1).
10. Marinangeli CP, Jones PJ, Kassis AN, Eskin MN. Policosanols as nutraceuticals: Fact or fiction. *Crit Rev Food Sci Nutr*. 2010;50(3):259–267.
11. Cho KH, Kim SJ, Yadav D, Kim JY, Kim JR. Consumption of cuban policosanol improves blood pressure and lipid profile via enhancement of HDL functionality in healthy women subjects: randomized, double-blinded, and placebo-controlled study. *Oxid Med Cell Longev*. 2018;2018:4809525.

12. Kim SJ, Yadav D, Park HJ, Kim JR, Cho KH. Long-term consumption of cuban policosanol lowers central and brachial blood pressure and improves lipid profile with enhancement of lipoprotein properties in healthy korean participants. *Front Physiol.* 2018;9:412.
13. Park HJ, Yadav D, Jeong DJ, et al. Short-term consumption of cuban policosanol lowers aortic and peripheral blood pressure and ameliorates serum lipid parameters in healthy korean participants: randomized, double-blinded, and placebo-controlled study. *Int J Environ Res Public Health.* 2019;16(5).
14. Castaño G, Arruzazabala ML, Fernández L, et al. Effects of combination treatment with policosanol and omega-3 fatty acids on platelet aggregation: a randomized, double-blind clinical study. *Curr Ther Res.* 2006;67(3):174–192.
15. Castaño G, Canetti M, Moreira M, et al. Efficacy and tolerability of policosanol in elderly patients with type II hypercholesterolemia: A 12-month study. *Curr Ther Res.* 1995;56(8):819–828.
16. 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 hypercholesterolaemia. *Drugs R D.* 2005;6(4):207–219.
17. Castano G, Mas R, Fernandez J, Illnait J, Fernández L, Alvarez E. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J Gerontol A Biol Sci Med Sci.* 2001;56(3) M186-M93.
18. Castano G, Más R, Fernández J, et al. Effects of policosanol on borderline to mildly elevated serum total cholesterol levels: A prospective, double-blind, placebo-controlled, parallel-group, comparative study. *Curr Ther Res.* 2003;64(8):522–537.
19. Castaño G, Más R, Fernández JC, Fernández L, Illnait J, López E. Effects of policosanol on older patients with hypertension and type II hypercholesterolaemia. *Drugs R D.* 2002;3(3):159–172.
20. Castaño G, Más R, Fernández L, Illnait J, Gámez R, Fernández JC. Comparison of two regimens of policosanol administered at 20 mg/d in patients with type II hypercholesterolemia: a randomized, double-blind, placebo-controlled study. *Curr Ther Res.* 2001;62(3):194–208.
21. Castaño G, Más R, Nodarse M, Illnait J, Fernández L, Fernández JC. One-year study of the efficacy and safety of policosanol (5 mg twice daily) in the treatment of type II hypercholesterolemia. *Curr Ther Res.* 1995;56(3):296–304.
22. Castaño G, Tula L, Canetti M, et al. Effects of policosanol in hypertensive patients with type II hypercholesterolemia. *Curr Ther Res.* 1996;57(9):691–699.
23. Crespo N, Alvarez R, Más R, Illnait J, Fernández L, Fernández JC. Effects of policosanol on patients with non—Insulin-dependent diabetes mellitus and hypercholesterolemia: A pilot study. *Curr Ther Res.* 1997;58(1):44–51.
24. Granja AL, Hernandez JM, Quintana DC, Valmana LA, Ferreiro RM, Mesa MG. Mixture of higher primary aliphatic alcohols, its obtention from sugar cane wax and its pharmaceutical uses. Google Patents; 1999.
25. Pons P, Rodríguez M, Más R, et al. One-year efficacy and safety of policosanol in patients with type II hypercholesterolemia. *Curr Ther Res.* 1994;55(9):1084–1092.
26. Zardoya R, Tula L, Castaño G, et al. Effects of policosanol on hypercholesterolemic patients with abnormal serum biochemical indicators of hepatic function. *Curr Ther Res.* 1996;57(7):568–577.
27. Marcello S, Gladstein J, Tesone P, Más R. Effects of bezafibrate plus policosanol or placebo in patients with combined dyslipidemia: A pilot study. *Curr Ther Res.* 2000;61(6):346–357.
28. H-y Wang, Q-p Jiao, S-y Chen, et al. Efficacy and safety of policosanol plus fenofibrate combination therapy in elderly patients with mixed dyslipidemia: a randomized, controlled clinical study. *Am J Med Sci.* 2018;356(3):254–261.
29. Picot J, Hartwell D, Harris P, Mendes D, Clegg A, Takeda A. *The preferred reporting items for systematic reviews and meta-analyses checklist.* 2012; 2012.
30. Higgins JP, Green S. *Cochrane handbook for systematic reviews of interventions.* John Wiley & Sons; 2011.
31. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Introduction to meta-analysis.* John Wiley & Sons; 2011.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ: Br Med J.* 2003;327(7414):557.
33. Mitchell MN. *Interpreting and visualizing regression models using Stata.* TX: Stata Press College Station; 2012.
34. Tobias A. Assessing the influence of a single study in the meta-anyalysis estimate. *Stata Technical Bulletin.* 1999;8(47).
35. Mas R, Castano G, Illnait J, et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther.* 1999;65(4):439–447.
36. Más R, Castaño G, Fernández L, Illnait J, Fernández J, Alvarez E. Effects of policosanol on lipid profile and cardiac events in older hypercholesterolaemic patients with coronary disease. *Clin Drug Investig.* 2001;21(7):485–497.
37. Saiz LC, Gorricho J, Garjon J, Celaya MC, Erviti J, Leache L. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. *Cochrane Database Syst Rev.* 2018;7:CD010315.
38. Menendez R, Fernandez S, Del AR, et al. Policosanol inhibits cholesterol biosynthesis and enhances low density lipoprotein processing in cultured human fibroblasts. *Biol Res.* 1994;27(3-4):199–203.
39. Johnson HM, Bartels CM, Thorpe CT, Schumacher JR, Pandhi N, Smith MA. Differential diagnosis and treatment rates between systolic and diastolic hypertension in young adults: A multidisciplinary observational study. *J Clin Hypertens (Greenwich).* 2015;17(11):885–894.
40. Yaxley JP, Thambar SV. Resistant hypertension: An approach to management in primary care. *J Family Med Prim Care.* 2015;4(2):193–199.
41. Hu J, Zhao L, Thompson B, Zhang Y, Wu Y. Effects of salt substitute on home blood pressure differs according to age and degree of blood pressure in hypertensive patients and their families. *Clin Exp Hypertens (New York, NY: 1993).* 2018;40(7):664–672.
42. Perez PP. High molecular weight primary aliphatic alcohols obtained from beeswax and pharmaceutical use thereof. Google Patents; 2001.
43. Gong J, Qin X, Yuan F, et al. Efficacy and safety of sugarcane policosanol on dyslipidemia: A meta-analysis of randomized controlled trials. *Mol Nutr Food Res.* 2018;62(1).
44. Berthold HK, Unverdorben S, Degenhardt R, Bulitta M, Gouni-Berthold I. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: A randomized controlled trial. *Jama.* 2006;295(19):2262–2269.
45. Backes JM, Gibson CA, Ruisinger JF, Moriarty PM. Modified-policosanol does not reduce plasma lipoproteins in hyperlipidemic patients when used alone or in combination with statin therapy. *Lipids.* 2011;46(10):923–929.
46. Cicero AFG, Colletti A, Bajraktari G, et al. Lipid lowering nutraceuticals in clinical practice: Position paper from an International Lipid Expert Panel. *Arch Med Sci.* 2017;13(5):965–1005.
47. Sun GQ, Li YB, Du B, Meng Y. Resveratrol via activation of AMPK lowers blood pressure in DOCA-salt hypertensive mice. *Cli Exp Hypertens (New York, NY:1993).* 2015;37(8):616–621.
48. Kim JY, Kim SM, Kim SJ, Lee EY, Kim JR, Cho KH. Consumption of policosanol enhances HDL functionality via CETP inhibition and reduces blood pressure and visceral fat in young and middle-aged subjects. *Int J Mol Med.* 2017;39(4):889–899.
49. Mirkin A, Mas R, Martinto M, et al. Efficacy and tolerability of policosanol in hypercholesterolemic postmenopausal women. *Int J Clin Pharmacol Res.* 2001;21(1):31–41.
50. Fernandez S, Mas R, Gamez R, et al. A pharmacological surveillance study of the tolerability of policosanol in the elderly population. *Am J Geriatr Pharmacother.* 2004;2(4):219–229.
51. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature.* 2011;478(7367):103.
52. Campo C, Segura J, Ruilope LM. Factors influencing the systolic blood pressure response to drug therapy. *J Clin Hypertens (Greenwich).* 2002;4(1):35–40.
53. Midha T, Lalchandani A, Nath B, Kumari R, Pandey U. Prevalence of isolated diastolic hypertension and associated risk factors among adults in Kanpur, India. *Indian Heart J.* 2012;64(4):374–379.