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The effects of policosanol supplementation on creatinine: a systematic review and dose–response meta-analysis of randomized controlled trials

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Abstract

Objective Policosanol, a compound generated from sugar cane, consists of alcohols such as octacosanol, hexacosanol, and triacontanol, which possess antioxidant properties. Evaluating the impact of this antioxidant on serum creatinine in clinical settings is essential because of the contradictory findings. This comprehensive review and dose–response meta-analysis attempts to evaluate the impact of policosanol supplementation on creatinine levels.

Methods A comprehensive search was performed in bibliographic databases such as Cochrane, PubMed, Google Scholar, Scopus, and Web of Science, covering the period from inception to November 2023. The necessary data was retrieved, and pertinent randomized controlled trials (RCTs) that satisfied the inclusion criteria were included. Weighted mean differences (WMDs) were the reported measure of the pooled effects. To find between-study heterogeneities, the I-squared test was employed.

Results A total of 2427 participants were involved in the twenty-one RCTs that were included. A meta-analysis showed that policosanol had no significant change in creatinine levels in participants consuming policosanol compared to placebo consumers (WMD = 0.21 µmol/l; 95% CI = −0.85 to 1.26; *P* = 0.70). Policosanol consumption for durations ≥ 24 weeks significantly decreased creatinine, according to subgroup studies. There was a non-linear correlation between changes in creatinine levels and the dosage of prescription policosanol ($P_{non\_linearity} = 0.002$). However, the treatment time did not have a significant impact on creatinine levels in a non-linear manner ($P_{non\_linearity} = 0.24$).

Conclusion Policosanol supplementation has no significant effect on creatinine levels.

Keywords Policosanol, Creatinine, Randomized controlled trials, Meta-analysis

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Introduction

Creatinine, a nitrogenous organic acid, is predominantly produced in the kidneys and liver, with some contribution from the pancreas [1]. It serves as the final product of the metabolism of creatine and creatine phosphate [2]. Serum creatinine serves as the predominant biomarker for assessing kidney function [3]. In situations of equilibrium, serum creatinine proves valuable in estimating glomerular filtration rate, employing formulae such as the modification of diet in renal disease [3] or the chronic kidney disease epidemiology collaboration (CKD-EPI) [4]. Moreover, the literature highlights the role of serum [5] and urinary creatinine [6] in estimating muscle mass during periods of stable kidney function, and also a measurement for predictive mortality among end-stage kidney disease patients [7].

Oxidative stress, defined as disturbances in the pro-/antioxidant balance, is harmful to cells because of the extra generation of highly reactive oxygen (ROS) and reactive nitrogen species (RNS) [8, 9]. Oxidative stress has been reported in kidney disease [10], cardiovascular disease [11], and metabolic syndrome [12] due to both antioxidant depletions as well as increased ROS production.

Policosanol, with anti-oxidant features, derived from sugar cane, comprises alcohols like octacosanol, hexacosanol, and triacontanol [13]. It is assumed that polycosanol can modify dyslipidemia profiles by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase [14] or by increasing receptor-mediated uptake of low-density lipoprotein cholesterol (LDL-C) in the liver [15]. It consistently lowers LDL-C and total cholesterol while increasing high-density lipoprotein cholesterol (HDL-C) levels in both clinical and animal studies [16–18]. Additionally, it may alleviate intermittent claudication by suppressing platelet aggregation and enhancing endothelial function [19]. Notably, policosanol exhibits a generally safe profile, with no serious side effects reported in most clinical studies [20, 21].

Most studies have investigated the effects of policosanol on the lipid profile [22–24] but its impact on serum creatinine remains unclear. Assessing the role of policosanol on serum creatinine in clinical settings is crucial due to its potential renal protective effects. This antioxidant decreases the oxidized LDL-C, which accumulates in kidney tissues and enhances oxidative stress in renal cells [25]. This reduction in oxidized LDL-C leads to reduced release of High-Mobility Group Box 1 (HMGB1), a protein that causes inflammatory effects and tissue damage [26, 27]. Policosanol may also inhibit PI3 K/mTOR/NLRP3 pathway, resulting in a declined rate of NLRP3 (NOD-Like Receptor family, Pyrin domain-containing-3) [28].

The literature is inconsistent regarding the effects of policosanol on serum creatinine. For instance, a 10-week supplementation study in patients with type two hypercholesterolemia showed no significant improvement in the policosanol treatment group compared to controls [29]. Conversely, another study in a similar patient sample reported a significant increase in serum creatinine for both the intervention and control groups [22]. Clarification of these discrepancies is necessary for informed judgment.

Therefore, for the first time, the present systematic review and dose–response meta-analysis aims to assess the effects of policosanol supplementation on creatinine.

Methods

Search strategy

At every stage of the present study, we adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Handbook for systematic reviews [30, 31] (Supplementary Table 1). This study was registered in PROSPERO (CRD42023486367) on December 5, 2023. Two independent reviewers (MRA and MS) carried out a systematic search in bibliographical databases including Cochran, PubMed, Google Scholar, Scopus, and Web of Science from inception to November 2023. We used the search framework known as Participant, Intervention, Comparison/Control, Outcome (PICOS) [32] denoting population (healthy/unhealthy adults), intervention (policosanol supplementation), comparison (placebo group), outcome (alteration in creatinine), and type of research (parallel and crossover). The following combination of medical subject headings (MESH) and non-MESH keywords was used to find the pertinent studies: (policosanol[tiab] OR Octacosanol[tiab]) AND (intervention[tiab] OR RCT[tiab] OR randomized[tiab] OR random[tiab] OR Randomly[tiab] OR Placebo[tiab] OR Assignment[tiab] OR trial[tiab] OR trials[tiab] OR randomised[tiab] OR Cross-Over[tiab] OR "Double-Blind"[tiab] OR OR "Placebos"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh]) (Supplementary Table 2). A manual search of the references list of trials and earlier related reviews helped us find further possibly eligible randomized controlled trials (RCTs) and complete our search. Reviewers discussed and resolved disagreements until consensus was achieved. Not each search section was subject to language limitations.

Study selection

When duplicated papers were removed, two independent authors (MRA and MS) selected studies for inclusion based on the title, abstract, and full text. Cohen's kappa

coefficient of 0.76 was calculated between two researchers' (MRA and MS) assessments. Disagreements were then discussed with the third reviewer (AH). Articles investigating how policosanol consumption affected creatinine levels and satisfying the following criteria were selected for this meta-analysis: adult population (≥ 18 years old), oral supplementation of policosanol, comparison between experimental and placebo groups, provided baseline and at the end of study creatinine levels for both study groups, reported means and standard deviations (SDs), or any other alternative effect sizes, for creatinine, and RCTs (parallel or crossover) design. If the trials had over one eligible arm, we regarded them as independent RCTs. We excluded case reports, reviews, animal studies, and abstracts, as well as observational studies as they are unable to prove cause-and-effect relationships.

Data extraction and quality assessment

Two investigators (MRA and MS) independently filled the standardized data extraction forms to glean the following data: first author's name, publication year, location of study, type of RCT, health status and body mass index (BMI) of participants, sex, age, number of participants, blinding, dosage and time of policosanol intake, and mean and SD of creatinine before and after supplementation for both policosanol and placebo groups. If policosanol doses were prescribed in grams or other units, they were converted to milligrams per day. For studies that lack the needed data, efforts were made to contact corresponding authors for supplementary details. The quality of included trials was assessed based on the Cochrane criteria [30]. Two reviewers (MRA and MS) separately evaluating the methods resolved the raised discrepancies through discussion. All included RCTs were checked for potential bias resulting from randomized sequence generation, allocation concealment, blinding, imperfect outcome data, selective reporting, and other possible biases. Therefore, the following three categories were created: (1) low risk of bias; all domains with "low risk", (2) moderate risk of bias; at least one domain with "unclear risk", and (3) high risk of bias; at least one domain with "high risk".

Statistical analysis

Using Stata 14.0, all statistical analyses were carried out (Stata Corp, College Station, TX, USA). All two-tailed tests were deemed statistically significant if the p-value was less than 0.05. In studies where the SD of the mean difference was unavailable, the following appropriate procedure [33] helped us calculate it: $SD_{difference}$ = Square Root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2 \times R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$. The correlation coefficient (R) was regarded as 0.8 in the aforementioned formula. The provided effect sizes are weighted mean difference (WMD) and 95% CI computed based on the random-effects model. The model was developed by Der Simonian and Laird,considering any heterogeneity that may exist [34]. In trials only reporting SEM (standard error of the mean), it was converted to SD using the following formula: $SD = SEM \times \sqrt{n}$ where n is the number of participants in each study group [35]. Data from studies with graphical results were extracted using the GetData Graph Digitizer version 2.24 [36]. I^2 statistic and Cochrane's Q test assisted us in detecting the heterogeneity [37]. The significant heterogeneity was defined as I^2 values > 50% or $P < 0.05$. The priori subgroup analysis and meta-regression were conducted to find the potential causes of heterogeneity. The former focused on dosage and duration of intervention, and the dose of policosanol was regarded as covariate in meta-regression. The nonlinear probable effects of policosanol dosage (mg/day) and supplementation duration (weeks) on creatinine levels were figured out using fractional polynomial modeling [38]. Publication bias was checked through visual inspection of the funnel plot and Egger's test [39]. To examine how RCTs can affect the overall results, we did a sensitivity analysis through removing one trial from each analysis.

Certainty assessment

To rate the evidence across the trials, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) assessment was carried out using the GRADEPro guideline development tool (GDT) sorting the quality of evidence into high, moderate, low, and very low groups [40].

Results

Flow of study selection

Figure 1 describes the selection process of eligible trials from databases. Systematic and manual searching resulted in 712 studies, 314 of which were duplicates excluded. Following the screening of 398 articles based on titles and abstracts, reviewing the full texts of 33 potentially relevant led to the exclusion of 13 studies because of medicine prescription for the control group ($n = 4$), being irrelevant ($n = 7$), and children's participation ($n = 1$). Eventually, 22 eligible studies were selected for inclusion in the current systematic review and meta-analysis, and their risk of bias evaluation is reported in Table 1.

Study characteristics

Out of 22 included RCTs, there was one crossover and 21 parallel articles. Studies were carried out between 1992 and 2023. Except for two studies conducted in

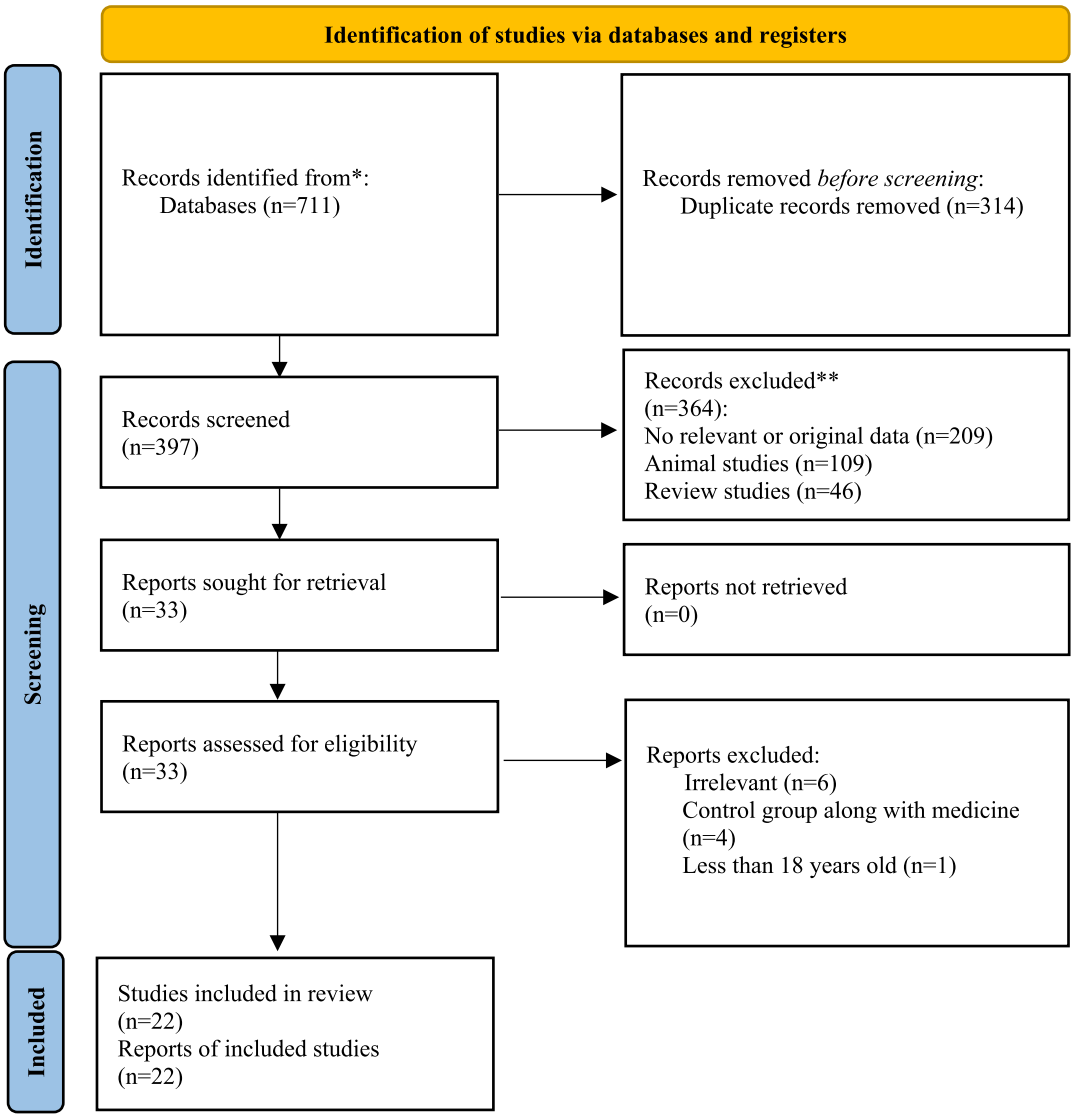

Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

Chicago [54], Japan [57] and China [55], other studies were from Cuba [22, 23, 29, 41–53, 56, 59, 60]. All studies included both males and females who were overweight and obese. In total, 2462 individuals participated. In terms of health status, most of the study participants suffered from hypercholesterolemia [22, 23, 29, 41, 43–50, 52, 56, 59, 60] while others developed metabolic syndrome [42], combined dyslipidemia [53, 55], coronary or cerebrovascular diseases [51] HIV and at least one lipid abnormality [54], and healthy participants [57]. RCTs administered policosanol for a length ranging from 3 to 144 weeks. Between 5 and 20 mg/day policosanol was prescribed in the selected articles. The features of included trials are presented in Table 2.

Meta-analysis results

Base on pooling 23 effect sizes from 22 studies, we observed no significant change in creatinine level of participants consuming policosanol compared to placebo consumers (WMDs = 0.21 µmol/l; 95% CI, −0.84 to 1.26; $P = 0.69$) ($I^2 = 18.1\%$, $P = 0.21$) (Fig. 2). According to the results of subgroup analysis, the impact of policosanol on creatinine was significant in RCTs

Table 1 Risk of bias for randomized controlled trials, assessed according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 1)

Publications	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	other source of bias
1. Aneiros (1993) [41]	L	U	L	L	H	L	L
2. Aneiros (1995) [22]	L	U	L	L	H	L	L
3. Arteche-Hidalgo (2020) [42]	L	U	L	L	H	L	L
4. Castano (1) (1995) [43]	L	U	L	L	H	L	L
5. Castano (1996) [44]	L	U	L	L	H	L	L
6. Castano (1) (2001) [45]	L	U	L	L	H	L	L
7. Castano (2002) [46]	L	U	L	L	H	L	L
8. Castano (2003) [47]	L	U	L	L	H	L	L
9. Castano (2005) [48]	L	U	L	L	H	L	L
10. Castano (2006) [49]	L	U	L	L	H	L	L
11. Castano (2) (1995) [50]	L	U	L	L	H	L	L
12. Castano (1997) [29]	L	U	L	L	H	L	L
13. Castano (2007) [51]	L	U	L	L	H	L	L
14. Castano (2) (2001) [52]	L	U	L	L	H	L	L
15. Marcello (2000) [53]	L	U	L	L	H	L	L
16. Más (1999) [23]	L	U	L	L	H	L	L
17. Pons (1992) [50]	L	U	L	L	H	L	L
18. Pons (1994) [44]	L	U	L	L	H	L	L
19. Swanson (2011) [54]	L	U	L	L	H	L	L
20. Wang (2018) [55]	L	U	L	L	H	L	L
21. Zardoya (1996) [56]	L	U	L	L	H	L	L
22. Cho (2023) [57]	L	U	L	L	H	L	L

L Low risk of bias, *H* High risk of bias, *U* Unknown

lasting ≥ 24 weeks (WMD = − 1.45 µmol/l; 95% CI, − 2.66 to − 0.24; P = 0.01) with no significant heterogeneity among studies (I^2 = 0.0%; *P* = 0.82). Moreover, a significant rise in creatinine levels was found in trial duration < 24 weeks (WMD = 1.27 µmol/l; 95% CI, 0.08 to 2.47; *P* = 0.037). Our subgroup analyses did not consider studies lasting < 24 weeks heterogenous (I^2 = 0.0%; *P* = 0.492) (Table 3).

After restricting the studies to hypercholesterolemia patients, the study results did not change (WMDs = 0.33 µmol/l; 95% CI, − 0.84 to 1.49; *P* = 0.58) (I^2 = 24.1%, *P* = 0.15).

Nonlinear dose–response analysis

We used dose–response meta-analysis to explore the association between intervention effect and policosanol dose. Changes in creatinine levels were correlated with the dosage of prescribed policosanol in a linear fashion ($P_{nonlinearity}$ = 0.002) (Fig. 3). However, policosanol supplementation did not significantly alter creatinine levels based on treatment duration ($P_{nonlinearity}$ = 0.24) in the nonlinear manner (Fig. 4).

Meta-regression analyses

According to the meta-regression findings, no significant reduction in creatinine levels was found as the dose of policosanol supplementation increased (slope: −1.04; SE: 4.66; *P* = 0.82) (Fig. 5).

Grading of evidence

The evaluation of the certainty of evidence using the GRADE approach is indicated in Supplementary Table 3. We graded the quality of evidence as high as there were no serious limitations in terms of risk of bias, inconsistency, Indirectness, and imprecision.

Publication bias and sensitivity analysis

Visual inspection of the funnel plot revealed no indication of publication bias in the meta-analysis of the

Table 2 Demographic characteristics of the included studies

First Author (year)	Location	Study Design	Health status	Sex	Sample size	Duration (week)	Mean age (year) ± SD		Baseline BMI (kg/m2) ± SD		Baseline creatinine values (μmol/L)		Intervention group	Control group	Outcome
							Intervention groupp	Control group	Intervention group	Control group	Intervention group	Control group			
1. Aneiros (1993) [41]	Cuba	RCT, double-blind, parallel	Primary hypercholesterolemia	Both	30	6	60	58	27		76.4	81.7	5 mg policosanol twice daily (10 mg/day)	Placebo	Creatinine
2. Aneiros (1995) [22]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	45	6	58	60	NA		79.7	81.8	5 mg policosanol twice daily (10 mg/day)	Placebo	Creatinine
3. Arteche-Hidalgo (2020) [42]	Cuba	RCT, double-blind, parallel	Metabolic syndrome	Both	100	24	51 ± 8	50 ± 9	30.8 ± 4.8	30 ± 4.7	102	102	10 mg/day policosanol	Placebo	Creatinine
4. Castano (1) (1995) [43]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	68	48	52	52	NA		87.0	85.2	5 mg policosanol twice daily (10 mg/day)	Placebo	Creatinine
5. Castano (2) (1995) [50]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	58	48	64	65	NA		87.2	86.4	10 mg/day policosanol	Placebo	Creatinine
6. Castano (1996) [44]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	54	48	56 ± 9	58 ± 8	57		92.0	86.2	5 mg policosanol twice daily (10 mg/day)	Placebo	Creatinine
7. Castano (1) (2001) [45]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	41	8	63 ± 6	61 ± 8	26.4 ± 5.1	27 ± 4.6	95.6	95.0	10 mg twice daily (20 mg/day)	Placebo	Creatinine
8. Castano (2) (2001) [52]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia and more than one concomitant atherosclerotic risk factor	Both	179	12	67 ± 5	66 ± 4	27.7 ± 5.6	27.1 ± 5.9	88.9	88.1	5 mg/day policosanol	Placebo	Creatinine

Table 2 (continued)

First Author (year)	Location	Study Design	Health status	Sex	Sample size	Duration (week)	Mean age (year) ± SD		Baseline BMI (kg/m2) ± SD		Baseline creatinine values (μmol/L)		Intervention group	Control group	Outcome
							Intervention groupp	Control group	Intervention group	Control group	Intervention group	Control group			
9. Castano (2002) [46]	Cuba	RCT, double-blind, parallel	Hypertension and type II hypercholesterolaemia	Both	589	48	66 ± 5	66 ± 5	27.5 ± 4.8	27 ± 4.9	91.5	91.9	5 mg/day policosanol	Placebo	Creatinine
10. Castano (2003) [47]	Cuba	RCT, double-blind, parallel	Borderline to mildly elevated serum total cholesterol levels	Both	100	14	52 ± 9	52 ± 11	25.9 ± 4.7	25.4 ± 3.5	87.7	91.7	5 mg/day policosanol	Placebo	Creatinine
11. Castano (a) (2005) [48]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	45	8	65 ± 8	67 ± 7	25.4 ± 3.5	26.1 ± 3.5	81.7	78.3	5 mg/day policosanol + omega-3 FA	Placebo + omega-3 FA	Creatinine
12. Castano (b) (2005) [48]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	45	8	65 ± 8	67 ± 7	25 ± 4.2	26.1 ± 3.5	77.7	78.3	10 mg/day policosanol + omega-3 FA	Placebo + omega-3 FA	Creatinine
13. Castano (2006) [41]	Cuba	RCT, double-blind, parallel	Hypercholesterolemia	Both	54	3	58 ± 11	58 ± 14	26.1 ± 3.1	26.4 ± 4.8	72.9	73.9	10 mg/day policosanol + 1 g/d omega-3 FA	Placebo + 1 g/d omega-3 FA	Creatinine
14. Castano (1997) [29]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	39	10	57 ± 13	59 ± 7	31.9 ± 7.9	32.2 ± 8	88.5	83.2	5 mg policosanol twice daily (10 mg/day)	Placebo	Creatinine

Table 2 (continued)

First Author (year)	Location	Study Design	Health status	Sex	Sample size	Duration (week)	Mean age (year) ± SD		Baseline BMI (kg/m2) ± SD		Baseline creatinine values (μmol/L)		Intervention group	Control group	Outcome
							Intervention groupp	Control group	Intervention group	Control group	Intervention group	Control group			
15. Castano (2007) [51]	Cuba	RCT, double-blind, parallel	Documented coronary or cerebrovascular disease, hypertension, dyslipidemia, smoking habits and (or) diabetes	Both	239	144	65 ± 5	66 ± 5	25.6 ± 4.5	25.1 ± 6	90.3	90.6	5 mg/day policosanol + benzodiazepinas	Placebo + benzodiazepinas	Creatinine
16. Marcello (2000) [53]	Cuba	RCT, double-blind, parallel	Combined dyslipidemia	Both	29	8	55 ± 7	53 ± 7	27.7 ± 4.1	31.2 ± 9.2	96.0	95.0	10 mg/day policosanol +400 mg/day bezafibrate	Placebo + bezafibrate	Creatinine
17. Más (1999) [23]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia and additional coronary risk factors	Both	437	12	57 ± 9	58 ± 10	28.4 ± 5.7	28.8 ± 5.8	87.4	87.3	5 mg/day policosanol	Placebo	Creatinine
18. Pons (1992)[50]	Cuba	RCT, double-blind, parallel	Primary hypercholesterolemia	Both	48	8	60		NA		97.8	94.7	5 mg/day policosanol	Placebo	Creatinine
19. Pons (1994)[44]	Cuba	RCT, double-blind, parallel	Type II hypercholesterolemia	Both	57	48	61	60	NA		97.7	97.2	5 mg/day policosanol	Placebo	Creatinine
20. Swanson (2011) [54]	Chicago	RCT, double-blind, crossover	Stable HIV-infected people (91% black) with at least one lipid abnormality	Both	54	12	44.6 ± 5.4	46.8 ± 6.5	26.7	28.4	97.2	97.2	20 mg/day policosanol	Placebo	Creatinine

Table 2 (continued)

First Author (year)	Location	Study Design	Health status	Sex	Sample size	Duration (week)	Mean age (year) ± SD		Baseline BMI (kg/m2) ± SD		Baseline creatinine values (μmol/L)		Intervention group	Control group	Outcome
							Intervention groupp	Control group	Intervention group	Control group	Intervention group	Control group			
21. Wang (2018) [55]	China	RCT, parallel	Mixed dyslipidemia	Both	64	24	68.8 ± 8.1	68.7 ± 7.4	24.7 ± 3.6	25.4 ± 2.1	74.3	86.2	20 mg/day policosanol +200 mg/day fenofibrate	200 mg/day fenofibrate	Creatinine
22. Zardoya (1996) [56]	Cuba	RCT, double-blind, parallel	Primary hypercholesterolemia and abnormal serum biochemical indicators of hepatic function	Both	22	12	55 ± 8	50 ± 7	25.4		92.4	96.5	5 mg/day policosanol	Placebo	Creatinine
23. Cho (2023) [57]	Japan	RCT, double-blind, parallel	Healthy	Both	65	12	52		22.1		64.5	66.3	10 mg cuban policosanol twice daily (20 mg/day)	Placebo	Creatinine

Abbreviations: RCT Randomized controlled trial, *BMI* Body mass index, *SD* Standard deviations, *NA* Not available

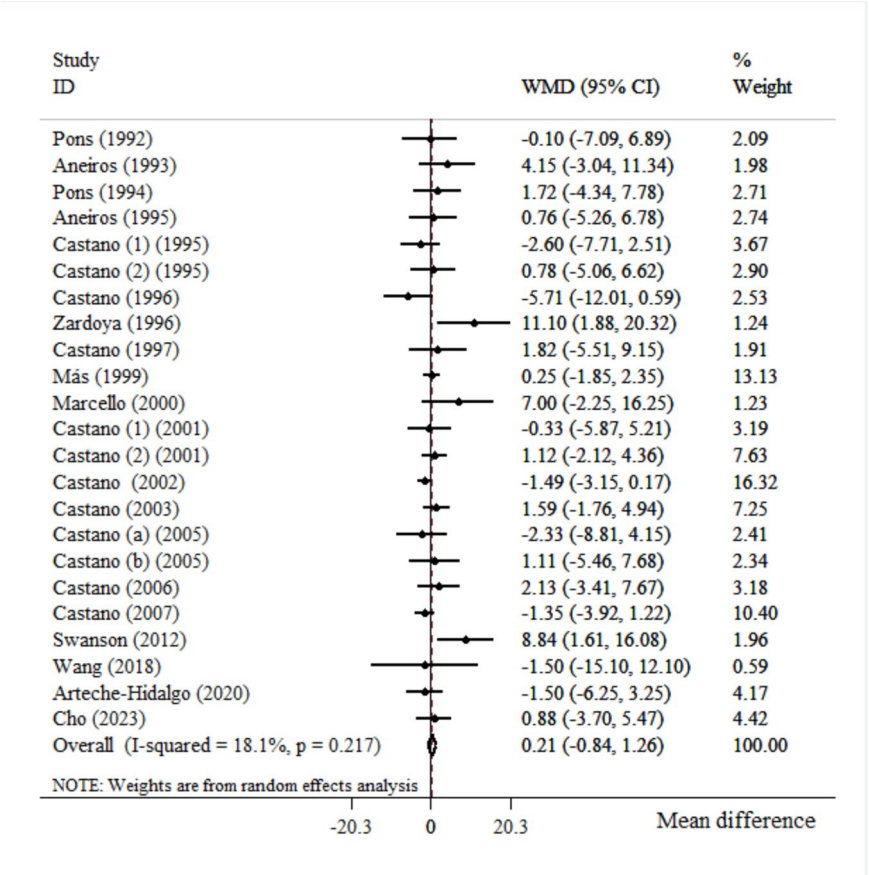

Fig. 2 Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of policosanol on creatinine

Table 3 Subgroup analysis of included randomized controlled trials in meta-analysis of the effect of policosanol on creatinine

Group	No. of effect size	WMD (95% CI)	*P* value	I^2 (%)	P-heterogeneity	P for between subgroup heterogeneity
Creatinine						
Pooled effect size	22	0.21 (−0.90, 1.32)	0.706	21.3	0.181	-
Duration (week)						0.002
< 24	14	1.27 (0.08, 2.47)	0.037	0.0	0.492	
≥ 24	8	−1.45 (−2.66, −0.24)	0.019	0.0	0.828	
Dose (mg/day)						0.644
5	9	−0.32 (−1.31, 0.68)	0.534	30.5	0.174	
10	11	0.67 (−1.19, 2.53)	0.480	30.0	0.160	
20	2	0.27 (−3.15, 3.69)	0.876	0.0	0.914	

Abbreviations: WMD Weight mean difference

effects of policosanol supplementation on creatinine levels (Fig. 6). The same result was found with Begg's regression test ($P = 0.06$). The total effect size of creatinine remained unchanged when each trial was excluded individually by the sensitivity analysis.

Discussion

Serum creatinine is one of the most important indicators of kidney function that is used in clinical practice [61]. Renal function decline is a leading cause of poor health-related quality of life (HRQOL) among the patients,

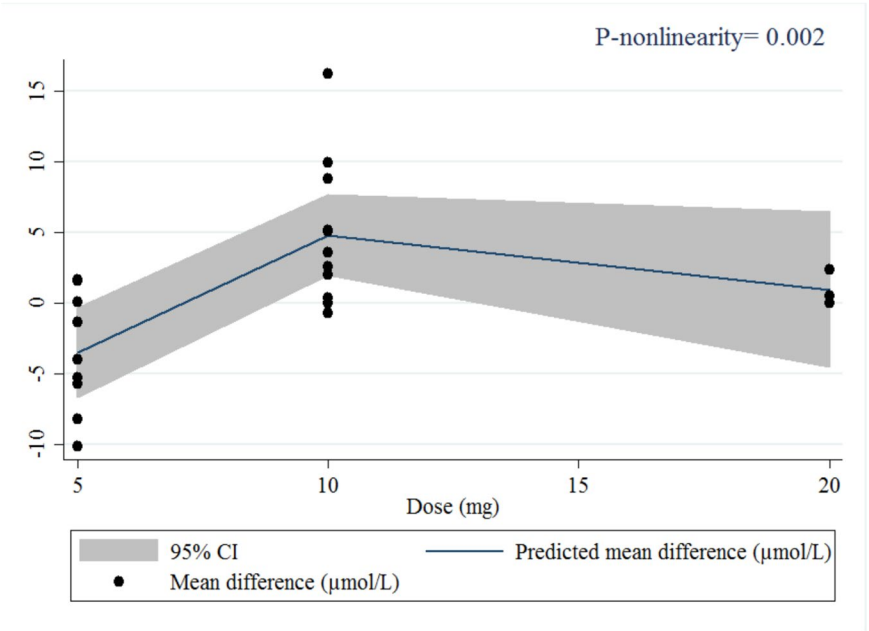

Fig. 3 Non-linear dose–response relations between policosanol dosage (mg/d) and unstandardized mean difference in creatinine. The 95% CI is revealed in the shaded regions

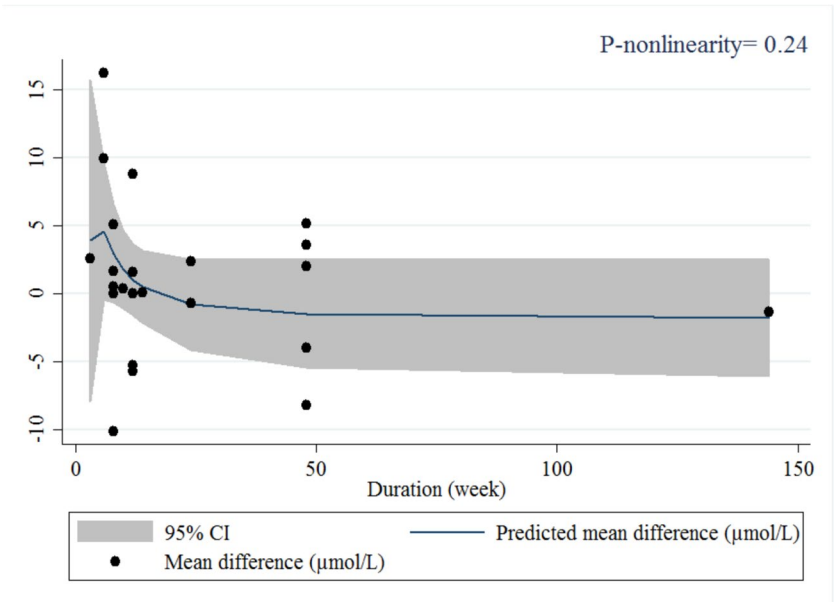

Fig. 4 Non-linear dose–response relations between duration of treatment (weeks) and unstandardized mean difference in creatinine. The 95% CI is revealed in the shaded regions

and the probability of premature death in these patients is 5–10 times higher than progression of the disease to end stages [62, 63]. Without preventive measures, serum creatinine gradually increases and patients eventually develop End Stage Renal Disease (ESRD) [64]. Therefore, various preventive and therapeutic strategies have been developed to prevent the complications of renal function decline. In this regard, policosanol is a dietary supplement and its beneficial effects have been observed in various diseases such as hyperlipidemia, hyperglycemia, hypertension, etc. [65–67]. Hence, the purpose of this review is to investigate the effectiveness of policosanol

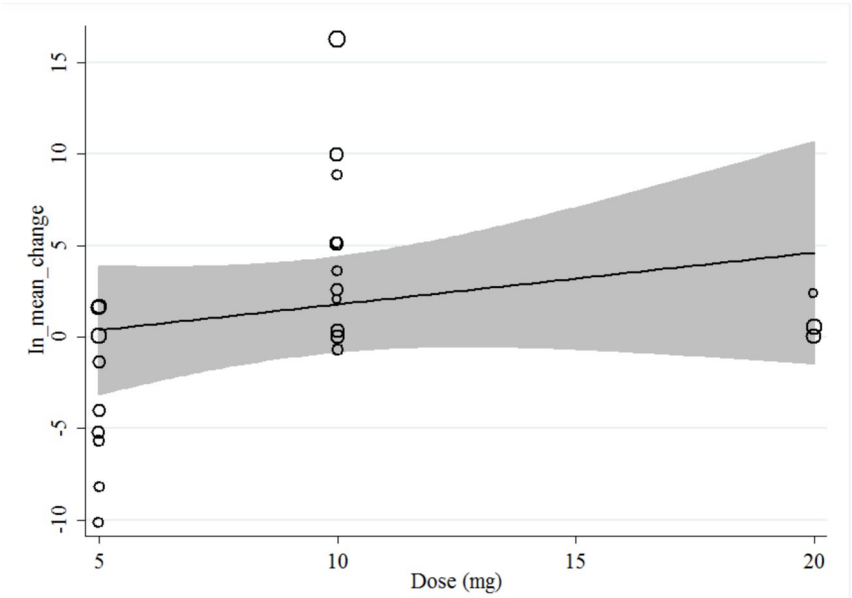

Fig. 5 Funnel plot demonstrating publication bias in the studies reporting the effect of policosanol on creatinine

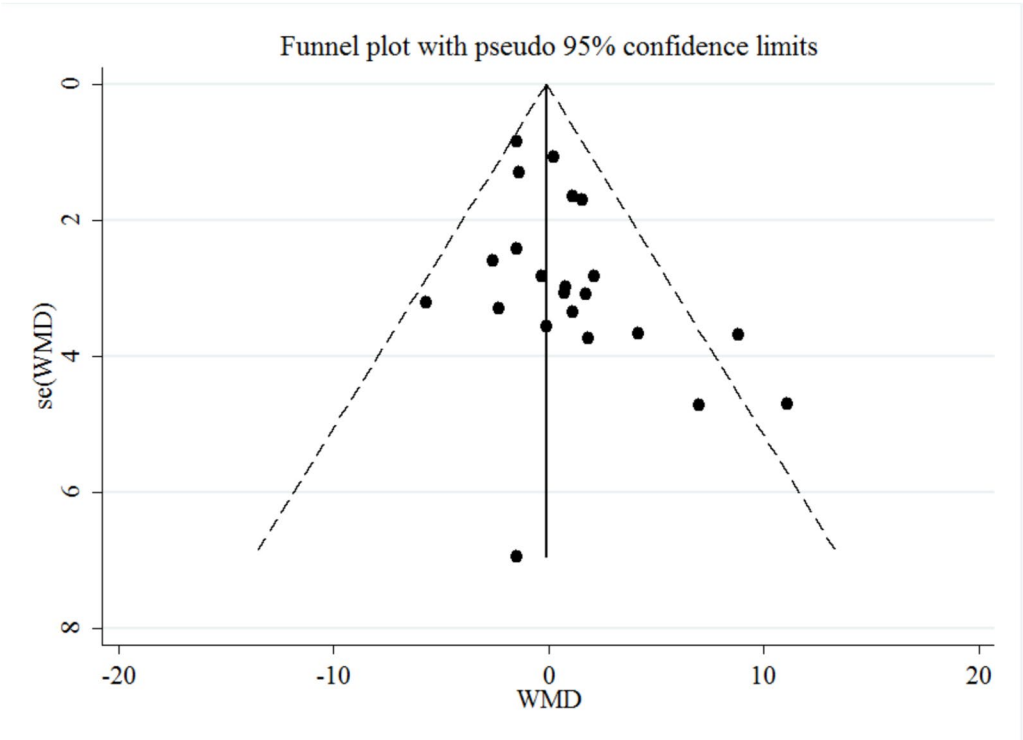

Fig. 6 Funnel plot displaying publication bias in the studies reporting the impact of policosanol on creatinine

supplementation on serum creatinine levels and compare the results with the placebo group. To our knowledge, this is the first meta-analysis in this context. Based on the obtained results, policosanol supplementation was not significantly associated with serum creatinine levels. As a consequence of significant heterogeneity, subgroup

analysis was performed to find the source of heterogeneity. The results of subgroup analysis showed that serum creatinine significantly reduced in trials that administered policosanol with more than 6 months duration. While our findings show a statistically significant reduction in creatinine levels with policosanol administration, the clinical significance of this reduction requires further investigation. Moreover, the results of the dose–response analysis indicated that more than 10 mg per day of policosanol supplementation significantly decreased serum creatinine.

Although the exact reasons for the discrepancies in the results are not fully understood, several factors may contribute to this variability, including observer bias and the placebo effect. Additionally, the characteristics of study populations varied significantly across studies, with differences in age, baseline creatinine levels, presence of comorbidities, and ethnic backgrounds. These population differences may influence the observed effects of policosanol. Furthermore, a range of confounding factors, such as dietary habits, especially the protein content of the diet, physical activity levels, and concomitant medications (including angiotensin-converting enzyme inhibitors), were not consistently controlled for across all studies [68, 69]. Such variability underscores the complexity of interpreting the effects of policosanol on creatinine levels. There was no sufficient information regarding these factors in the included studies in our meta-analysis.

In line with our findings, in a randomized placebo-controlled and double-blinded study with healthy and middle-aged Japanese participants, daily administration of 20 mg of policosanol for 12 weeks had no significant effect on serum creatinine levels; while it significantly reduced Blood urea nitrogen (BUN) and uric acid levels [58]. In most of the clinical trials, whose target population were patients with lipid abnormalities, with the policosanol daily dosage varying from 5 to 20 mg and intervention duration of 3 to 48 weeks, the effect of policosanol supplementation on serum creatinine levels was not significant [46, 49, 55, 60, 70]. In order to achieve more accurate results, future long-term large-scale trials are needed.

The mechanism of action of policosanol on serum creatinine levels has not been clearly defined yet. However, according to the results obtained from previous studies; hyperlipidemia may increase the possibility of kidney injury [71] and according to the proven hypolipemic effects of policosanol [65], the use of this functional food can play a pivotal role in preventing the progression of kidney damage. Hyperlipidemia, which is an elevated level of fats in the blood, can lead to increased production of inflammatory molecules, including HMGB-1 in certain kidney cells, contributing to tissue damage and fibrosis [72]. One key pathway involved in this process is the PI3 K-mTOR signaling pathway, which regulates various biological functions and is linked to the body's inflammatory response [73]. HMGB-1 acts as a regulator of this pathway in animal studies, initially increasing its activity, and then further promoting inflammation through a process called NLRP-3 inflammasome activation. This sequence of events can worsen tissue fibrosis [74]. In addition, the production of oxidized LDL (ox-LDL) is also increased in hyperlipidemia. Ox-LDL causes glomerular mesangial proliferation and inflammation, through which glomerulosclerosis and reduction of the number and function of nephrons might occur [75]. A study conducted by Elnagar et al. indicated that the administration of policosanol with a high-cholesterol diet significantly modulated the activation of the ox-LDL/HMGB1/PI3 K/mTOR/NLRP3 signalling pathway [28]. Consequently, it can be said that the positive effect of policosanol supplementation on kidney function and serum creatinine levels is applied by reversing the pathways mentioned above [76–78].

There are a number of studies that have investigated the safety and tolerability of policosanol in various situations including hyperlipidemia and high cardiovascular risk. The results of the studies showed that policosanol is well tolerated in the study patients and does not have an adverse effect on liver and kidney parameters [65, 79, 80]. But in general, there is no study that ensures the safety of regular use of policosanol for a long time in patients with kidney dysfunction and high levels of serum creatinine. For this reason, its use is considered safe by this time.

Strengths and limitations

First, the main strength of our study is that it is the first meta-analysis study that aims to investigate the clinical efficacy of policosanol supplementation on kidney function parameters such as serum creatinine levels. Second, we have performed subgroup analysis in order to investigate the effect of different subgroups and find the source of heterogeneity. Third, in this study, dose–response analysis was also performed to find the optimal dosage of supplementation. However, our study had some limitations. First, the randomized clinical trials included in our meta-analysis were heterogeneous in some factors such as supplement dosage, study duration, and the health status of the participants. In most of the included studies, the dietary intake of the participants was not specified. Because the intake of some dietary components such as protein could significantly affect the kidney function parameters [69]; the importance of this issue is quite comprehensible. Second, while our search strategy aimed for a broad search, it is acknowledged as a limitation that gray literature, such as unpublished studies and preprints, was not explicitly included in the search strategy. The exclusion of gray literature might have resulted

in an incomplete representation of the available evidence on this topic. Third, language limitations could have excluded relevant studies published in non-English languages, leading to a narrower perspective on the effects of policosanol.

Conclusion

Results from the systematic review and meta-analysis demonstrated that policosanol supplementation has no significant effect on creatinine levels. While policosanol has shown promise in other areas, its impact on kidney function—as indicated by serum creatinine levels—remains unclear. Therefore, future large-scale clinical trials worldwide are essential to further assess the efficacy and safety of policosanol.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
The research was done by MRA. MRA and MS performed data screening and literature searches. MRA extracted the data on its own and assessed its quality. Following data interpretation, MRA, SSM, MS, and FDJ wrote the paper. The leaders of the study were AH and GA. Every writer has read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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