

## Nutraceuticals in Hyperlipidemic Children: a Systematic Review and Meta-analysis

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### Abstract

#### Background

Dyslipidemia is a major risk for cardiovascular diseases. The aim of this study is to review the effects of nutraceuticals to modify lipid disorders in children.

#### Materials and Methods

The literature research was conducted in EMBASE, Medline, PubMed, Scopus, ISI Web of Science, and Cochrane library from 2002 until January 2015. The following keywords were used: dyslipidemia, hyperlipidemia, hypercholesterolemia, dietary intervention, nutraceutical, functional food, herbal treatment, non-chemical treatment, children, adolescents, clinical trial.

#### Results

13 eligible articles were entered in this study. Consumption of nutraceuticals had significant negative effect sizes (weighted mean differences) for triglycerides (-0.97, 95% CI: -1.49, -0.46), total cholesterol (-0.96, 95% CI: -1.67, -0.26), and low density lipoprotein-cholesterol (-0.54, 95% CI: -0.95, -0.13), it had positive effect size for changes of high density lipoprotein-cholesterol (0.43, 95% CI: 0.04, 0.82).

#### Conclusion

Findings of this metaanalysis suggest that consumption of nutraceuticals might have beneficial effects on improving dyslipidemia in the pediatric age group.

**Key Words:** Adolescents, Children, Dyslipidemia, Medicinal plants, Metaanalysis.

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## 1- INTRODUCTION

Nowadays, non-communicable diseases (NCDs), notably atherosclerotic cardiovascular diseases are considered as a major health problem, and are the main reasons of mortality at global level (1-4). Although they become symptomatic in adulthood, it is well documented, that their risk factors track from childhood to adulthood (3, 5-7). A growing body of evidence underscores the necessity of primary prevention of atherosclerotic diseases (3, 7-10).

The rapid changes in life-style habits and environmental factors, and in turn the escalating trend of childhood obesity have resulted in increasing prevalence of cardiometabolic risk factors including dyslipidemia in the pediatric age group (6, 11). Dyslipidemia in terms of high serum total cholesterol, low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG) concentrations, and low high-density lipoprotein-cholesterol (HDL-C) concentrations has several adverse health effects (12-14). Therefore, its prevention and early control is important. In addition to life-style change, diverse types of medications are used in this regard. Statins and fibrates are the most frequent medications used for treatment of dyslipidemia, but their side effects limit their use in the pediatric age group (3,4,11). Thus attentions have been attracted to non-pharmacological approaches like consumption of nutraceuticals, functional foods, supplements and other dietary modification.

Functional foods are enriched or enhanced foods with particular ingredients supplying health profits for consumer when it is used regularly. When they are used as an aid for prevention and or treatment of diseases, they are considered as nutraceutical. In addition, dietary supplements containing an extracted form of a nutraceutical like

vitamins, minerals etc in a non-food matrix (typically in a tablet or capsule dosage form), might be used to boost the dosage intake in comparison with the dose obtained from normal food. Some studies support the efficacy of dietary interventions in improving lipid profiles (16-18).

This review focuses on the effectiveness of natural fibers, phytosterols, stanols, and rice red yeast as a natural rich in statins, and herbal medications containing polyphenols on improving lipid disorders in children and adolescents. This study aimed to evaluate the effects of nutraceuticals in improving lipid disorders in children and adolescents by a systematic review and meta-analysis.

## 2- MATERIALS AND METHODS

### 2-1. Search strategy

We attempted to explore the papers describing clinical trials in which dietary interventions were employed in children and adolescents with dyslipidemia. Literature search was done in following databases: EMBASE, Medline, PubMed, Scopus, ISI Web of Science, and Cochrane library on papers published from 2002 to Jan 2015, our major concentration was on latest papers. The medical subject headings, keywords or their combinations were used: "dyslipidemia", "hyperlipidemia", "hypercholesterolemia", "dietary intervention", "nutraceutical", "functional food", "herbal treatment", "non-chemical treatment", "children", "adolescents", and "clinical trial". Further studies were observed by a manual research through references of relevant manuscripts, relevant reviews, and consultation with experts in this field. Paper language selection was restricted to English. Dyslipidemia was considered as the pediatric definition, i.e. TG or TC or LDL-C more than the age-and gender specific 90<sup>th</sup> percentile or HDL-C less than the 10<sup>th</sup> percentile (15).

## 2-2. Study design

Two independent reviewers determined the appropriateness of studies according to the pre-arranged criteria and subsequent extracted characteristics including related data of participants (number, age, type of disorder), study features (type, duration, applied intervention), measured parameters (TC, LDL-C, HDL-C, TG,) and outcomes. Differences in judgments were solved by discussion and consensus.

## 2-3. Studies selection

After screening the papers, titles and abstracts, relevant papers were selected. Then, their full texts were read and the findings were re-screened. Two independent reviewers screened the titles and abstracts of selected papers for their potential relevance or assessed the full text for inclusion in the review. In the case of disagreement, the discrepancy was resolved by consultation with a third investigator. The full texts of searched documents were extracted. After reviewing and studying the titles, author(s), journal name and publication year, the repeated items were excluded. In order to avoid the cross publication bias, investigators reviewed the findings to find and to omit duplicates. Then, researchers carefully studied the texts of articles, and the relevant articles were selected and the irrelevant ones were excluded.

## 2-4. Data collection

### 2-4-1. Study inclusion eligibility

- Children and adolescents aged less than 20 years with dyslipidemic condition (15) without any underlying metabolic disease;
- Studies with clinical trial design, conducted either as randomized controlled or open labeled;
- Intervention type involving non-synthesized drugs including bulk herb drugs, herbal formulations, nutraceuticals, supplements etc.;

- Laboratory measurement of lipid profile including TC, TG, LDL-C, and HDL-C;
- Study duration of at least four weeks (11, 15).

Studies without above mentioned criteria were not included in the systematic review.

### 2-4-2. Statistical analysis

We pooled data with random effects meta-analysis, weighted mean differences and 95% confidence intervals (CIs) are reported. We extracted the means and standard deviations (SDs) for the baseline and post-treatment for both groups when available. To assess the heterogeneity and inconsistency in results of individual studies, we used Cochran's Q test results and the  $I^2$  statistic (low heterogeneity: 25.0%, moderate heterogeneity: 50.0%, high heterogeneity: 75.0%) (19). The sensitivity analysis was done by successively removing a particular study or group of studies (if any), which had the highest impact on the heterogeneity test. Publication bias was examined through visual inspection of funnel plot asymmetry and the Egger's regression-based method (20). To adjust for results from possible publication bias and/or selective reporting, we used the standard methods of trim-and-fill analysis (21). We analyzed the data with Comprehensive Meta-Analysis software (CMA) version 2.

## 3- RESULTS

### 3-1. Study selection

According to search practice depicted in (Figure.1), 603 likely relevant articles were found out of which 583 items did not fulfill the inclusion eligibility criteria and removed. In remained 20 articles, 7 other papers were excluded (4- item because of cross-sectional interventions and 3 for treatment duration less than 4- week). Finally, 13 eligible articles were entered in the systematic review and meta-analysis. As explained before, 13 studies fulfilled

the inclusion criteria and were selected (Table.1). Among them, one study had no control group (Guardamagna et al, 2011), but others were randomized controlled trials. Three of 13 articles were open labeled studies (Asgary et al., 2013, Guardamagna et al., 2011, Amundsen et al., 2004). According to the interventions, the selected studies were categorized into three following groups:

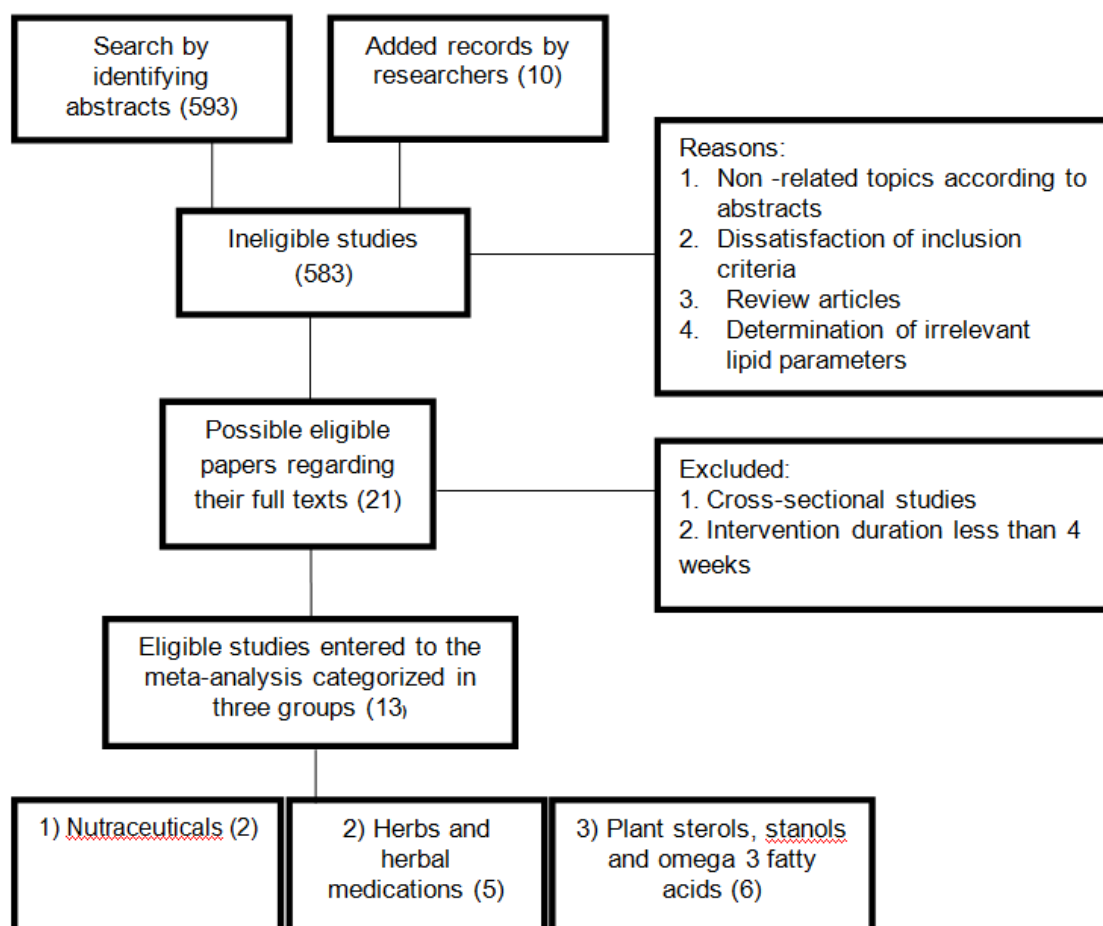
- Nutreaceuticals;
- Bulk herb drugs and herbal formulations;
- Plant derived sterols, stanols, and/or omega 3 fatty acids.

Consumption of neutraceuticals had significant negative effect sizes (weighted mean differences) on TG (-0.97, 95% CI: -1.49, -0.46), TC (-0.96, 95%CI: -1.67, -

0.26), and LDL-C (-0.54, 95%CI: -0.95, -0.13), as well as positive effect size on HDL-C changes (0.43, 95%CI: 0.04, 0.82) compared to the control groups.

The between-study heterogeneity was significant for all studies: TG ( $I^2 = 91.54\%$   $P=0.002$ ). TC ( $I^2 = 94.86\%$   $P=0.001$ ), LDL-C ( $I^2 = 87.53\%$   $P=0.001$ ), HDL-C ( $I^2 = 86.33\%$   $P=0.001$ ).

Funnel plots and Egger tests suggested no significant asymmetry in the meta-analyses of TG, TC, and LDL-C (TG Egget test:  $P=0.065$ , TC Egger test:  $P=0.65$ , LDL-C Egger test:  $P=0.79$ , with proposed significant asymmetry for HDL-C (Egger test:  $P=0.007$ ). Under the random-effect model, the trim-and-fill adjusted overall mean changes was -0.64 (95% CI = -0.77, -0.51) for HDL-C.



**Fig.1:** PRISMA flow diagram of search results

**Table 1:** Summary of trials included in the systematic review and meta-analysis

First author's name	Sample size (n)	Age range (year)	Trial type	Duration (wk)	Outcome
<b>Nutraceutical</b>					
1. Guardamagna et al(22)	36	6-15	Double-blind, randomized, placebo-controlled, cross-over trial	24	Reduction of LDL-C and TC
2. Martino et al(3)	120	5-12	Double blind randomized placebo controlled trial	8	Reduction of LDL-C and TC
<b>Herbs and herbal medications</b>					
1.Guardamagna et al(23)	40	8-16	Double-blind, randomized, placebo-controlled,cross-over trial	8	Improvement of lipid profile
2. Sabzghabae et al(!1)	72	12-18	Triple-blind randomized placebo-controlled clinical trial	4	Reduction of LDL-C, TC and TG
3. Asgary et al(12)	40	9-16	Randomized controlled clinical trial	6	Reduction of LDL-C, TC and TG
4. Sabzghabae et al(15)	70	12-18	Triple-blind randomized placebo-controlled clinical trial	4	Reduction of LDL-C, TC and TG
5.Wong et al(24)	32	8-18	Placebo-controlled, blinded, randomized clinical trial	4	Improvement of lipid profile , reduction of LDL-C
<b>Plant: sterols, stanols</b>					
1.Guardamagna et al(25)	32	8-16	Open labeled clinical trial	12	Reduction of LDL-C
2.Jakulj et al(26)	42	7-12	Randomized double-blind placebo-controlled cross-over trial	4	Reduction of TC and LDL-C
3.De jongh et al(27)	42	5-12	Randomized double-blind placebo-controlled crossover trial	4	Reduction of TC and LDL-C
4.Garaiova et al(28)	25	8-21	Randomized, double-blind, placebo-controlled, cross-over study	6 wks	Increasing (large and buoyant, less atherogenic particles of LDL-C and HDL-C) , compared with the placebo phase and (small and dense, more atherogenic particles) decreased
5.Amundsen et al (29)	38	7-12	Randomized, double-blind crossover study	8	Reduction in LDL-C
6.Amundsen et al (30)	37	7-13	Open-label follow-up of children who were previously studied in a controlled cross-over study	26	Sustained efficacy of cholesterol reduction and long-term compliance of PSE intake were demonstrated in this study

TC: Total cholesterol, LDL-C: Low-density lipoprotein-cholesterol (LDL-C), HDL-C: High-density lipoprotein-cholesterol, TG: Triglycerides.

## 5- DISCUSSION

The main objective of this systematic review and meta-analysis is to investigate the efficacy of nutraceuticals for improving lipid disorders in children and

adolescents. In eligible included studies the interventions were including fibers, herbal medications rich in anthocyanosides and polyphenols, phytosterols, and stanols. To the best of our knowledge, no previous meta-analysis had evaluated the effects of

all above-mentioned compounds on dyslipidemia in the pediatric age group.

Overall, the trials included in the current review showed significant beneficial effects in reducing serum concentrations of TC, LDL-C, and TG, as well as elevating HDL-C. However, the results of various studies were inconsistent, attributed to the wide variation in the type of nutraceuticals, study duration and other differences in study designs.

A narrative review that included randomized and non-randomized clinical trials showed that consumption of 0.5 g/day of glucamnan is effective in reducing TC and LDL-C (18). It is inconsistent with the study which included in our study. In addition, this narrative review reported that dietary fiber intake had no effect on HDL-C concentration (18). A meta-analysis showed glucamnan could significantly reduce serum TC and TG concentrations (31).

Glucamnan is a small heteroglycan of  $\beta$ -(1 $\rightarrow$ 4)-linked D-mannose and D-glucose branched with  $\beta$ -(1 $\rightarrow$ 6)-glucosyl linkages. It is found in the cell walls of the corns of *Amorphophallus konjac* (Devil's tongue), the roots of certain orchids, the wood of conifers and in smaller amounts in the wood of dicotyledons (32). Galactoglucamnan is a similar structure with  $\alpha$ -(1 $\rightarrow$ 6)-linked galactose units in side branches which its main source is guar gum (33). There are other sources of water-soluble fibers from oat bran, psyllium, or locust bean gum, which are also used in the treatment of hypercholesterolemia in children and adolescents (34). Water-soluble fibers like glucamnan are hydrated in water and increase gastrointestinal transitional rate which in turn decrease absorption of sugars and lipids from the gut (35). Glucamnans reduce also reabsorption of bile acids and steroids by binding with them or increasing their excretion (36). It

reduces both the amount of exogenous cholesterol absorbed from food and the reabsorption of the bile acids. The body produces about 800 mg of cholesterol per day and about half of that is used for bile acid synthesis producing 400–600 mg daily to replace bile acids lost normally in the feces (37). The body secretes about 10 gr of bile acids into the intestine each day, which means that bile acids are recycled several times each day by reabsorption from small intestine. Decreasing the amount of reabsorbed bile acids, increase endogenous cholesterol uptake from circulation for bile acid synthesis to maintain a steady bile flow, and the overall effect is a reduction in circulating cholesterol by excreting excess cholesterol as bile acids (37). As another possible mechanism, a delay in sugar absorption by glucomannan leads to increased insulin sensitivity which increases lipogenesis in liver and reduces lipolysis from peripheral tissues and adipocytes as a source of endogenous cholesterol and TG (38).

Several studies have confirmed these effects of such small molecule heteroglycan fibers on lipid profile (39-41). In the pediatric age group, the recommended doses begin from 5-10 g/day for children older than 2 years and reaching gradually to adult doses during adolescence (42-43). However, heteroglycan fibers may have adverse effects if taken without enough water. Due to their thickening properties and hydration by throat, esophagus or intestine fluids, they might make lockage in gastric ways (38).

Medicinal plants use has been worldwide spread from hundreds years ago. Some ingredients like flavonoids, anthocyanides, polyphenols, and antioxidant ingredients in herbal originated drugs may responsible of their hypolipidemic effects specially, in early stages of dyslipidemia and prevent the need of chemical drugs (43, 44). The

high incidence of side effects in synthesized hypolipidemic drugs limits their applications (45, 46).

Although some of included articles with herbal medicine interventions showed prominent hypolipidemic effects, but some studies showed no significant effects on lipid profiles in children, for instance the effects of garlic were not observed on their lipid levels (47).

Digestion and transport of lipids because of their insolubility in water, is dependent to detergent properties of bile acids. They emulsify fatty acylglycerols and cholesterol as globules into small micelles. Phytosterols with low enteric absorption competed with cholesterol to be incorporated in the micelles in a way that majority of cholesterol is not emulsified and excreted via feces (48). Phytosterols including  $\beta$ -sitosterol, campesterol, and stigmasterol with cholesterol related structure occurred mostly in vegetable oils like soybean, corn, and rapeseed or from tall oil in pine trees, nuts, wheat, rye and whole grain foods. Phytosterols could be saturated into stanols which have 10 times less enteric absorption than phytosterols. A review article revealed the LDL-C lowering effect of phytosterols in adults (49). In our study, the number of studies that evaluated the sterol effects in children, were more than stanol effects. The lowering effects of plant sterols were shown in all types of hypercholesterolemia including familial hypercholesterolemia (FH), familial combined hypercholesterolemia (FCH) and undefined hypercholesterolemia (UH) (28). Plant stanols effects were evaluated in one study which showed lowering of LDL-C. One of 13 articles included in our study had evaluated the effects of red rice in hyperlipidemic children (23). Red yeast rice is another natural cholesterol lowering supplement with monacolin type diterpenes, which are similar to statins. They inhibit HMG-CoA reductase enzyme and reduce cholesterol synthesis in liver.

An review article, showed that red yeast may reduce TC, LDL-C and TG in humans and animals (50)

## 5- CONCLUSION

In summary, this study showed the effectiveness of nutraceuticals used for improving lipid profiles and their applications in dyslipidemic children until they reach the adolescence that aggressive lipid lowering strategies should be started. It seems that a mixed therapy consisting of two or more types of mentioned compounds are more effective than one alone. For instance, co-administration of red yeast rice with stanols could reduce both indigenous and exogenous cholesterol in the serum. In addition, nutraceutical-enriched foods with low fat like foods rich in water-soluble fibers that contain low cholesterol and saturated fats might be also recommended to increase the cholesterol and LDL-C lowering effects in the pediatric age group. Further longitudinal studies are necessary to assess the clinical impact of these findings.

**6- CONFLICT OF INTEREST:** None.

**7- ACKNOWLEDGMENTS:**

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