Polyphenol in Reducing Cardiovascular Outcomes in Adult: a Rapid Review and Meta Analysis

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ABSTRACT

Objectives: This review has an objective to determine the effectiveness of polyphenol intervention for the primary prevention of cardiovascular disease events and others surrogate endpoint which may correlate with cardiovascular disease events

Data Sources: These electronic databases were used to search the appropriate trials: MEDLINE (OvidSP, 1946 to March week 2 2020); The Cochrane Central Register of Controlled Trials (CENTRAL, week 2 March 2020). We only used English language trials that were available on these two databases.

Review Methods: We chose randomized controlled trials both in healthy or having high risk of cardiovascular diseases. Polyphenol as intervention was described as any food or drink that has polyphenol or its derived substance as main content. Placebo or no intervention is the comparison group. Cardiovascular clinical events and surrogate endpoints or cardiovascular disease risk factors are included in the outcome. Revman 5.5 software was used to analyze all the trials and to assess the risk of bias each trial. We selected random or fixed effects depend on the heterogeneity between trials in the meta analysis.

Results: Seven trials were included with 49200 participants randomized. Heterogeneity was shown between trials regarding the characteristic of participants, types of polyphenol intervention, and follow up periods. Cardiovascular event outcomes are only available in one trial (Howard et al 2006), with the intervention not clearly defined as polyphenol but increasing fruit and grain consumption. This trial shows no evidence was shown on fatal and non-fatal cardiovascular outcome by consuming more fruit and grain with 8 years mean of follow up. By analyzing remaining trials, which provide surrogate endpoints or cardiovascular risk factors, there is no evidence that polyphenol intervention reduce systolic and diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol level, and triglyceride level. However, reduction total cholesterol level was shown from the baseline (MD -5.41 mg/dl, 95% CI -8.21 to -2.62, P=0.0001). Subgroup analyses were done with dividing the trials that involve women only and both men and women. This analysis shows the reduction of both systolic (MD -2.78 mmHg, 95% CI -5.47 to -0.08, P=0.04) and diastolic blood pressure (MD -2.59 mmHg, 95% CI -4.84 to -0.34, P=0.02) in trials involving both men and women. A sensitivity analysis was done by excluding the trials with risk of bias with no different results effect. Moreover, not any trials reported adverse events of polyphenol.

Conclusion: Due to the limitation evidence or trial available, we could not obtain meta analysis on the primary outcome. Nevertheless, this review suggests that polyphenol intervention does show favorable effect on

surrogate endpoints which was total cholesterol levels. Besides, systolic blood pressure and diastolic blood pressure in trials which involves both

men and women also shown an improvement. The high heterogeneity in this review also suggests that more evidence are needed to assess the effectiveness of polyphenol intervention in reducing cardiovascular event outcomes and risk factors in the future.

INTISARI

Tujuan: Tinjauan ini memiliki tujuan untuk melihat efektifitas intervensi polyphenol untuk prevensi primer terhadap kejadian penyakit kardiovaskular dan luaran tambahan yang mungkin memiliki korrelasi terhadap kejadian penyakit kardiovaskular

Sumber Data: Database elektronik yang digunakan pada tinjauan ini: MEDLINE (OvidSP, 1946 hingga minggu 2 Maret 2020); The Cochrane Central Register of Controlled Trials (CENTRAL, minggu 2 Maret 2020). Kami hanya menggunakan uji coba bahasa Inggris yang tersedia pada dua database ini.

Metode Tinjauan: Kami memilih uji coba terkontrol secara acak baik pada populasi sehat atau memiliki risiko oenyakit kardiovaskular. Polyphenol sebagai intervensi didefinisikan sebagai makanan atau minuman yang mengandung polyphenol atau bahan turunannya sebagai kandungan utamanya. Kelompok pembandingnya berupa plasebo atau tidak ada intervensi. Kejadian kardiovaskular dan luaran tambahan atau faktor risiko penyakit kardiovaskular termasuk dalam luaran pada tinjauan ini. Piranti lunak Revman 5.5 digunakan untuk menganalisis semua uji coba dan untuk menilai risiko bias setiap uji coba. Pada proses meta-analysis, analisis efek acak atau tetap akan dilakukan bergantung pada heterogenitas dalam studi.

Hasil: Tujuh studi dilibatkan dengan 49200 peserta secara acak. Heterogenitas ditunjukkan antara studi mengenai karakteristik partisipan, jenis intervensi polyphenol, dan periode tindak lanjut. Hasil yang menyertakan kejadian kardiovaskular hanya tersedia dalam satu studi, dengan intervensi tidak secara jelas didefinisikan sebagai polyphenol tetapi disebutkan populasi yang meningkatkan konsumsi buah dan biji-bijian. Studi ini menunjukkan tidak ada bukti yang ditunjukkan pada luaran kardiovaskular yang fatal dan non-fatal dengan mengkonsumsi lebih banyak buah dan biji-bijian dengan rata-rata masa tindak lanjut selama 8 tahun. Dengan menganalisis studi yang lain, dengan luaran berupa luaran tambahan pengganti atau faktor risiko kardiovaskular, tidak ada bukti bahwa intervensi polyphenol menurunkan tekanan darah sistolik dan diastolik, lipoprotein densitas rendah, lipoprotein densitas tinggi, dan level trigliserida. Namun, penurunan kadar kolesterol total terlihat dari baseline (MD -5.41 mg / dl, 95% CI -8.21 hingga -2.62, P = 0,0001). Analisis subkelompok dilakukan dengan membagi studi yang hanya melibatkan perempuan saja dan studi yang membagi populasi menjadi laki-laki dan perempuan. Analisis ini menunjukkan penurunan tekanan darah sistolik (MD -2,78 mmHg, 95% CI -5,47 menjadi -0,08, P = 0,04) dan tekanan darah diastolik (MD -2,59 mmHg, 95% CI -4,84 menjadi -0,34, P = 0,02) dalam studi yang melibatkan pria dan wanita. Analisis sensitivitas dilakukan dengan eksklusi studi dengan risiko bias dengan ditemukannya luaran yang tidak berbeda. Selain itu, tidak ada studi yang melaporkan efek samping polyphenol.

Kesimpulan Penulis: Karena keterbatasan bukti atau studi yang tersedia, kami tidak dapat melakukan meta-analysis pada luaran utama yang diharapkan. Namun demikian, tinjauan ini menunjukkan bahwa intervensi polyphenol menunjukkan efek yang menguntungkan pada luaran tambahan pengganti yaitu kadar kolesterol total. Selain itu, tekanan darah sistolik dan tekanan darah diastolik dalam studi yang melibatkan pria dan wanita juga menunjukkan perbaikan. Heterogenitas yang tinggi dalam tinjauan ini juga menunjukkan bahwa lebih banyak bukti atau studi diperlukan untuk menilai

efektivitas intervensi polyphenol dalam mengurangi luaran kejadian kardiovaskular dan faktor risiko di masa depan.

Introduction

Description of the condition

Cardiovascular diseases are defined as disease that involves in vascular and heart. Cerebrovascular disease, rheumatic heart disease, peripheral arterial disease, congenital heart disease, pulmonary embolism, deep vein thrombosis, and coronary heart disease are included in cardiovascular diseases.[1] In 2011, cardiovascular diseases were responsible for about 17 million people.[2] Ischemic heart disease was responsible for 7 million deaths, while stroke was responsible in approximately 6.2 million.[2] Moreover, not only those cardiovascular diseases have high prevalence in developed countries, but also in developing countries.[3]

Description of the intervention

Polyphenols as one of the antioxidants are found in natural diets including grape, cranberry, cocoa, wine, tea, onions, and apples.[3,4,5,6] Studies conducted by Khan et al suggested that cocoa is the richest source of polyphenols, which is shown to have potential antioxidant, antiinflamatory, and reducing lipid level at bloodstream.[5,7,8]

How the intervention might work

In vitro studies as stated by Yubero et al shown that polyphenols deliver more antioxidant capacity to human body.[3] Polyphenols has been studied to advance endothelial function by increasing the production of nitric oxide and endothelium-derived hyperpolarizing factor and thus the reduction in blood pressure and slowing atherogenic growth were found.[8,9] In addition, animal model studies that are administered by red wine which contains rich source of polyphenol shown to prevent the raise of systolic blood pressure stimulated by deoxycorticosterone acetate-salts.[9]

Polyphenols in tea are also shown to have capacity to inhibit LDL oxidation, therefore it attenuates the lipid peroxide generation.[10] Cocoa or dark chocolate is also shown to reduce the risk of hypertension and all cause mortality by advancing nitric oxide dependent vasodilatation in research involving healthy patient and patient with cardiovascular disease risk.[11]

Why it is important to do this review

As the rich source of polyphenols, fruit and grain are known as two daily natural diet which considered to reduce all cause mortality with their benefits. Furthermore, it is known by studies that polypheno; is one of the substances that support this theory. However, studies that have been conducted produce inconsistent data. For instance, the different of the dosage, period of administration, subject characteristic, and the study design might give different results of polyphenols.[9] In addition, the subject characteristics that involved of most

studies were high risk of cardiovascular diseases, therefore the prospective capacity to the healthy or low-risk populations is not clearly described.[8] Due to the lack of large randomized controlled trials[3] and inconsistent result of polyphenols in this circumstance, this study deserves further examination. Moreover, since cardiovascular diseases are considered as one of the biggest burden diseases in the world, preventing them by affordable natural diets such as polyphenol could prevent the events to be happened.

Objectives

To conclude the effectiveness of administering polyphenols for reducing the cardiovascular diseases events and surrogate endpoints of cardiovascular event among adult people.

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled parallel or crossover trials were included with no language and time restrictions. All other study types in the articles are excluded.

Types of participants

Adult people are considered as inclusion with no restriction of age, sex, or risk stratified. Since this review will study effect the benefits or harms of the polyphenol in cardiovascular event not only in the primary prevention but as well as the secondary prevention, we do not exclude any patient that have already had cardiovascular event. The studies that are using animals or children as the population are excluded in this review.

Types of interventions

The interventions were all preparation or dose of polyphenols including red wine, cocoa, cranberry juice, tea, synthetic regimen such as intravenous and pill are included in the inclusion. Substances that are similar to polyphenol (e.gisoflavon, flavonoid, phytoestrogen) are also included in this review. Comparator includes placebo or no intervention are used in this review.

Types of outcome measures

Primary outcomes

1. Cardiovascular events (myocardial infarction, stroke, coronary heart disease, or unstable angina).
2. Cardiovascular mortality
3. All cause mortality

Secondary outcomes

1. Surrogate endpoints of cardiovascular events: Changes in blood pressure; Changes in lipid profiles

including total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride level.

Possibility of harms

Reporting harms or adverse events in the studies will be analysed in this review.

Search methods for identification of studies

Electronic searches

This review is using these following electronic databases:

1. MEDLINE by OvidSP (1946 to March Week 2 2020), listed in Appendix 1;
2. Cochrane Central Register of Controlled Trials (March 2020);

The searches were using medical subject headings (MeSH) that sensitive maximizing RCTs for MEDLINE from Cochrane collaboration methodological filters.

Searching other resources

Identifying other resources were not done in this review.

Data collection, synthesis and analysis

Selection of studies

Endnote (version X6, Thomson Reuters) was used to Import and remove duplication of the records. From the searches, title and abstract were initially screened before conducted the full text screenings in the remaining records.

Data extraction and management

One review author extracted data using particular extraction form. The study design, baseline characteristic of the participant, origin of study, intervention of polyphenol type including dosage, mean of follow ups, mean of age participants, and outcome data from each study that included in this review.

Using RevMan 5.2, these following data are assigned from each study:

1. Study Methods
2. Participants
3. Intervention type and the comparator
4. Outcomes

Assessment of risk of bias in included studies

Using Revman 5.2, the assessment of risk of bias was done. Based on the Cochrane handbook, these following criteria were assessed[12]:

1. Adequate random sequence generation such as computer-generated table or any methods that should be stated clearly in each study.
2. Adequate allocation concealment measurement. Allocation concealment in randomisation is considered important to avoid foreknowledge either to participants and physician.
3. Blinding of participants, personnel, and outcome measurement

4. The Completeness of outcome data including using of intention-to-treat principle in each trial.
5. Selective reporting issue to see that the authors report all the outcomes to avoid reporting bias
6. Other bias like conflict of interest in terms of funding of the study.

Low risk, high risk, and unclear bias in every criteria above were attached in each study.

Measures of treatment effect

The measurement was using Cochrane Handbook as the guidance.[12] Trial that uses dichotomous variables was measured using Hazard Ratio (HR). Trial that uses continuous variables was measured using Mean Differences (MD). Both measurement were using 95% Confidence Interval.

Unit of analysis issues

One trial has multiple treatment groups and thus we combine these groups to yield a new group.

Dealing with missing data

Intention-to-treat principle were using in the analysis although only one trial mentioned the ITT analysis. Lost to follow up were defined in the assessment risk of bias.

Assessment of heterogeneity

The heterogeneity was assessed using Chi2 and the I2 statistic in Revman 5.2 software. In the trials without visible heterogeneity, fixed effect was used. Using random-effects model is also considered if heterogeneity presents and cannot be explained. Study was considered have heterogeneity if the I2 statistic is more than 50%.

Assessment of reporting biases

The possibility of publication bias and heterogeneity were assessed using funnel plot in each analysis by Revman 5.2. The asymmetry of funnel plot may show the publication bias. However, it also might come from the result from clinical or methodological heterogeneity between each study. Distinguishing heterogeneity using statistical test (Egger's regression or Begg's correlation) could be done although this review did not perform it.

Analysis at the study level

Comparing the hazard risk in cardiovascular events between the treatment groups of polyphenol to the control group is done in this review (one trial). Then, the secondary outcomes were analyzed using risk difference between the treatment and control group. The heterogeneity was assessed using I2 statistic.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were done in trials with only involving women as the participants (2 trials) and trials involving both men and women.

Sensitivity analysis

The study qualities issues were explored using sensitivity analysis by repeating analysis without the studies that have risk of bias (4 trials).
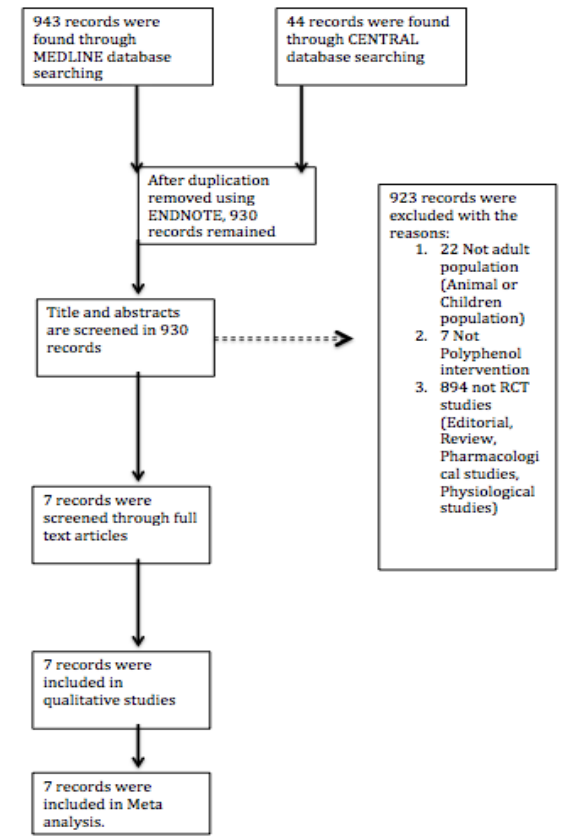
Result

Figure 1. Number of studies identified at each stage of the selection process and reasons for their exclusion

Description of studies

Results of the search

Using Medline by OvidSP, we did medical subject heading systematic search strategy as shown in APPENDIX 1. In addition, CENTRAL database was also used to obtain additional study. 943 and 44 studies were found respectively from these databases. Using Endnote to merge these studies, only 930 studies remained after any duplication has been removed. Then, from 930 studies, 923 were excluded based on our inclusion criteria after abstract and title assessment (Figure1). 7 studies were assessed through full text, then based on our criteria, these 7 remained studies were included in qualitative analysis. Lastly, only 6 studies were used in meta analysis since 1 study did not have the outcomes that we expect in meta analysis.

Included studies characteristics

Details of included studies are shown in APPENDIX 2.

Clinical heterogeneity

Seven trials were included in this study with total 49200 participants. 48835 participants were registered in one only study[13]. Each study has different type of intervention but polyphenol is still the main content of each intervention. The population were shown heterogeneity, 3 trials were done in Spain;[5,8,14] 1 trial was done in United States;[13] 1 trial was done in Poland;[15] 1 trial was done in Holland;[6] and 1 trial was done in Iran[16]. 2 trials were only included women;[8,13] 1 trial was only included men;[14] and the remaining trial were included both men and women. The baseline characteristic of included participants were also heterogeneous each study.

Excluded studies

Details of excluded studies are shown above in Figure 1.

Risk of bias in included studies

By using Revman, each included study was assessed the risk of bias of randomization, allocation concealment, blinding, lost to follow up, selective reporting, and possibility of other bias.[12] As shown in figure 2 and figure 3, 3 trials were considered for not having risk of bias.
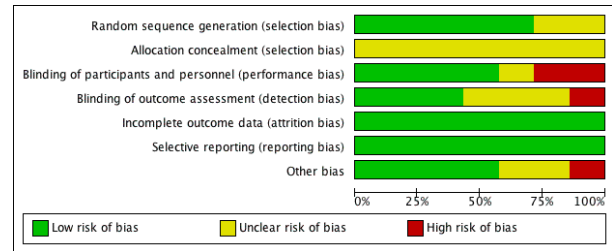

Figure 2. Risk of Bias Graph

Allocation

Adequate randomization was reported clearly in 5 trials [5,6,8,13,14,15,16] did not clearly report the randomization. However, not any trials reported of the treatment allocation to examine the allocation concealment.

Blinding

Outcome assessment were blinded in 2.[13,14] One trial reported the outcome were done by the participants using ambulatory blood pressure.[6] However, since the participants did not know in which arms they are involved in, we consider it as non-differential and thus yield low risk bias. Three trials did not report the outcome assessment clearly.[5,15,16] One trial reported that the outcome assessment were done by the researchers and the nurses in the researcher hospital and thus we consider it as high risk bias.[8]

Incomplete outcome data

Four studies had loss of follow up participants with provided reasons.[6,13,14] In addition, these four studies also used intention to treat principle. Other studies did not have loss of follow up participants.[5,8,15]

Selective reporting

Selective outcome reporting was not found in every trial.

Other potential sources of bias

One trial had the funding from a profit company that might give high risk bias.[6] Two trials did not report any statement of the funding body of their research.[13,15] Other trials reported the funding body which is unlikely to have conflict of interests.[5,8,14,16]

Figure 3. Risk of Bias Summary

Effects of interventions

Clinical events as primary outcomes

Clinical events as primary outcome were only reported in one trial.[13] Moreover, this particular trial is the largest trial with longest mean of follow up time up to eight years. In participants without prior history of cardiovascular diseases, consuming more fruit and grain that has polyphenol content was showing no statistically significant effects in reducing non-fatal myocardial infarct(MI) event (Hazard Ratio (HR) 0.91, 95% Confidence Interval (CI) 0.8 to 1.04), coronary heart disease (CHD) death (HR 1.01, 95% CI 0.81 to 1.27), non-fatal stroke (HR 1.04, 95% CI 0.90 to 1.19), fatal stroke (HR 0.94, 95 CI 0.65 to 1.35), and total cardiovascular diseases including clinical MI, silent MI, revascularization (coronary artery bypass graft or percutaneous coronary intervention), all death because of CHD, and stroke (HR 0.96, 95% CI 0.89 to 1.03)

Surrogate endpoints of cardiovascular events as secondary outcomes

Blood Pressure

Six trials measured blood pressures either systolic and diastolic,[5,6,8,13,15,16] with total 49176 participants). Due to its heterogeneity (I2 = 55%), in systolic blood pressure we conducted meta analysis with random effect model. One trial was showing statistically significant in systolic blood pressure (SBP) reduction[8] (Mean Difference (MD) -6.26 mmHg, 95% CI -11.29 to -1.23). The remaining 5 trials were showing no statistically significant SBP reduction. Furthermore, the pooled MD in these 6 trials is showing no statistically significant SBP reduction (MD -2.14 mmHg, 95% CI -4.72 to 0.44, P=0.1; Analysis 1).

In the diastolic blood pressure (DBP), heterogeneity was also present (I2 = 78%) and thus we used random effect in the meta analysis. Three trials were showing statistically significant in DBP reduction (MD -4 mmHg, 95% CI -5.73 to -2.27[15] MD -0.3 mmHg, 95% CI -0.47 to -0.13 [13]; MD -4.48; 95% CI -8.41 to -0.55.[8] The remaining 3 trials were showing no statistically significant in DBP reduction. Moreover, the pooled MD in these 6 trials is showing no statistically significant DBP reduction (MD -1.94 mmHg, 95% CI -4.21 to 0.33, P=0.09; Analysis 2). We also conducted subgroup and sensitivity analysis in further explanation below.

Lipid levels

Total cholesterol

Four trials (49099 participants) reported total cholesterol (TC) levels.[5,13,14,15] Heterogeneity was seen between trials (I2 = 98%). Hence, we used random effect to get the pooled MD. The polyphenol intervention was showing statistically significant TC levels reduction (MD -5.41 mg/dl, 95% CI -8.21 to -2.62, P=0.0001; analysis 3).

Low-density lipoprotein cholesterol

Three trials (48965 participants) reported low-density lipoprotein cholesterol (LDL-c) levels.[5,13,15] The high heterogeneity (I2 = 96%) between trials was shown so that we used random effect to the pooled MD. The pooled MD shows that there was no statistically significant LDL-c levels reduction with the polyphenol intervention (MD -6.5 mg/dl, 95% CI -16.7 to 3.66, P=0.21; analysis 4)

High-density lipoprotein cholesterol

Three trials (48965 participants) reported high-density lipoprotein cholesterol (HDL-c) levels.[5,13,15] Random effect was used due to the heterogeneity between trials (I2 = 99%). The pooled MD shows no statistically significant effect of polyphenol in increasing HDL-c levels (MD 1.92 mg/dl, 95% CI -0.57 to 4.42, P=0.13; analysis 5)

Triglycerides

Three trials (48965 participants) reported triglyceride (TG) levels.[5,13,15] There was high heterogeneity between these trials (I2 = 98%) and thus random effect is used to obtain the MD. There is no statistically significant effect of

polyphenol in reducing TG levels (MD -8.59 mg/dl, 95% CI -17.39 to 0.21, P=0.06; analysis 6)

Subgroup analyses

Subgroups of meta-analysis were conducted in systolic and diastolic blood pressure by grouping the trials, which only included women only and both men and women as participants (Analysis 7,8).

1. For trials which only included women as participants (2 trials[13,8]), there is no statistically significant effect on SBP reduction (MD -2.65 mmHg, 95% CI -8.59 to 3.3, P=0.38) and DBP reduction (MD-1.91 mmHg, 95% CI -5.9 to 2.08, P=0.35)
2. For trials which included men and women as participants (4 trials,[5,6,15,16] there is statistically significant effect on SBP reduction (MD -2.78 mmHg, 95% CI -5.47 to -0.08, P=0.04) and DBP reduction (MD -2.59 mmHg, 95% CI -4.84 to -0.34, P=0.02)
3. As stated above, the total pooled MD in these 6 trials showing no statistically significant effect both on SBP reduction (MD -2.14 mmHg, 95% CI -4.72 to 0.44, P=0.1) and DBP reduction (MD -1.94 mmHg, 95% CI -4.21 to 0.33, P=0.09)

Subgroup analyses were not done in other variables due to limitation amount of trials.

Sensitivity analysis

Sensitivity analyses on comparing the systolic and diastolic blood pressure with excluding the trials with risk of bias were done in this review (Analysis. By excluding 3 trials in which 2 trials have risk of blinding bias[5,8] and 1 trial has risk of other bias[6], the pooled MD is showing that polyphenol intervention has no statistically significant effect to reduce both SBP (fixed-effect (I2 = 19%), MD -0.11 mmHg, 95% CI -0.41 to 0.18, P=0.45)and DBP reduction (random-effect (I2 = 89%), MD -1.53 mmHg, 95% CI -4.73 to 1.67, P=0.35). This indicates no differences effect compared to analyses that do not exclude the study with risk of bias.

Adverse events

Only one trial did mention the adverse event of the polyphenol.[6] In this trial, the authors were using polyphenol-rich grape seed extract as the intervention. Moreover, headache, joint pain, allergic rhinitis, and nasopharyngitis were reported with low incidence. However, no statistically significant was found between two arms in terms of number of subjects experience adverse events. In addition, the other remaining trials did not report any adverse events and thus we conclude that polyphenol does not have serious adverse events.

Publication bias

Funnel plots to draw the possibility of publication bias were not done due to the limitation number of trials.

Discussion

Summary of main results

Seven Randomized Controlled Trials (RCT) were included in this review. Although all trials have different interventions, all the interventions are showing the polyphenol as the main contents. However, we only found one trial that reported clinical events as our primary outcomes.[13] Moreover, Howard paper also did not mention polyphenol as the interventions but we consider the increasing diet on fruit and grain on the intervention group as polyphenol intervention. Overall, this review shows that polyphenol intervention compared to placebo did not improve the cardiovascular outcome and most cardiovascular risk factors as surrogate outcome (Systolic and diastolic blood pressure, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level). Nevertheless, polyphenol intervention did reduce the total cholesterol level (MD -5.41 mg/dl, 95% CI -8.21 to -2.62, P=0.0001; analysis 3). In addition, by analyzing only the trials that involve men and women as participants, polyphenol intervention reduces both the systolic (MD -2.78 mmHg, 95% CI -5.47 to -0.08, P=0.04) and diastolic blood pressure (MD -2.59 mmHg, 95% CI -4.84 to -0.34, P=0.02).

Biological and clinical interpretation

Based only one trial, polyphenol intervention has no effect on reducing the cardiovascular event outcome and cardiovascular risk factors as surrogate outcomes. It only reduces the total cholesterol levels. However, consuming fruit, chocolate, and tea that contain polyphenol are believed for having beneficial effects in the body. Hence, the limitation of this study will be explained further in this review.

Limitations of the Study

We only searched the trials from two databases without did a hand search. Hence, we might not include other trials that should be included in this review. These few trials that included in meta analysis will implicate that this review is underpowered. We also only found one trial that has our primary outcome in included study and thus meta analysis of this outcome were not done.

Comparison to previous works

One review has been conducted by Harley et al.[17] This particular review used black tea and green tea as intervention whereas our review is using all polyphenol as intervention. Hartley paper concluded that both black and green tea reduced the blood pressures and low-density lipoprotein cholesterol. However, other surrogate endpoint or outcome cardiovascular (i.e. high-density lipoprotein cholesterol, total cholesterol, and triglyceride) also mentioned not to reducing by black and green tea intervention. In addition, Hartley paper stated that only small numbers of studies were involved in each analysis. Furthermore, the primary outcome of this study was to observe the cardiovascular and all cause mortality but no evidence or trial available to analyze them.

Applicability of findings

One trial that reported cardiovascular event outcome[13] only involved women as participants and thus the applicability to men population could not be concluded since women and men have differences in cardio-metabolic profile.[18] However, for surrogate endpoints or cardiovascular risk factors the results are varied. Subgroup analysis to examine the polyphenol effect in trial involving both men and women shows that polyphenol intervention reduces both systolic and diastolic blood pressure. Besides, there is large variability of baseline characteristic in each trial. Two trials involved participants who have high cardiovascular disease risks aged ≥55 year old.[5,14] Two trials involved participants who are on the pre or stage 1 hypertension.[6,8] One trial involved post menopause women only.[13] One trial involved hypertensive and obese participants.[15] And one remaining trial involved diabetic participants.[16] Therefore, to apply these results to different population is not certain. Moreover, all trials were conducted in developed countries and thus to generalize these results to population in other setting, for instance in developing countries is unclear. Nevertheless, this review shows that polyphenol does not have major adverse effect and thus the benefit outweighs the potential harm.

Future research directions

Although no adverse effects or harms present on this review, future research might be conducted to assess the harms of polyphenol. Nevertheless, it might be difficult to assess food or drink-containing polyphenol since people regularly consumes them. In addition, future review should be conducted with more databases included to reduce the heterogeneity as it is obviously visible on this review. Lastly, large randomized controlled trials by measuring clinical events as the outcome should be conducted since only one study available to assess this particular outcome.

Conclusion

This review shows that polyphenol intervention reduce total cholesterol level by 5.41mg/dl in daily uses but not in other surrogate endpoints or cardiovascular risk factors. Furthermore, subgroup analysis is showing that polyphenol intervention reduces both systolic and diastolic blood pressure by 2.78 mmHg and 2.59 mmHg respectively. However, further investigation should be conducted since this review has some limitations.

Figures of Analysis

Figure 4. Analysis 1 Forest plot of comparison: Reduction of systolic blood pressure (SBP) with polyphenol intervention compared to placebo (mmHg), outcome: SBP Reduction from the baseline.
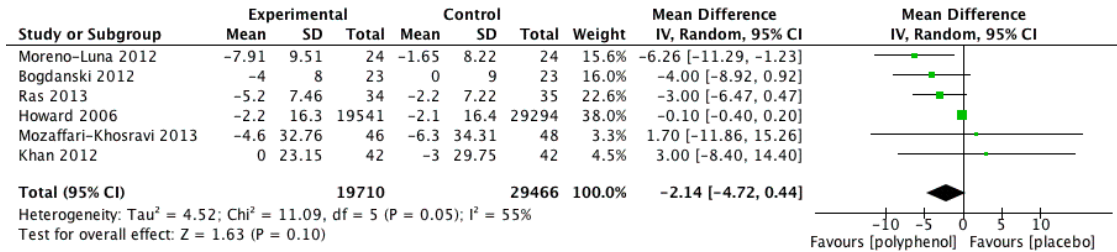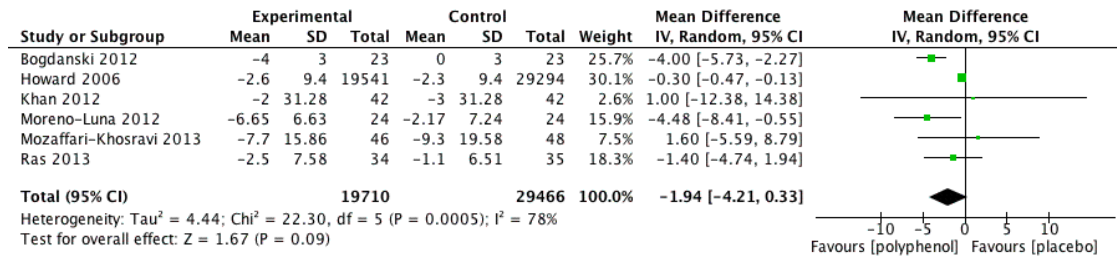

Figure 5. Analysis 2 Forest plot of comparison: Reduction of diastolic blood pressure (DBP) with polyphenol intervention compared to placebo (mmHg), outcome: DBP Reduction from the baseline.
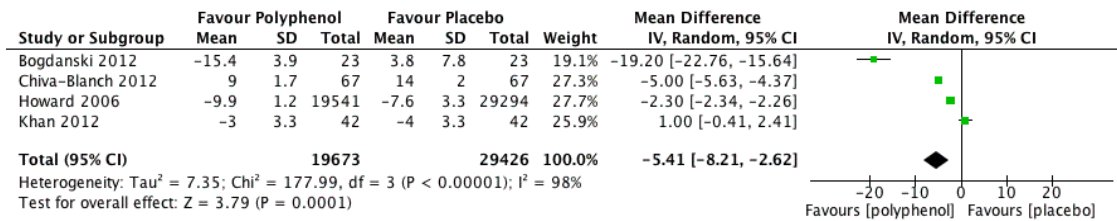

FIGURE 6. Analysis 3 Forest plot of comparison: Reduction of total cholesterol levels with polyphenol intervention compared to placebo (mg/dl), outcome: TC reduction from the baseline.
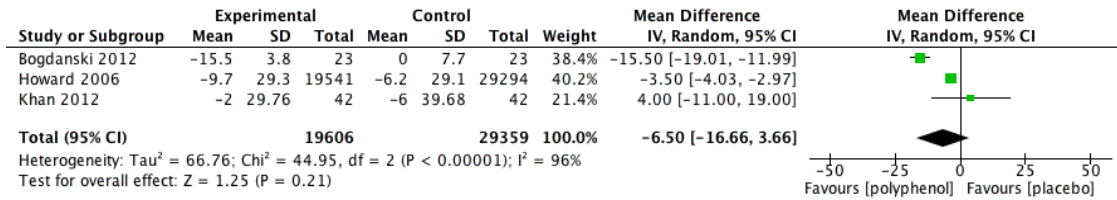
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bogdanski 2012	-15.5	3.8	23	0	7.7	23	38.4%	-15.50 [-19.01, -11.99]
Howard 2006	-9.7	29.3	19541	-6.2	29.1	29294	40.2%	-3.50 [-4.03, -2.97]
Khan 2012	-2	29.76	42	-6	39.68	42	21.4%	4.00 [-11.00, 19.00]
Total (95% CI)			19606			29359	100.0%	-6.50 [-16.66, 3.66]

Heterogeneity: Tau² = 66.76; Chi² = 44.95, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.25 (P = 0.21)

Figure 7. Analysis 4 Forest plot of comparison: Reduction of low density lipoprotein cholesterol levels with polyphenol intervention compared to placebo (mg/dl), outcome: LDL-c Reduction from the baseline
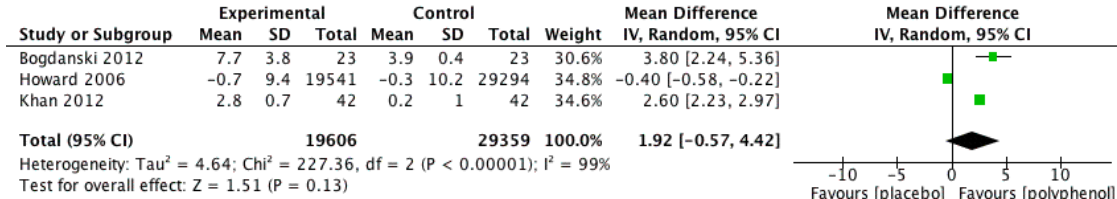
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bogdanski 2012	7.7	3.8	23	3.9	0.4	23	30.6%	3.80 [2.24, 5.36]
Howard 2006	-0.7	9.4	19541	-0.3	10.2	29294	34.8%	-0.40 [-0.58, -0.22]
Khan 2012	2.8	0.7	42	0.2	1	42	34.6%	2.60 [2.23, 2.97]
Total (95% CI)			19606			29359	100.0%	1.92 [-0.57, 4.42]

Heterogeneity: Tau² = 4.64; Chi² = 227.36, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.51 (P = 0.13)

Figure 8. Analysis 5 Forest plot of comparison: Increase of high density lipoprotein cholesterol levels with polyphenol intervention compared to placebo (mg/dl), outcome: HDL-c Increase from the baseline.
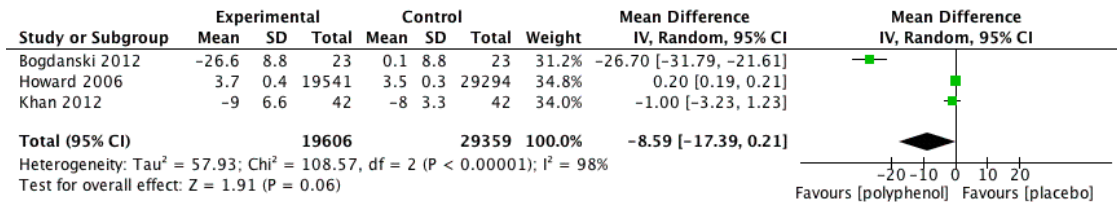
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bogdanski 2012	-26.6	8.8	23	0.1	8.8	23	31.2%	-26.70 [-31.79, -21.61]
Howard 2006	3.7	0.4	19541	3.5	0.3	29294	34.8%	0.20 [0.19, 0.21]
Khan 2012	-9	6.6	42	-8	3.3	42	34.0%	-1.00 [-3.23, 1.23]
Total (95% CI)			19606			29359	100.0%	-8.59 [-17.39, 0.21]

Heterogeneity: Tau² = 57.93; Chi² = 108.57, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.91 (P = 0.06)

Figure 9. Analysis 6 Forest plot of comparison: Reduction of trygliceride levels with polyphenol intervention compared to placebo (mg/dl), outcome: TG reduction from the baseline.
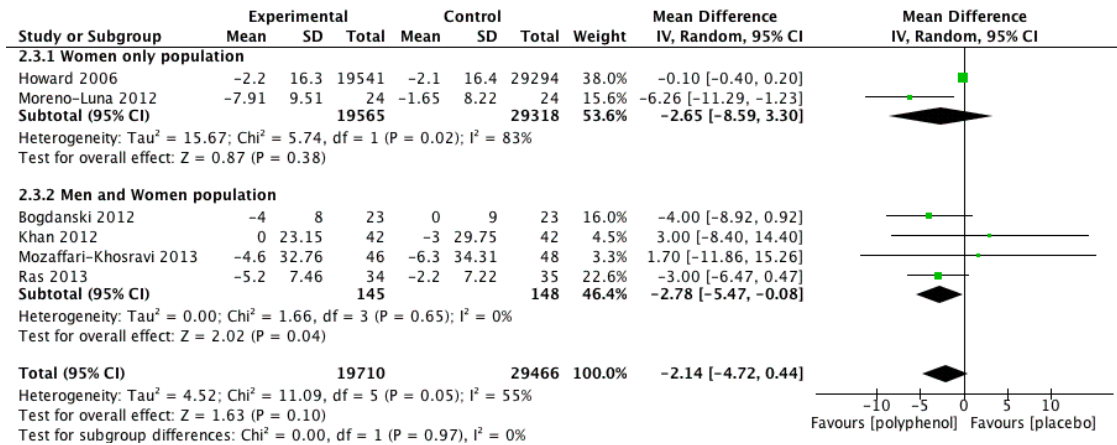
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Women only population								
Howard 2006	-2.2	16.3	19541	-2.1	16.4	29294	38.0%	-0.10 [-0.40, 0.20]
Moreno-Luna 2012	-7.91	9.51	24	-1.65	8.22	24	15.6%	-6.26 [-11.29, -1.23]
Subtotal (95% CI)			19565			29318	53.6%	-2.65 [-8.59, 3.30]
2.3.2 Men and Women population								
Bogdanski 2012	-4	8	23	0	9	23	16.0%	-4.00 [-8.92, 0.92]
Khan 2012	0	23.15	42	-3	29.75	42	4.5%	3.00 [-8.40, 14.40]
Mozaffari-Khosravi 2013	-4.6	32.76	46	-6.3	34.31	48	3.3%	1.70 [-11.86, 15.26]
Ras 2013	-5.2	7.46	34	-2.2	7.22	35	22.6%	-3.00 [-6.47, 0.47]
Subtotal (95% CI)			145			148	46.4%	-2.78 [-5.47, -0.08]
Total (95% CI)			19710			29466	100.0%	-2.14 [-4.72, 0.44]

Heterogeneity: Tau² = 15.67; Chi² = 5.74, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 0.87 (P = 0.38)

Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)

Heterogeneity: Tau² = 4.52; Chi² = 11.09, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%

Figure 10. Analysis 7 Forest plot of comparison: Reduction of systolic blood pressure (SBP) with polyphenol intervention compared to placebo (mmHg), outcome: Subgroup analysis in systolic blood pressure reduction
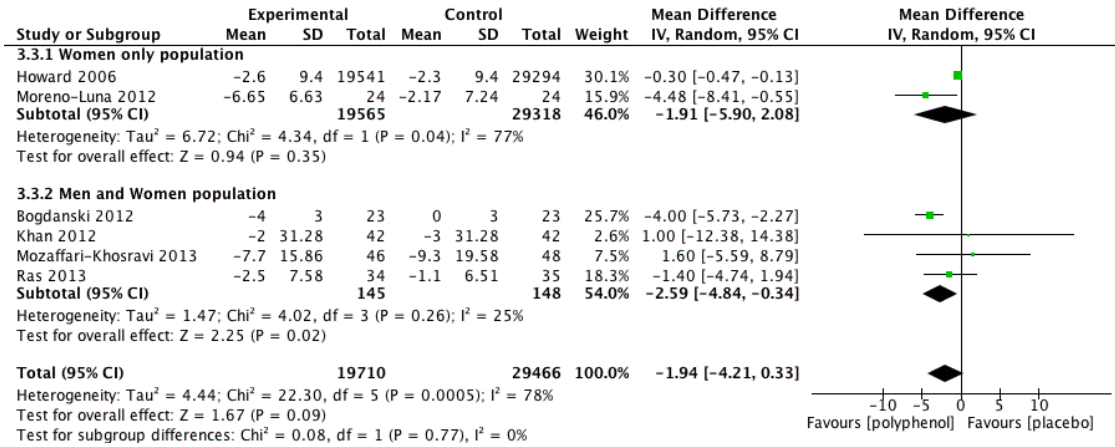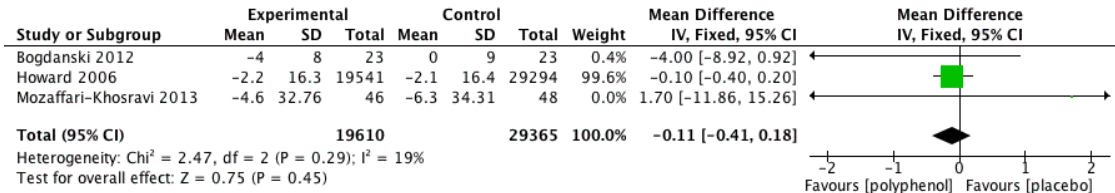
Figure 11. Analysis 8 Forest plot of comparison: Reduction of diastolic blood pressure (DBP) with polyphenol intervention compared to placebo (mmHg), outcome: Subgroup analysis in diastolic blood pressure reduction.

Figure 12. Analysis 9 Forest plot of comparison: Reduction of systolic blood pressure (SBP) with polyphenol intervention compared to placebo (mmHg), outcome: SBP Reduction excluding trials with bias
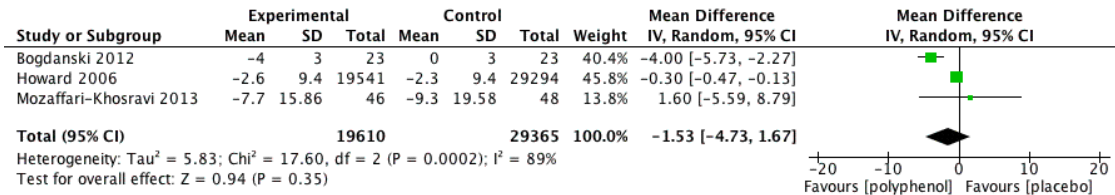

Figure 13. Analysis 10 Forest plot of comparison: Reduction of diastolic blood pressure (DBP) with polyphenol intervention compared to placebo (mmHg), outcome: DBP reduction excluding trials with bias.

Appendices

Appendix 1

Database: Ovid MEDLINE(R) <1946 to March Week 2 2020>

Search Strategy:

1. exp Cardiovascular Diseases/ (1846776)
2. coronary disease.tw. (11229)
3. unstable angina.tw. (10396)
4. stroke.tw. (131097)
5. acute coronary syndrome.tw. (9279)
6. myocardial infarction.tw. (123527)
7. 1 or 2 or 3 or 4 or 5 or 6 (1881674)
8. Phenols/ or exp Polyphenols/ (35083)
9. exp Phytoestrogens/ (7913)
10. wine.tw. (10678)
11. chocolate.tw. (2860)
12. tea.tw. (17426)
13. cocoa.tw. (1432)
14. grape.tw. (4955)
15. berry.tw. (1878)
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (75577)
17. randomized controlled trial.pt. (367081)
18. controlled clinical trial.pt. (87836)
19. randomized.ab. (266543)
20. placebo.ab. (143845)
21. drug therapy.fs. (1677126)
22. randomly.ab. (189718)
23. trial.ab. (275601)
24. groups.ab. (1222202)
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (3141971)
26. exp animals/ not humans.sh. (3903058)
27. 25 not 26 (2673042)
28. 7 and 16 and 27 (943)

Appendix 2. Table of baseline of the included studies

Study	Number of samples	Origin	Intervention	Control	Population	Mean of follow ups	Mean of age (years old)	Male (%)
Moreno-Luna 2012	24	Spain	Polyphenol-rich olive oil	Polyphenol-free olive oil	Women that were newly diagnosed with pre hypertension or stage 1 essential hypertension	4 months	26	0
Howard 2006	48835	United States	20% low-fat dietary pattern with increased vegetables, fruits and grains	Usual diet	Postmenopausal women aged 50-79 years were recruited and enrolled between 1993 and 1998 at 40 clinical centers across the US	8.1 years	62.3	0
Khan 2011	42	Spain	40g soluble cocoa with skimmed milk	Skimmed milk only	Patients with high cardiovascular disease risks aged ≥55 years old	4 weeks	69.5	45.2
Chiva Blanch2012	73	Spain	Red wine 30g alcohol/day or Same amount of polyphenols as red wine in the form of dealcoholized red wine (DRW)	Gin 30g alcohol/day	Patients with high cardiovascular disease risks aged between 55-75 years old	4 weeks	60	100
Ras 2013	70	Holland	300 mg/d of Grade Seed Extract	Placebo	Patients with systolic BP between 120 and 159 mmHg	8 weeks	63.7	54.3
Mozaffari-Khosravi 2013	100	Iran	Green tea infusion	Sour tea	Mildly hypertensive patients with diabetes	4 weeks	52.2	21.3
Bogdanski 2012	56	Poland	379 mg of GT extract (GTE)	Placebo	Obese and hypertensive subjects	3 months	50.4	50

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