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Effects of high phenolic olive oil on cardiovascular risk factors: A systematic review and meta-analysis

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ABSTRACT

Background: Cardiovascular diseases are the world's leading cause of death. Prevention by nutrition is an easy and effective approach especially by advising foods with nutraceutic properties like high phenolic olive oil (HPOO).
Aim: The aim of this review was to systematically access and meta-analyse the effects of HPOO on risk factors of the cardiovascular system and thusly to evaluate its use as a nutraceutical in prevention.
Data synthesis: Medline/PubMed, EMBase, the Cochrane Library, CAMbase and CAM-QUEST were searched through July 2013. Randomized controlled trials (RCTs) comparing high vs. low (resp. non) phenolic olive oils in either healthy participants or patients with cardiovascular diseases were included. For study appraisal the Cochrane Collaboration's risk of bias tool was used. Main outcomes were blood pressure, serum lipoproteins and oxidation markers. Standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated and analysed by the generic inverse variance methods using a random effects model. Eight cross over RCTs comparing ingestion (21–90 d) of high vs. low (resp. non) phenolic olive oils with a total of 355 subjects were included.
Results: There were medium effects for lowering systolic blood pressure ($n = 69$; SMD −0.52; CI −0.77/−0.27; $p < 0.01$) and small effects for lowering oxLDL ($n = 300$; SMD −0.25; CI [−0.50/0.00]; $p = 0.05$). No effects were found for diastolic blood pressure ($n = 69$; SMD −0.20; CI −1.01/0.62; $p = 0.64$); malondialdehyde ($n = 71$; SMD −0.02; CI [−0.20/0.15]; $p = 0.79$), total cholesterol ($n = 400$; SMD −0.05; CI [−0.16/0.05]; $p = 0.33$); HDL ($n = 400$; SMD −0.03; CI [−0.14/0.08]; $p = 0.62$); LDL ($n = 400$; SMD −0.03; CI [−0.15/0.09]; $p = 0.61$); and triglycerides ($n = 360$; SMD 0.02; CI [−0.22/0.25]; $p = 0.90$).
Limitations: The small number of studies/participants limits this review.
Conclusions: HPOO provides small beneficial effects on systolic blood pressure and serum oxidative status (oxLDL). HPOO should be considered as a nutraceutical in cardiovascular prevention.

Introduction

Cardiovascular diseases (CVDs) are still the leading causes of death in the world (WorldHealthOrganisation 2013). Risk factors like dyslipidaemias and hypertension are of significant importance for the pathophysiology of CVD (Foody 2006). The Mediterranean diet was found to be effective in the prevention and treatment of CVD (Finks et al. 2012). Olive oil as its primary source of fat is seen as a key factor of this diet (Bullo et al. 2011). The focus of research was set on fatty acids during the last decades. But besides the favourable high content in monounsaturated fatty acids (MUFA), olive oil contains a notable amount of active micro compounds. Among them the phenols oleuropein and (hydroxy-) thyrosol were identified as the most important active substances. These phenols are able to modulate cardiovascular pathogenesis specifically referring to its inflammative aspects (Cicerale et al. 2010; Urpi-Sarda et al. 2012).

Generally, there is clear evidence for the positive effects of MUFA as well as the negative effects of saturated fatty acids on the serum lipoprotein profile (Mensink and Katan 1992; Michas et al. 2014). Positive effects on serum lipids have also been found for olive oil in some studies without specific consideration of micro compounds (Williams 2001; Violante et al. 2009). Only high quality olive oils, sold as virgin or extra virgin olive oil, contain sufficient amounts of phenols. To preserve the phenols these oils must not be processed or refined e.g. filtered or washed (Covas et al. 2009). The bioavailability of the

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Table 1
Complete search strategy for PubMed.

Concept	Search strategy
Olive oil	"olive"[Title/Abstract] AND "oil"[Title/Abstract]
	AND
Cardiovascular risk factors	"Blood pressure"[Mesh] OR "Blood pressure"[Title/Abstract] OR "BP"[Title/Abstract] OR "RR"[Title/Abstract] OR "Lipoproteins"[Mesh] OR "HDL"[Title/Abstract] OR "LDL"[Title/Abstract] OR "Triglyceride*"[Title/Abstract] OR "oxidized LDL"[Title/Abstract] OR "oxLDL"[Title/Abstract] OR "ox-LDL"[Title/Abstract] OR "dimethylarginine" [Title/Abstract] OR "malondialdehyde"[mesh] OR "malondialdehyde" [Title/Abstract] OR "MDA" [Title/Abstract]
	AND
Cardiovascular or metabolic diseases or healthy subjects	"Cardiomyopathies"[MeSH] OR "Coronary Disease"[MeSH] OR "heart failure"[MeSH] OR "hypertension"[MeSH] OR "prehypertension"[MeSH] OR "Myocardial Ischemia"[MeSH] OR "Coronary Artery Disease"[Mesh] OR "peripheral arterial disease"[mesh] OR "CHD"[Title/Abstract] OR "Cardiomyopathy"[Title/Abstract] OR "Coronary Disease"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "hypertension"[Title/Abstract] OR "prehypertension"[Title/Abstract] OR "Myocardial Ischemia"[Title/Abstract] OR "CAD"[Title/Abstract] OR "Coronary Heart Disease"[Title/Abstract] OR "Coronary Artery Disease"[Title/Abstract] OR "peripheral arterial disease"[Title/abstract] OR "gene*"[Title/Abstract] OR "Metabolic Syndrome X"[Mesh] OR "Metabolic Syndrome"[Title/Abstract] OR "MetS"[Title/Abstract] OR "dyslipidemias"[Mesh] OR "dyslipidemia"[Title/Abstract] OR "hyperglycemia"[Mesh] OR "hyperglycemia"[Title/Abstract] OR "healthy subjects"[Title/Abstract] OR "Metabolic Syndrome X"[Mesh] OR "Metabolic Syndrome"[Title/Abstract] OR "MetS"[Title/Abstract] OR "insulin resistance"[Mesh] OR "insulin resistance"[Title/Abstract] OR "healthy subjects"[Title/Abstract]"

phenols is high after ingestion (Cicerale et al. 2010). It has been shown that the mentioned phenols affect the plasmatic oxidative status and several inflammative pathways. Investigated outcomes include NF-κB, MCP-1, TNF-α, oxidized LDL (oxLDL), malondialdehyde (MDA), asymmetric dimethylarginase (ADMA), IL-2 and 6 (Covas et al. 2009; Cicerale et al. 2010). Clinical trials found promising results like increase of the anti-inflammatory activities of PON1. More recently, inflammation related nutrigenomic effects turned into focus like lower postprandial expression of p65 or MCP-1 (Camargo et al. 2012).

To date several narrative reviews about olive oil and cardiovascular effects exist (Covas et al. 2009; Badimon et al. 2010; Bullo et al. 2011; Rees et al. 2013). All of them deliver an extensive overview about the topic, but none of them are systematic or include a meta-analysis. Hence the aim of this review and meta-analysis is to systematically assess and to summarize the state of knowledge about the effects of high phenolic olive oil on cardiovascular risk factors either in healthy human beings or in patients suffering from CVDs by analysing randomised controlled and cross over studies that compared the ingestion of low/no phenolic olive oil to HPOO.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009) and the recommendations of the Cochrane Collaboration (Furlan et al. 2011) were followed. A systematic review protocol was developed a priori and not modified after beginning of the review process. The review was not registered and provides therefore no registration number.

Eligibility criteria

Types of studies

Randomized controlled trials (RCTs) and randomized crossover studies were eligible. No language restrictions were applied.

Types of participants

Either healthy adults or adult patients with

- heart diseases namely heart failure, myocardial ischemia, cardiomyopathy and coronary (arterial) disease,
- peripheral vascular disease
- hypertension or prehypertension
- metabolic disorders namely metabolic syndrome, dyslipidaemia, hyperglycaemia

were eligible. No restrictions were made in sex, participants had to be at least 18.

Types of interventions

Studies that compared mid-term, semi long-term or long-term interventions with HPOO vs. low phenolic olive oil (LPOO) were included. Mid term was defined as $\geq$3 to $<$6 weeks, semi-long term as $\geq$6 weeks to $<$3 months and long term as $\geq$3 months. Low phenolic was defined as $\leq$5 mg/kg and high phenolic as $\geq$150 mg/kg.

Types of outcome measures

For inclusion, RCTs had to assess at least one primary outcome, i.e. blood pressure, lipids (total cholesterol, HDL, LDL, TG) or serum markers of oxidative status (e.g. oxLDL, malondialdehyde). Safety was defined as secondary outcome and assessed as adverse events or other reported items e.g. laboratory parameters.

Search methods

The following electronic databases were searched from their inception through July 23, 2014:

Medline/PubMed, EMBase, the Cochrane Library, CAMbase and CAM-QUEST. Search terms for cardiovascular and metabolic diseases or diagnoses were combined with search terms for cardiovascular risk factors (e.g. plasma lipoproteins) and search terms for olive oil. Table 1 shows the complete search strategy for PubMed.

The search strategy was adapted for each database as necessary. Reference lists of identified original articles or reviews were searched manually. Two review authors independently screened abstracts identified during the literature review and potentially eligible articles were read in full to determine whether they met the eligibility criteria.

Data extraction and management

Two authors independently extracted data on patients (e.g. age, gender, diagnosis), methods (e.g. randomization, allocation concealment), interventions (e.g. HPOO/LPOO, frequency, and duration), control interventions (e.g. phenols, frequency, duration), outcomes (e.g. outcome measures, assessment time points), and results. An a priori developed data extraction form was used. Discrepancies were discussed with a third review author until consensus was reached. If necessary, the study authors were contacted for additional information.

Risk of bias in individual studies

Risk of bias was assessed by two authors independently using the Cochrane risk of bias tool (Higgins et al. 2008). This tool assesses risk of