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Margaret Murray BNut(Hons), Aimee L Dordevic PhD, Maxine P Bonham PhD & Lisa Ryan PhD

Accepted author version posted online: 17 Apr 2017.

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Do marine algal polyphenols have antidiabetic, anti-hyperlipidaemic or anti-inflammatory effects in humans? A systematic review

Margaret Murray[1], BNut(Hons)

margaret.murray@monash.edu

Aimee L Dordevic[1], PhD

aimee.dordevic@monash.edu

Maxine P Bonham[1], PhD

maxine.bonham@monash.edu

Lisa Ryan[2], PhD

lisa.ryan@gmit.ie

1. Department of Nutrition & Dietetics, Monash University, VIC, Australia, 3168

2. Department of Natural Sciences, Galway-Mayo Institute of Technology, Galway, Ireland

Corresponding Author: Associate Prof Maxine Bonham

Department of Nutrition & Dietetics

Monash University

Level 1, 264 Ferntree Gully Rd

Notting Hill, VIC 3168

Australia

Phone: +61 3 9902 4272

Facsimile: +61 3 9902 4278

Email: maxine.bonham@monash.edu

Conflicts of interest: none to declare

Abstract

Cardiovascular disease and type 2 diabetes are leading causes of morbidity and mortality globally. Marine algal polyphenols have potential to reduce the risk of these conditions, however little is known about their impact in humans. This systematic review investigates the antidiabetic, anti-hyperlipidaemic and anti-inflammatory effects of marine polyphenols in humans. Scopus, Medline, PsychInfo, Embase and Cochrane Library databases were searched in November 2016. Eligible studies included 1) human adults, 2) marine polyphenol intervention, 3) blood lipid, glucose, insulin or inflammatory marker outcomes, and 4) were a randomised-controlled trial. One postprandial cross-over trial and four parallel design trials were included involving 271 adults. Analysis across studies was performed using Cohen's d effect sizes. Supplementation with polyphenol-rich extracts had small to medium positive effects on fasting blood glucose, total cholesterol and LDL-cholesterol; however, there is inadequate evidence as yet to confirm if

these are consistent effects. Further randomised-controlled trials should investigate polyphenols from *Ecklonia cava* and other macroalgal sources, to determine if there is a role for marine polyphenols in reducing the risk factors of chronic disease in humans.

(PROSPERO registration number CRD42015016890)

Key words

cardiovascular disease, diabetes, macroalgae, phlorotannin, polyphenol

Introduction

Obesity is a global epidemic, affecting over 600 million adults in 2014 (World Health Organization 2015a). In conjunction with the rise in obesity is an increased prevalence of physiological co-morbidities; hyperlipidaemia, hyperglycaemia and chronic inflammation, which have contributed to an increase in cardiovascular disease (CVD) and type 2 diabetes, two of the leading causes of morbidity and mortality around the world (Ridker et al. 2000, Wellen and Hotamisligil 2005, Greenberg and Obin 2006, O Keefe and Bell 2007, World Health Organization 2015a, World Health Organization 2015b, World Health Organization 2015c). While weight management is a successful treatment for reducing the risk of chronic diseases, long term maintenance of weight loss is challenging (Anderson et al. 1999, McGuire et al. 1999, Jeffery et al. 2000, Wing and Phelan 2005, Lang and Froelicher 2006, Christiansen et al. 2007). Therefore it is important to consider other strategies to prevent or manage type 2 diabetes and CVD.

Promising research from cell culture and animal models suggests that marine algal polyphenols may be effective in the prevention and management of such chronic diseases (Okada et al. 2004, Zhang et al. 2007, Jung et al. 2008, Yoon et al. 2008, Heo et al. 2009, Kim et al. 2009, Lee et al. 2009, Lee et al. 2010, Wijesekara et al. 2010, Nwosu et al. 2011, Yeo et al. 2012, Lee and Jeon 2013, Murugan et al. 2015, Murray et al. 2016). If they are also effective in humans, marine algal polyphenols have potential to be used as a functional food ingredient for health promotion and disease prevention (Murray et al. 2016). This is in line with trends that have shown an increase in

consumer preferences for natural and sustainable health products and an interest in marine-based products (Blandon et al. 2007, Mouritsen et al. 2013, Murugan et al. 2015).

Polyphenols are secondary metabolites produced by terrestrial plants and marine algae that show potential as moderators of the risk factors associated with CVD and type 2 diabetes (Wijesekara et al. 2010, Lee and Jeon 2013, Murugan et al. 2015). The health effects of terrestrial polyphenols in humans have been previously described (Higdon and Frei 2003, Hursel et al. 2009, Rains et al. 2011). This review focuses on polyphenols from marine algal sources, as the harsh environments (including exposure to varying light intensity, salinity, pressure and temperatures) in which marine algae thrive, means that they produce a variety of potent polyphenolic substances, which are not found in terrestrial plants (Hamed et al. 2015). A variety of polyphenols can be found in marine algae, the majority of which are classified as phlorotannins, a type of polyphenol that is unique to marine sources (Heffernan et al. 2015). Phlorotannins are commonly found in brown algae, and are the most significant contributor to the biological activity of the organism (Bocanegra et al. 2009, Wijesekara et al. 2010, Lee and Jeon 2013). Phlorotannins consist of phloroglucinol (1,3,5-tryhydroxybenzene) monomer units, linked together through the acetate-malonate pathway, and exist in a range of molecular sizes from 126Da to 650kDa (Bocanegra et al. 2009, Wijesekara et al. 2010, Lee and Jeon 2013).

Antidiabetic effects

Phlorotannins from the macroalgae genera *Alaria, Pulmaria, Ecklonia* and *Ascophyllum* have demonstrated antidiabetic effects, including the inhibition of α-amylase and α-glucosidase *in vitro* (Iwai 2008, Apostolidis and Lee 2010, Nwosu et al. 2011)*,* and the stimulation of basal

glucose uptake in 3T3-L1 adipocytes (Zhang et al. 2007). These effects have been replicated in streptozotocin-induced diabetic mice, resulting in reduced fasting blood glucose (FBG) levels and a lowered postprandial blood glucose response (Zhang et al. 2007). Furthermore, phlorotannins from the *Ecklonia cava* (*E. cava*) species have reduced postprandial blood glucose area under the curve (AUC), FBG, fasting plasma insulin, homeostatic model assessment of insulin resistance (HOMA-IR) and glycated haemoglobin (HbA1c) in obese (Park et al. 2012, Eo et al. 2015) and diabetic mice (Lee et al. 2012, Kang et al. 2013).

Anti-hyperlipidaemic effects

There is strong evidence from cell and animal models that marine algal polyphenols possess anti-hyperlipidaemic properties (Murray et al. 2016). Treatment with marine polyphenols inhibits the activity of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, a rate-controlling enzyme in the metabolic pathway that produces cholesterol (Yeo et al. 2012). Phlorotannins from *E. cava* have reduced total cholesterol (TC), triglyceride (TG) and free fatty acid levels in diabetic (Lee et al. 2012) and obese mice (Park et al. 2012, Eo et al. 2015), compared with placebo. Treatment with isolated eckol and dieckol, particular types of phlorotannin, also reduced TC, TG and low density lipoprotein cholesterol (LDL-C) levels in hyperlipidaemic rats (Yoon et al. 2008) and high fat diet-fed mice (Yeo et al. 2012).

Anti-inflammatory effects

Chronic inflammation is a key contributing factor to the long-term complications of diabetes (Elmarakby et al. 2010, Bahadoran et al. 2013, Roy et al. 2013, Jialal and Devaraj 2014, Roy et al. 2015) and increases the risk of CVD (Osiecki 2004, Willerson and Ridker 2004, Libby 2006,

Bahadoran et al. 2013). Phlorotannin-rich extracts have exhibited anti-inflammatory activity in LPS stimulated RAW 264.7 macrophages through a variety of mechanisms, including the inhibition of lipopolysaccharide (LPS)-stimulated nitric oxide production, the suppression of inducible nitric oxide synthase and cyclooxygenase 2 expression, and the reduction of tumour necrosis factor alpha and interleukin-6 secretion levels (Yang et al. 2014, Kang et al. 2015). Phlorotannin extracts have also inhibited the activity of inflammatory genes and reduced mRNA expression of acute and chronic inflammatory markers, and toll-like receptors (TLR4 and TLR9) in 3T3-L1 adipocytes (Kellogg et al. 2015). Similarly, phlorotannins, reduce inflammatory gene levels and macrophage marker f4/80 in obese mice (Park et al. 2012, Eo et al. 2015).

If the same antidiabetic, anti-hyperlipidaemic and anti-inflammatory effects observed in cell culture and animal models also occur in a human population, marine algal polyphenols may be useful as a functional food ingredient for the prevention and management of CVD and type 2 diabetes. This review of randomised controlled trials investigates the antidiabetic, anti-hyperlipidaemic and anti-inflammatory effects of marine polyphenols in humans, compared with placebo.

Method

This review was registered with PROSPERO International prospective register of systematic reviews (registration number CRD42015016890) and is reported in accordance with the PRISMA statement (available as eTable 1 in supporting information) (Moher et al. 2015).

Literature search

A literature search was carried out in April 2015 then updated in November 2015 and again in November 2016 in the Scopus, Medline, PsychInfo, Embase and Cochrane Library databases. Terms to describe the population (e.g. adult, human) and intervention (e.g. marine, phytochemical) were included in the search strategy (full search strategy available as eTable 2 in supporting information). No additional limits were added so as to not unnecessarily limit the search.

Criteria for inclusion in this review were: 1) a human adult (aged 18 or above) population, 2) marine algal polyphenol intervention, 3) included blood lipids, glucose, insulin or inflammatory markers as an outcome, 4) randomised-controlled trial (RCT) design, and 5) written in English. Due to the small number of eligible papers, studies both with and without dietary restriction were included, despite the potential for weight change to influence results, and there was no limit placed on study duration or follow up. Papers were excluded if they were not original research; if the population consisted of cell culture or animals; or if the polyphenol treatment product was not from a marine source.

Data extraction

Data extraction was performed independently by two authors (MM and LR) using a tool adapted from the National Health and Medical Research Council data extraction tool for RCT and cohort studies. Data regarding study design, intervention and control conditions, sample size, recruitment and allocation procedures, population characteristics, statistical analysis, follow up and relevant outcomes were extracted from each paper (example of data extraction available as eTable 3 in supporting information). The extracted data was then combined and checked for

consistency to ensure correct interpretation. No additional data was sought from the study authors.

Risk of Bias

The American Dietetic Association Quality Criteria Checklist was used to assess the quality of included studies (Academy of Nutrition and Dietetics 2012). Ten criteria were independently checked by two researchers (MM and LR) for which each paper was given either a 'yes', 'no' or 'NA' response (results of quality assessment available as eTable 4 in supporting information). Use of randomisation, research question, participant selection and comparability, description of intervention and control conditions, blinding, outcomes and measures used, handling of withdrawals, statistical analysis, and potential for bias from funding were all assessed to determine the risk of bias within each study. Studies were designated either a positive, neutral or negative rating based on the criteria. Four of the criteria had to be met for a study to receive a positive quality rating. The remaining six criteria contributed to the overall rating but were not compulsory for a positive rating to be assigned. Publication bias was not assessed as there were a limited number of papers identified published in this area.

Statistical Analysis

Cohen's *d* effect sizes were calculated using the reported sample sizes, means, and standard deviations pre- and post-intervention, to represent the magnitude of the change in outcomes following intervention, and allow for comparison between studies. A positive effect size indicates the intervention had the desired effect on the outcome; i.e. increased high density lipoprotein cholesterol (HDL-C), or decreased FBG; where ≥ 0.2 was considered a small effect,

≥ 0.5 a medium effect and ≥ 0.8 a large effect. For presentation of the biomarkers in tables 2 to 6, data from the original papers, where necessary, were converted to mmol/L or pmol/L to allow for easier comparison of results.

Results for postprandial blood glucose and insulin were only examined qualitatively due to the small number of papers reporting these outcomes. A meta-analysis was not possible in this review due to the heterogeneity across the studies (differences in polyphenol dosage, outcomes reported) and small number of eligible studies.

Results

Database searches identified 8116 articles. Following title and abstract screening, 34 full papers were retrieved and assessed for inclusion. Five papers were eligible for inclusion in the review. Figure 1 illustrates the flow of studies and reasons for exclusion of full papers.

Description of Included Studies

Four studies examined the antidiabetic effects of polyphenol-containing marine extracts in humans (Paradis et al. 2011, Shin et al. 2012, Hernandez-Corona et al. 2014, Lee and Jeon 2015) and three reported anti-hyperlipidaemic effects (Shin et al. 2012, Hernandez-Corona et al. 2014, Choi et al. 2015). No studies were identified that examined the anti-inflammatory effects of marine polyphenols in humans (Table 1).

One postprandial study was identified in which participants consumed a supplement containing 250 mg of a brown seaweed blend (*Ascophyllum nodosum (A. nodosum)* and *Fucus vesiculosus*

(F. vesiculosus)), with a minimum of 25 mg polyphenols (Paradis et al. 2011). The remaining four studies were 12 weeks to three months in duration, with no longer term follow up. Shin et al. (2012) tested an extract from *E. cava*, in doses of 72 mg polyphenols (low dose) and 144 mg polyphenols (high dose) daily. Lee and Jeon (2015) also tested an *E. cava* extract, at a dose which provided 690 mg polyphenols (of which 150 mg was dieckol) daily. Choi et al. (2015) administered a 400 mg *E. cava* extract, containing 32.8 mg dieckol, daily. Hernandez-Corona et al. (2014) did not specify which algal species their polyphenol product was obtained from, but used a commercially available supplement (F-fucoidan (500 mg), Green Foods, Swanson Health Products, Fargo, ND, USA) which contained 5% seaweed phenolics, equating to 25 mg of polyphenols daily.

Study populations ranged from 23 up to 97 participants (mean = 54) and included healthy weight, overweight and obese individuals (Table 1). Three studies required participants to be non-diabetic (Paradis et al. 2011, Shin et al. 2012, Hernandez-Corona et al. 2014), one study required participants to have a fasting plasma glucose level between 100 and 180 mg/dL (5.6 and 10.0 mmol/L) (Lee and Jeon 2015), and one study required participants to have elevated TC (>200 mg/dL (5.2 mmol/L)) or LDL-C (>110 mg/dL (2.8 mmol/L)) (Choi et al. 2015).

Three studies reported the use of a power calculation; Hernandez-Corona et al. (2014) was powered to detect a change in β-cell function, Paradis et al. (2011) to detect a change in postprandial blood glucose incremental AUC (iAUC), and Choi et al. (2015) to detect a change in TC level. No other studies described a power calculation. Completion rates across the studies were high. One study retained 100% of participants (Paradis et al. 2011). Shin et al. (2012) and

Hernandez-Corona et al. (2014) retained 91% and 76% of participants, respectively. Choi et al. (2015) and Lee and Jeon (2015) both reported that 79% of participants completed their studies. The quality of included studies was generally high, with studies assigned either a positive (Paradis et al. 2011, Shin et al. 2012, Hernandez-Corona et al. 2014, Choi et al. 2015) or neutral rating (Lee and Jeon 2015).

Risk of Bias

Of the four compulsory criteria to receive a positive rating, all studies met the requirements for comparability of participant groups at baseline, intervention and control conditions were described in adequate detail, and outcome measures were reliable and clearly defined. Only Lee and Jeon (2015) did not meet the criteria for the selection of study participants being free from bias, due to inadequate reporting of the procedure used to recruit and allocate participants, resulting in a neutral rating being assigned. Of the six non-compulsory criteria, all studies met the requirements for a clearly stated research question, handling of withdrawals, use of blinding, conclusion supported by results with limitations taken into consideration, and lack of bias due to study funding. Lee and Jeon (2015) and Shin et al. (2012) did not meet the criteria for statistical analysis due to the lack of a power calculation, however this did not alter their overall rating. Choi et al. (2015), Hernandez-Corona et al. (2014), Paradis et al. (2011), and Shin et al. (2012) received positive quality ratings.

Effect of marine polyphenols on postprandial blood glucose and insulin

Paradis et al. (2011) reported no differences between the treatment and placebo groups for each time point of postprandial blood glucose or insulin levels, and no difference in overall blood

glucose iAUC in normal-weight and overweight adults. However, a significant treatment x sequence interaction was observed; the group who received the placebo first followed by the intervention had a significantly lower blood glucose iAUC following consumption of the brown seaweed extract (94.0 (136.5) mmol/L/min) compared with placebo (181.9 (142.2) mmol/L/min). Baseline adjusted iAUC for plasma insulin was lower following the intervention (279.1 (29.7) $x10^2$ pmol/L/min) compared with placebo (317.5 (34.9) $x10^2$ pmol/L/min) (Paradis et al. 2011). Lee and Jeon (2015) examined two hour postprandial blood glucose response, following a standard meal of cooked rice, before and after 12 weeks intervention. Postprandial blood glucose response was reduced in the intervention group at week 12 (211.0 (46.9) mg/dL (11.7 (2.6) mmol/L)), compared with baseline (223.3 (37.1) mg/dL (12.4 (2.1) mmol/L)). Whereas in the placebo group, blood glucose response was higher at 12 weeks (226.0 (44.2) mg/dL (12.5 (2.5) mmol/L)) compared with baseline (216.4 (40.4) mg/dL (12.0 (2.2) mmol/L)).

Effect of marine polyphenols on fasting blood glucose and insulin

Hernandez-Corona et al. (2014) reported no significant change in FBG following three months of intervention in overweight and obese adults. Similarly, Lee and Jeon (2015) reported no change in FBG following 12 weeks of intervention. Shin et al. (2012) found their high dose (144 mg/day) intervention group significantly reduced FBG from baseline to post-intervention (12 weeks), however this change was not different from the non-significant reductions in FBG that were observed in the low dose (72 mg/day) and placebo groups. Effect sizes indicated a dose-response relationship between polyphenol supplement and FBG; no effects observed with placebo small effects with a low dose and a medium effect following a higher dose (Shin et al.

2012). However, effect sizes indicated a small effect on FBG following the intervention by Lee and Jeon (2015) despite this intervention using the highest dose (Table 2). Hernandez-Corona et al. (2014) reported a significant increase in fasting insulin level in overweight and obese adults following three months of intervention, compared with no change following placebo. However, effect size analysis showed a negative treatment effect following both the intervention and placebo, suggesting the increase in insulin may not have been as a result of the intervention. Lee and Jeon (2015) observed a significant reduction in fasting insulin level following 12 weeks of intervention, compared with no change following placebo.

Effect of marine polyphenols on blood lipids

Total cholesterol

Both Shin et al. (2012) and Choi et al. (2015) reported that TC levels were significantly reduced in overweight adults following 12 weeks of intervention with marine polyphenols, but not with placebo (Table 3). Whereas, Hernandez-Corona et al. (2014) reported no changes in TC levels after three months treatment in overweight and obese adults, although the calculated effect sizes indicated a positive treatment effect following both intervention and placebo.

High density lipoprotein cholesterol

Only the high dose intervention administered by Shin et al. (2012) resulted in increased serum HDL-C levels. However, effect sizes indicated small and medium positive treatment effects on HDL-C levels following the low dose and high dose interventions, respectively, suggesting a possible dose-dependent effect (Table 4). Conversely, HDL-C levels were reduced following

intervention by Choi et al. (2015) compared with no change following placebo. Hernandez-Corona et al. (2014) separated results for serum HDL-C levels according to gender. While no significant changes were identified for either gender following intervention or placebo, a small negative effect on HDL-C levels was calculated following the intervention in overweight and obese men.

Low density lipoprotein cholesterol

Changes in LDL-C were consistent across studies; Shin et al. (2012) Hernandez-Corona et al. (2014) and Choi et al. (2015) reported reduced LDL-C levels following supplementation, and these changes were significantly different to placebo after 12 weeks (Table 5). Effect sizes all indicated positive treatment effects following intervention, compared with no effect following placebo.

Triglycerides

No changes in TG levels were reported for any of the intervention or control groups (Shin et al. 2012, Hernandez-Corona et al. 2014, Choi et al. 2015). Effect size analysis indicated both positive and negative effects on TG levels following intervention (Table 6).

Discussion

Antidiabetic effects

Postprandial glycaemia

Maintaining fasting and postprandial blood glucose within normal ranges can help to prevent progression to type 2 diabetes (Lee et al. 2009). Through inhibition of the intestinal enzymes, α-amylase and α-glucosidase, that break down carbohydrates during digestion marine polyphenols influence postprandial glycaemia (Lee et al. 2009). Studies conducted *in vitro* (Lee et al. 2009, Nwosu et al. 2011) and in diabetic mice (Zhang et al. 2007, Heo et al. 2009) suggest that this occurs in a dose-dependent manner. In this review a reduction in postprandial blood glucose response was only observed following the intervention using the higher of the two doses (690 mg/day) (Lee and Jeon 2015), however there is currently inadequate evidence to establish whether or not a dose-response relationship exists in humans.

The two studies that assessed postprandial blood glucose in this review are not directly comparable as one was a single dose postprandial test (Paradis et al. 2011), whereas the other was a 12 week intervention with daily polyphenol supplementation and postprandial tests conducted at baseline and completion. The success of the latter study at improving postprandial blood glucose response may indicate that longer term supplementation with marine polyphenols is required to impact postprandial blood glucose in humans, although plant polyphenols have been shown to impact blood glucose acutely. A reduction in postprandial blood glucose iAUC was observed in a single dose postprandial cross-over study in humans using polyphenol-rich foods (green tea and berries) (Nyambe-Silavwe and Williamson 2016). This study also indicated a dose-response effect on postprandial blood glucose (Nyambe-Silavwe and Williamson 2016). It is more likely that the polyphenol dose, rather than the time period of supplementation, administered by Paradis et al. (2011) was insufficient to cause an effect on postprandial blood glucose.

A further difference between the two postprandial papers was that Lee and Jeon (2015) used a dieckol-rich *E. cava* extract which contained 46% polyphenols, whereas Paradis et al. (2011) used a blend of *A. nodosum* and *F. vesiculosus* which contained at least 10% polyphenols. Different types of polyphenols, from different sources, don't necessarily behave the same way in the body (Tsao 2010, Malik and Mukherjee 2014), which may explain why a reduction in postprandial blood glucose was observed following the intervention by Lee and Jeon (2015) but not Paradis et al. (2011). *E. cava* is currently the most extensively investigated source of marine polyphenols for anti-hyperglycaemic effects and has shown the most promise in this area (Kang et al. 2010, Lee et al. 2012, Park et al. 2012, Shin et al. 2012, Kang et al. 2013, Eo et al. 2015, Lee and Jeon 2015, Murray et al. 2016). Furthermore, Lee and Jeon (2015) involved participants with a high baseline fasting blood glucose level (100 to 180 mg/dL), whereas Paradis et al. (2011) examined healthy subjects. This may also have affected the magnitude of the change in postprandial blood glucose caused by polyphenol supplementation.

In vitro research suggests that marine algal polyphenols may be more effective than acarbose, a diabetic drug, at inhibiting α-amylase and α-glucosidase (Heo et al. 2009, Apostolidis and Lee 2010). In order to establish the therapeutic effects of marine polyphenols on glycaemic control further research to investigate an effective polyphenol dose, treatment time frame, and marine algal source is warranted.

Fasting blood glucose

There were mixed results for FBG in this review. Effect size analysis suggested a dose-dependent relationship, with effect sizes increasing from no effect to a medium effect with

increasing dose (25 mg, 72mg and 144mg polyphenols/day) (Shin et al. 2012, Hernandez-Corona

et al. 2014). However, in contrast, there was no significant improvement in FBG following the

highest dose of polyphenols (690 mg/day from *E. cava* extract) (Lee and Jeon 2015). These

results suggest a limit to the dose-response effect on FBG levels, and may indicate a saturation

effect and upper limit for an effective dose, as was observed with doses over 500 mg

polyphenols/day from dark chocolate on FBG, in fourteen overweight and obese adults

(Almoosawi et al. 2010). Furthermore, the participants in the two studies in which the dose-

dependent relationship was consistent were overweight/obese but otherwise healthy (Shin et al.

2012, Hernandez-Corona et al. 2014), whereas Lee and Jeon (2015) used participants with a

raised baseline fasting plasma glucose level. These metabolic differences mean that these two

populations may respond differently to different doses of marine polyphenols and therefore

should not be directly compared. However, the difference in reduction in FBG levels between

Shin et al. (2012) and Lee and Jeon (2015) was only approximately 0.1 mmol/L; with a reduction

of approximately 0.2 mmol/L observed by Shin et al. (2012) (5.6 mmol/L to 5.4 mmol/L) and 0.1

mmol/L observed by Lee and Jeon (2015) (7.0 mmol/L to 6.9 mmol/L). Furthermore, impaired

fasting glucose is categorised as a FBG level of 6.1 mmol/L to less than 7 mmol/L (Diabetes

Australia 2009), so a reduction in FBG from 7.0 to 6.9 mmol/L would change the diagnosis from

type 2 diabetes to pre-diabetes. Whereas, from 5.6 to 5.4 mmol/L the diagnosis remains as

diabetes unlikely (Diabetes Australia 2009). Marine polyphenols show potential for improving

FBG levels in humans, however further investigation is required to determine if there is a

consistent dose-response pattern and to identify the threshold for an effective treatment dose in a

clinical population.

Fasting insulin

Conflicting effects on fasting insulin levels were observed following marine polyphenol supplementation. Fasting insulin increased following three months of supplementation with a low dose of polyphenols (25mg/d) (Hernandez-Corona et al. 2014), whereas with a high dose (690mg/d) it decreased (Lee and Jeon 2015). While inconsistent with each other, these results do reflect the changes in FBG observed in each of the studies; Hernandez-Corona et al.(2014) reported a non-significant increase in FBG and an increase in fasting insulin levels; Lee and Jeon (2015) reported a non-significant reduction in FBG and a reduction in fasting insulin levels. Treatment with marine polyphenols has successfully reduced fasting insulin levels alongside reduced FBG levels in both healthy and type 2 diabetic mice, however the doses administered to mice were much larger than those given to humans (Murray et al. 2016). This may indicate that the lower dose identified here was insufficient to cause a reduction in fasting insulin levels, especially considering that an increase in fasting insulin was also observed in the control group (Hernandez-Corona et al. 2014).

Another factor that may have influenced the effect on fasting insulin is that the high-dose supplement was a dieckol-rich *E. cava* extract (46% polyphenols) (Lee and Jeon 2015), whereas the product used by Hernandez-Corona et al. (2014) was from a non-specific source and contained only 5% polyphenols. *E. cava* is a well investigated source of marine polyphenols, with evidence for its antidiabetic effects, including reduction of fasting blood insulin levels, in multiple animal studies (Kang et al. 2010, Lee et al. 2012, Park et al. 2012, Kang et al. 2013, Eo et al. 2015). The present results, alongside evidence from animal models suggest that high doses

of marine polyphenols from *E. cava* show potential for reducing fasting insulin levels in humans (Lee et al. 2012, Kang et al. 2013). However, further research in humans is required to determine whether there is a consistent effect. The identification of an effective dose threshold also requires further investigation.

Anti-hyperlipidaemic effects

A defining characteristic of obesity is dyslipidaemia; elevated levels of LDL-C and TG in the blood, and reduced HDL-C (National Institutes of Health 1998, National Institutes of Health 2013). A key preventative measure for reducing the risk of CVD is to lower TC levels, LDL-C and TG levels in the blood (World Health Organization 2015b).

Total cholesterol

A possible dose-response relationship exists between marine polyphenol supplementation and improvements in TC. The highest dose of polyphenols elicited the largest improvement in TC levels (Shin et al. 2012), with lower doses eliciting small improvements, although in no particular order. Small to medium positive effects were observed on TC levels across all four intervention groups, with significant reductions reported for three intervention groups. These results are supported by evidence from animal models which show fairly consistent reductions in TC levels following treatment with marine polyphenols (Murray et al. 2016). Interestingly, in this review, the smallest effect on TC levels was observed in participants with high baseline cholesterol levels (Choi et al. 2015), whereas larger effects were seen in studies with overweight and obese participants who had healthy fasting TC levels at baseline (Shin et al. 2012, Hernandez-Corona et al. 2014). A similar phenomenon was seen in regard to FBG levels, where

the effect was diminished in a population with raised baseline FBG levels. It is unclear why

marine algal polyphenol supplementation may be less effective at reducing TC and FBG in

clinical human populations than healthy human populations. Future research should focus on

clinical human populations as it is in this population group that a supplement would be of most

use. While supplementation with marine algal polyphenols has shown fairly consistent

reductions in TC level in humans in this review, before any health recommendations can be

made, additional research is required to prove that this effect is consistent.

HDL cholesterol

A significant increase in HDL-C levels, following marine polyphenol intervention, was only

observed by Shin et al. (2012). Effect size analysis indicated small positive effects on HLD-C

following the control, but not intervention, condition in studies by Choi et al. (2015) and

Hernandez-Corona et al. (2014) These inconsistent results suggest that no conclusions can be

made about the ability of marine polyphenols to increase HDL-C. However, the goal of treatment

for dyslipidaemia is to achieve an HDL-C level of greater than 1.0 mmol/L (Dietitians

Associaiton of Australia 2006, National Heart Foundation of Australia and the Cardiac Society

of Australia and New Zealand 2012), and all of the included studies reported mean baseline

HDL-C levels of 1.0 mmol/L or above, indicating already healthy levels of HDL-C.

Furthermore, the reported mean HDL-C levels remained quite stable throughout the

interventions, only changing up or down by about 0.1 mmol/L. So although marine polyphenol

supplementation did not increase HDL-C levels in these human studies, *in vitro* and animal

model evidence suggest it does have an effects on lipid regulation and blood lipid levels (Murray

et al. 2016), so it would be inappropriate to conclude no effect on HDL-C as yet with so little research available.

LDL cholesterol

In the present review, a reduction in LDL-C levels was consistently observed following 3 months of marine polyphenol supplementation, compared with placebo (Shin et al. 2012, Hernandez-Corona et al. 2014, Choi et al. 2015). This finding is in line with evidence from *in vitro* and *in vivo* studies that show LDL-C lowering effects following marine polyphenol supplementation (Yoon et al. 2008, Yeo et al. 2012). The results suggest that a saturation effect occurred at the doses given in the present studies, as all studies observed similar effects on LDL-C despite the highest dose of polyphenols (144 mg/day (Shin et al. 2012)) being almost six times larger than the lowest dose (25 mg/day (Hernandez-Corona et al. 2014)). Further research is required to determine the lowest effective dose and most effective source of marine polyphenols for reducing LDL-C levels in humans. There is as yet inadequate evidence to make recommendations on the use of marine polyphenols for LDL-C reduction, further human trials are required to confirm a consistent effect.

Triglycerides

In hyperlipidaemic rats and mice treatment with marine polyphenols reduced circulating TG levels (Yoon et al. 2008, Yeo et al. 2012) with the observed change being comparable to existing drug treatments (Yoon et al. 2008). However, in humans, TG levels were not improved from baseline following three months of treatment, and effect size analysis indicated small effects in both positive and negative directions. This may be due to the short term effects of dietary intake

on TG levels (diet was not controlled by Shin et al. (2012) or Choi et al. (2015)) or inadequate doses of polyphenols to elicit an effect (the largest dose was 144 mg polyphenols/day (Shin et al. 2012)). Both Hernandez-Corona et al. (2014) and Shin et al. (2012) enrolled participants with healthy fasting TG levels at baseline so a further reduction may not have been expected. However, participants in the study by Choi et al. (2015) had very high fasting TG levels at baseline, and yet an increase of 1.1 mmol/L was seen following supplementation. Findings from the present review suggest that it is unlikely that marine polyphenols reduce TG levels in humans, however conclusions should not be made until further quality research in humans has been conducted, controlling for the short term effects of diet.

Limitations

There were a number of limitations both across and within studies in this review. The source of the extract as well as the type of polyphenol present varied across studies and may have influenced the effectiveness of the interventions, due to variations in structure and mechanism of action (Tsao 2010, Malik and Mukherjee 2014). Four of the five studies reported the source of their extract (Paradis et al. 2011, Shin et al. 2012, Choi et al. 2015, Lee and Jeon 2015), but only two reported details of the specific polyphenols present (Choi et al. 2015, Lee and Jeon 2015). A further limitation was the variability in population characteristics, with non-diabetic populations (Paradis et al. 2011, Shin et al. 2012, Hernandez-Corona et al. 2014), populations with raised FBG (Lee and Jeon 2015) or raised cholesterol (Choi et al. 2015), and healthy weight (Paradis et al. 2011), overweight (Paradis et al. 2011, Shin et al. 2012, Hernandez-Corona et al. 2014) and obese participants (Hernandez-Corona et al. 2014) included across the studies. Additionally, a

small amount of weight loss (approximately 1-3% of total body weight) was observed in two studies (Shin et al. 2012, Hernandez-Corona et al. 2014), which is a confounding factor for the outcomes of interest. Due to the small number of included studies it was difficult to determine whether the participant characteristics or weight loss influenced the outcomes, however all studies included a comparable control which should account for differences in population characteristics. Further limitations are the small sample sizes of the included RCTs (minimum 23 participants, maximum 97 participants) and lack of investigation of the effects of marine polyphenols on inflammation in humans. These limitations should provide guidance to future research studies as to areas in which study designs and reporting can be improved to enhance the quality of evidence in this field. Such studies should include acute investigation of the effects of marine polyphenols on postprandial glycaemic responses, and longer term studies to investigate the effects of chronic supplementation on FBG and cholesterol levels.

Future Applications

Marine polyphenols may be useful as a functional food ingredient or nutrition supplement for the management or prevention of hyperglycaemia and hyperlipidaemia in humans, to prevent the progression of diseases like type 2 diabetes and CVD. A small amount of evidence in mice and rats has shown that these products are as effective as current drug treatments for reducing serum TC, LDL-C, and TG levels (Zhang et al. 2007, Yoon et al. 2008) and postprandial hyperglycaemia (Heo et al. 2009). This review indicated that marine polyphenols may also be effective at reducing FBG levels, TC and LDL-C levels in humans, with the most promising research involving polyphenols from the brown macroagla *Ecklonia cava*. Marine nutraceuticals

are of particular relevance given the current consumer preference for natural health products and functional foods (Wijesekara et al. 2010, Lee and Jeon 2013), and the ongoing rise in obesity and chronic disease prevalence (Ridker et al. 2000, Wellen and Hotamisligil 2005, Greenberg and Obin 2006, O'Keefe and Bell 2007, World Health Organization 2015a, World Health Organization 2015b, World Health Organization 2015c). Furthermore, the marine environment is an abundant and sustainable source of biologically active compounds (Kim 2013), making marine ingredients a good candidate for commercialisation. With the global functional food market rapidly expanding (Abu-Ghannam and Cox 2014, Mordor Intelligence 2016) and a growing interesting marine products (Murugan et al. 2015), it is vital that research is carried out to investigate the efficacy of such products, including marine algal polyphenols, for disease prevention and management in humans.

Conclusion

Findings from this review indicate that polyphenol-rich marine extracts may help to reduce FBG levels, TC and LDL-C levels in humans. However there is inadequate evidence as yet to confirm if these are consistent effects. Findings for postprandial blood glucose, fasting insulin, HDL-C and TG levels were inconsistent. Due to the limited number of studies it is difficult to make conclusions about how the dosage and the source of polyphenols may have influenced the effectiveness. However, *E. cava* extracts appeared to be more effective at influencing postprandial blood glucose, FBG and fasting insulin than extracts from other sources in this review. Marine polyphenols, particularly from *E. cava*, show potential as natural functional ingredients for the prevention and management of type 2 diabetes and CVD. However further

high quality RCTs are required to determine the most effective dose, treatment schedule and macroalgal source to produce consistent effects on glycaemia and dyslipidaemia in humans.

Acknowledgements

Declaration of Interest

The authors have no conflicts of interest to declare.

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Table 1 Study design, population, intervention and control conditions, duration and outcomes measures of studies

Study (author, year, location)	Study Design, Quality Rating	Population	Intervention	Control	Duration	Outcome Measures
Choi et al. (2015) Korea	Double-blind, placebo-controlled, randomised clinical trial. Positive	63 healthy men and women aged 19 to 80, total cholesterol >200 mg/dL or LDL-cholesterol >110 mg/dL	Oral dose of 200 mg *Ecklonia cava* extract (8.2% dieckol) twice daily. Consumed in a 600 mg capsule containing 200 mg *E. cava* extract, 100 mg dextrin, 270 mg crystallised cellulose, 6 mg silicon dioxide, 6 mg magnesium stearate, 18 mg coating with HPMC. Participants asked to maintain usual lifestyle patterns and were prohibited from taking other functional foods or dietary supplements.	Placebo capsule containing 120 mg dextrin, 426 mg crystallised cellulose, 3 mg silicon dioxide, 3 mg magnesium stearate, 30 mg caramel.	12 weeks	Total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), Triglycerides (mg/dL)
Hernandez-Corona et al. (2014) Mexico	Double-blind, placebo-controlled, randomised clinical trial. Positive	25 overweight or obese (BMI 25-34.9 kg/m^2) adults. Non-smokers with stable weight for past 3 months	Oral dose of 500 mg F-fucoidan (5% seaweed phenolics), extracted from marine brown algae, once daily before breakfast. Participants were asked not to alter their normal exercise habits and were given general recommendations regarding their medical nutrition therapy. Three days prior to testing an isocaloric diet containing 250 g of CHO/day was provided. Testing was conducted at 8:00am following a 12 hour fast.	Placebo, with all other treatment identical	Three months	Fasting plasma glucose (mmol/L), Fasting plasma insulin (pmol/L), Total cholesterol (mmol/L), HDL cholesterol (mmol/L), LDL cholesterol (mmol/L), Triglycerides (mmol/L)
Lee and Jeon (2015) Korea	Double-blind, placebo-controlled, randomised clinical trial. Neutral	63 men and women aged 20 to 65, fasting plasma glucose between 100 and 180 mg/dL	Oral dose of 500 mg *E. cava* extract containing 230 mg polyphenols (including 50 mg dieckol) consumed three times daily. Energy and food intake was not limited throughout the study, although *E. cava* supplements, adrenocorticosteroid hormone, insulin and anti-hyperglycaemic agents were prohibited. Participants were asked to maintain usual diet and physical activity.	Comparable in all characteristics to the extract tablet	12 weeks	2 hour postprandial glucose (mg/dL), Fasting plasma glucose (mg/dL), Fasting plasma Insulin µU/mL
Paradis et al. (2011) Canada	Double-blind, placebo-controlled, cross-over randomised clinical trial. Positive	23 women and men aged 18 to 60, non-smokers, with BMI 20-30 kg/m^2	Single dose of 508 mg of InSea2 capsule, comprising 250 mg of a brown seaweed extract containing at least 10% polyphenols, plus fibres and minerals, 100 mg microcrystalline cellulose, 150 mg calcium phosphate dibasic, 5 mg magnesium stearate, 3 mg croscarmellose. Two 3 hour meal tolerance tests taken one week apart following 48 hours of avoiding intense physical activity and a	Placebo capsule containing 191 mg microcrystalline cellulose, 287 mg calcium phosphate dibasic, 25 mg caramel	Three hours post-prandial	Glucose iAUC (mmol/L) (3 hours postprandial), Insulin iAUC (pmol/L/min)

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			12 hour overnight fast. Capsules were consumed 30 minutes before test meal. Test meal consisted of 4 slices white bread (110 g) plus water (up to 500 mL) providing 50 g of available CHO. This had to be consumed within 7 minutes. Volunteers were asked to avoid health products/drugs that influence digestive enzyme activity for duration of study, including 2-week run in period.	(colour), 5 mg magnesium stearate. Participants received same protocol for placebo as for active treatment		
Shin et al. (2012) Korea	Double-blind, placebo-controlled, randomised clinical trial. Positive	97 women and men aged 19-55 years, with BMI 24-29 kg/m^2	246 mL test drink containing 72 mg *E. cava* polyphenols (ECP) (containing 98.5% phloroglucinol equivalents), 10 g fructose, 0.65 g dextrin, 12 mg of sucralose, 0.15 g sodium chloride, 0.6 g citric acid, 0.15 g vitamin C, lemon flavour. Two different intervention groups: low dose -- 72 mg per day, high dose -- 144 mg per day. Groups consumed either one test + one placebo drink or two test drinks daily. It was recommended that drinks be consumed between meals for compliance. Participants were prohibited from taking medications or health products that influence metabolism and instructed to maintain their normal diet and physical activity.	Test drink without ECP, delivered in identical cans, except for a serial number on the bottom. They could not be differentiated by taste. All other treatment was the same as intervention group - two cans of placebo drink were consumed daily.	12 weeks	Fasting plasma glucose (mg/dL), Total cholesterol (mg/dL), HDL cholesterol (mg/dL), LDL cholesterol (mg/dL), Triglycerides (mg/dL)

BMI -- Body Mass Index

CHO -- Carbohydrates

ECP -- Ecklonia Cava Polyphenols

HPMC -- Hydroxypropyl Methyl Cellulose

iAUC -- Incremental area under the curve

NHMRC -- National Health and Medical Research Council

Table 2 The effect of marine polyphenol-containing supplements on fasting blood glucose and fasting insulin over 3 months compared to placebo in humans

Outcome	Author, Year	Polyphenol dose	Intervention				Placebo			
			n	Pre Mean (SD)	Post Mean (SD)	Effect size (95% C.I.)	n	Pre Mean (SD)	Post Mean (SD)	Effect size (95% C.I.)
Fasting blood glucose (mmol/L)	Lee and Jeon (2015)	690 mg/day	32	7.0 (0.8)	6.9 (1.0)	**0.20 (-0.29, 0.70)**	31	7.2 (0.9)	7.2 (1.0)	-0.03 (-0.53, 0.46)
	Hernandez-Corona et al. (2014)	25 mg/day	13	5.0 (0.5)	5.1 (0.7)	-0.16 (-0.93, 0.61)	12	5.1 (0.4)	5.1 (0.3)	0.00 (-0.80, 0.80)
	Shin et al. (2012)	72 mg/day	33	5.6 (0.5)	5.4 (0.6)	**0.34 (-0.14, 0.83)**	32	5.6 (0.5)	5.5 (0.6)	0.10 (-0.39, 0.60)
	Shin et al. (2012)	144 mg/day	32	5.6 (0.5)	5.5 (0.6)	**0.55 (0.05, 1.05)***	As above			
Fasting insulin (pmol/L)	Hernandez-Corona et al. (2014)	25 mg/day	13	60.6 (24.0)	78.6 (32.4)	**-0.63 (-1.4, 0.16)**	12	87.0 (40.2)	108 (60.6)	**-0.41 (-1.21, 0.40)**
	Lee and Jeon (2015)	690 mg/day	32	58.3 (38.2)	45.8 (27.1)	**0.38 (-0.12, 0.87)**	31	52.8 (35.4)	50.0 (44.4)	0.07 (-0.43, 0.57)

SD -- standard deviation

95% C.I. -- 95 per cent confidence interval

* significant effect size

Effect sizes were calculated on raw data reported by studies (mg/dL and mmol/L for glucose, μU/mL or pmol/L for insulin). All results in tables have been converted to mmol/L or pmol/L for the purpose of comparison. **Bold** typeface indicates an effect size of small or greater. Pre data taken from baseline. Post data taken from end of study; all studies were either 12 weeks or three months in duration.

Table 3 The effect of marine polyphenol-containing supplements on total cholesterol level over 3 months compared with

placebo in humans

Outcome	Author, Year	Polyphenol dose	Intervention				Placebo			
			n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)	n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)
Total cholesterol (mmol/L)	Choi et al. (2015)	32.8 mg/day	33	11.5 (1.3)	11.2 (1.1)	**0.26 (-0.22, 0.75)**	30	11.2 (1.0)	11.6 (1.3)	**-0.32 (-0.82, 0.19)**
	Hernandez-Corona et al. (2014)	25 mg/day	13	5.1 (0.5)	4.9 (0.5)	**0.40 (-0.38, 1.18)**	12	5.2 (0.6)	5.1 (0.4)	**0.20 (-0.61, 1.00)**
	Shin et al. (2012)	72 mg/day	33	5.3 (1.1)	5.0 (1.0)	**0.36 (-0.13, 0.84)**	32	5.2 (1.0)	5.2 (0.9)	-0.01 (-0.50, 0.48)
	Shin et al. (2012)	144 mg/day	32	5.2 (0.9)	4.8 (0.8)	**0.59 (0.09, 1.09)***	As above			

SD -- standard deviation

95% C.I. -- 95 per cent confidence interval

* significant effect size

Effect sizes were calculated on raw data reported by studies (mg/dL and mmol/L). All results in tables have been converted to

mmol/L for the purpose of easier comparison. **Bold** typeface indicates an effect size of small or greater. Pre data taken from

baseline. Post data taken from end of study; all studies were either 12 weeks or three months in duration.

Table 4 The effect of marine polyphenol-containing supplements on HDL cholesterol level over 3 months compared to placebo in humans

Outcome	Author, Year	Polyphenol dose	Intervention				Placebo			
			n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)	n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)
HDL cholesterol (mmol/L)	Choi et al. (2015)	32.8 mg/day	33	2.7 (0.4)	2.7 (0.4)	-0.12 (-0.36, 0.61)	30	2.7 (0.5)	2.8 (0.5)	**0.31 (-0.82, 0.20)**
	Hernandez-Corona et al. (2014) women	25 mg/day	10	1.2 (0.3)	1.2 (0.3)	0.00 (-0.88, 0.88)	9	1.1 (0.1)	1.1 (0.1)	0.00 (-0.92, 0.92)
	Hernandez-Corona et al. (2014) men	25 mg/day	3	1.1 (0.1)	1.0 (0.3)	**-0.45 (-2.07, 1.17)**	3	1.1 (0.2)	1.2 (0.3)	**0.39 (-1.22, 2.01)**
	Shin et al. (2012)	72 mg/day	33	1.0 (0.3)	1.1 (0.2)	**0.32 (-0.16, 0.81)**	32	1.0 (0.3)	1.1 (0.2)	0.07 (-0.42, 0.56)
	Shin et al. (2012)	144 mg/day	32	1.0 (0.3)	1.2 (0.2)	**0.60 (0.10, 1.10)***	As above			

HDL-cholesterol -- high density lipoprotein cholesterol

SD -- standard deviation

95% C.I. -- 95 per cent confidence interval

* significant effect size

Effect sizes were calculated on raw data reported by studies (mg/dL and mmol/L). All results in tables have been converted to mmol/L for the purpose of easier comparison. **Bold** typeface indicates an effect size of small or greater. Pre data taken from baseline. Post data taken from end of study; all studies were either 12 weeks or three months in duration.

Table 5 The effect of marine polyphenol-containing supplements on LDL cholesterol level over 3 months compared to placebo in humans

Outcome	Author, Year	Polyphenol dose	Intervention				Placebo			
			n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)	n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)
LDL cholesterol (mmol/L)	Choi et al. (2015)	32.8 mg/day	33	7.8 (1.1)	7.0 (1.2)	**0.76 (0.26, 1.26)***	30	7.7 (1.1)	7.5 (1.4)	0.12 (-0.39, 0.62)
	Hernandez-Corona et al. (2014)	25 mg/day	13	3.1 (0.5)	2.7 (0.6)	**0.72 (-0.07, 1.52)**	12	3.2 (0.6)	3.1 (0.5)	0.18 (-0.62, 0.98)
	Shin et al. (2012)	72 mg/day	33	3.8 (1.0)	3.4 (0.8)	**0.41 (-0.08, 0.90)**	32	3.6 (0.9)	3.6 (0.8)	0.01 (-0.48, 0.50)
	Shin et al. (2012)	144 mg/day	32	3.7 (0.8)	3.2 (0.7)	**0.71 (0.21, 1.22)***	As above			

LDL-cholesterol -- low density lipoprotein cholesterol

SD -- standard deviation

95% C.I. -- 95 per cent confidence interval

* significant effect size

Effect sizes were calculated on raw data reported by studies (mg/dL and mmol/L). All results in tables have been converted to mmol/L for the purpose of easier comparison. **Bold** typeface indicates an effect size of small or greater. Pre data taken from baseline. Post data taken from end of study; all studies were either 12 weeks or three months in duration.

Table 6 The effect of marine polyphenol-containing supplements on triglyceride levels over 3 months compared to placebo in humans

Outcome	Author, Year	Polyphenol dose	Intervention				Placebo			
			n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)	n	Pre mean (SD)	Post mean (SD)	Effect size (95% C.I.)
Triglycerides (mmol/L)	Choi et al. (2015)	32.8 mg/day	33	6.8 (2.8)	7.9 (3.9)	**-0.33 (-0.82, 0.15)**	30	7.3 (3.8)	7.9 (3.8)	-0.15 (-0.66, 0.35)
	Hernandez-Corona et al. (2014)	25 mg/day	13	1.6 (0.6)	2.1 (1.7)	**-0.39 (-1.17, 0.38)**	12	1.7 (0.7)	1.8 (0.7)	-0.14 (-0.94, 0.66)
	Shin et al. (2012)	72 mg/day	33	1.4 (0.6)	1.4 (0.6)	**0.26 (-0.22, 0.75)**	32	1.5 (0.7)	1.5 (0.8)	**-0.32 (-0.82, 0.19)**
	Shin et al. (2012)	144 mg/day	32	1.5 (0.5)	1.4 (0.7)	**0.40 (-0.38, 1.18)**	As above			

SD -- standard deviation

95% C.I. -- 95 per cent confidence interval

No significant effect sizes

Effect sizes were calculated on raw data reported by studies (mg/dL and mmol/L). All results in tables have been converted to mmol/L for the purpose of easier comparison. **Bold** typeface indicates an effect size of small or greater. Pre data taken from baseline. Post data taken from end of study; all studies were either 12 weeks or three months in duration.
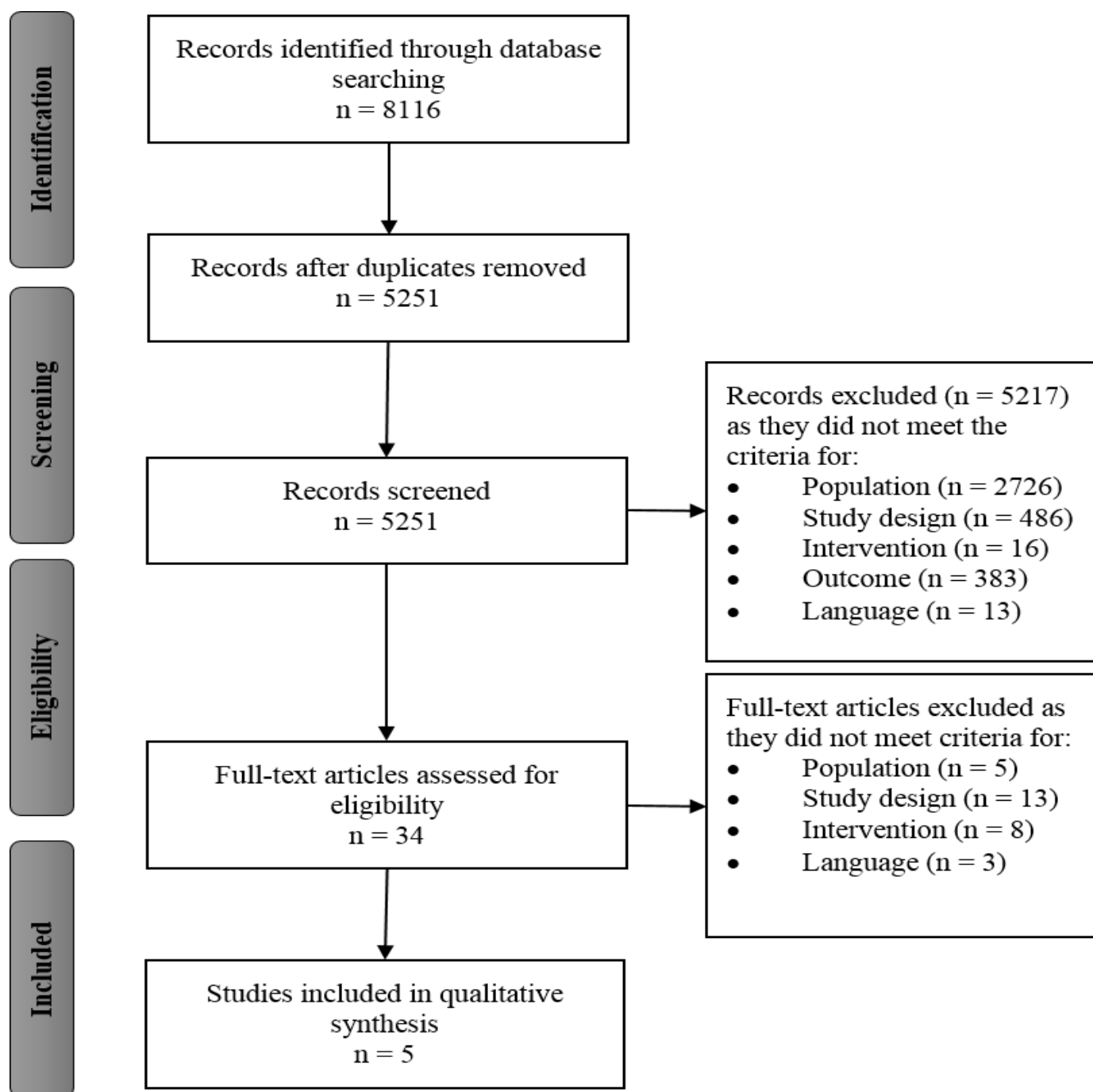
Figure 1 PRISMA flow diagram of included studies