The Effects of Prickly Pear Fruit and Cladode (*Opuntia spp.*) Consumption on Blood Lipids: A Systematic Review

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Abstract

Background: The current dietary recommendations for cardiovascular disease (CVD) risk reduction include increased fruit and vegetable consumption. The *Opuntia spp.*, Prickly Pear (PP) fruit is rich in dietary fiber and may have lipid-lowering effects but it is often confused with the PP stem/leaf (Cladode (CLD)), or not identified. The efficacy of the PP fruit and CLD in reducing CVD risk is a growing area of research.

Methods: This systematic review (PROSPERO: CRD42018110643), examined the effects of consuming the *Opuntia spp.* components (PP or CLD) on CVD risk factors, specifically total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). The review, performed from February through September 2019, used resources available through Food Science and Technology Abstracts (EBSCO), Medline, Scopus, CINAHL, Web of Science and Cochrane databases.

Results and Discussion: Eleven articles met the inclusion criteria, which *characterised Opuntia spp*. products as either PP (*n*=6), CLD (*n*=5) or commercial products' (*n*=1). Effects were investigated in healthy and obese populations as well as those with metabolic illnesses, specifically type 2 diabetes and metabolic syndrome. PP consumption was associated with significant reductions in TC ($p<0.05$) in all but one included study, whereas in the remaining studies (*n*=6), LDL-C levels decreased ($p<0.05$). Separately, the effect of CLD consumption on lipids was small with one study reporting a significant increase in plasma HDL-C in a subgroup of participants (>45 years of age) following consumption of a patented CLD powder product. It is plausible, that differences in overall effect may be due to compositional distinctions between CLD and PP, such as fiber composition. Care must be taken in future studies to accurately report the identity of the selected components of *Opuntia spp*.

Keywords: *Opuntia spp.*, Prickly Pear, Cladode, Cactus, CVD, Lipids, Cholesterol, Triglyceride, Human, RCT.

1. Introduction

Circulating lipoproteins are often monitored in CVD risk management due to their frequent accumulation and associated risk of atherosclerotic plaques [1]. Lipoproteins differ in size, density (high or low) and composition (i.e. cholesterol incorporation), and so do their association with CVD risk [1]. High-density lipoproteins (HDL) are reported to have anti-atherogenic effects, whereas low-density lipoproteins (LDL), are considered an atherogenic risk due to their affinity for cholesterol incorporation and resultant deposits, the atherosclerotic plaques, on blood vessel walls [1]. Within the class of LDL particles, are different LDL subclasses or sizes, and resultantly differ in associated effect with CVD risk [1]. Smaller LDL particles are reported to be associated with an increased CVD risk due their extended (blood) circulation life, increased susceptibility to modifications such as oxidation, or higher affinity for LDL receptors on foam cells [1].

Consensus exists in that of the lipoproteins, predominantly modified LDL (through oxidation, desialylation or glycation) contribute to the formation of the atherosclerotic plaques [1]. It is proposed that the modification of LDL, through oxidation for example, occurs when there is a high level of circulating free radicals within the circulatory system – a condition commonly seen in oxidative stress [1]. Oxidative stress is believed a result of mitochondrial dysfunction, pollution, poor diet and excessive alcohol consumption and smoking [2].

Emerging evidence supports the modifying effects of specific foods, nutrients or compounds on CVD risk, such as lipid-lowering effects, and indicates the importance of promoting ‘fruit and vegetable-rich' diets [3]. The lipid-lowering effects associated with fruit and vegetable consumption is often associated with changes to cholesterol regulation through either altered dietary fat absorption, increased secretion, altered receptor activity or reductions in oxidation (modification) of LDL [4]. For example, fruits and vegetables that are considered to have a substantial dietary fiber content are often associated with lipid-lowering effects low-density lipoprotein-cholesterol (LDL-C) levels as an independent risk factor of CVD [5, 6]. More specifically, consumption of water-soluble dietary fibers such as β-glucan, psyllium, pectin and guar gum are associated with an increase in bile acids in stool samples, up-regulation of LDL receptors and increased liver activity, resulting in reduced serum cholesterol and LDL concentrations [6].

Previous studies on the health effects of specific foods cover a range of conditions such as familial hypocholesterolemia [7]; induced post-prandial dyslipidemia [8]; or metabolic syndrome (MetS) [9]. The use of such nutritional aids over pharmaceutical interventions are often advised as the first line of treatment due to the lower associated costs and the potential of reduced side-effects. Research related to the health benefits of specific foods and their associations with positive health outcomes is becoming more prominent, particularly in the areas of food supplements, functional foods (modified or fortified food products with health benefits) and nutraceuticals (whole food with beneficial health effects based on a particular content, e.g. phytochemical content) [10, 11]. However, immediate use of dietary aids over pharmaceuticals is not yet implementable due to necessity for more research and the current variations between regulatory bodies globally [11].

Some popular foods investigated for reduced risk of CVD include probiotics [11], red yeast rice [10], fish oils [11] and plant-based materials such as soya bean [10], *Berberis aristata* root [10], and the fruit of interest, the Prickly Pear (PP) [12, 13]. Such foods are rich in phytochemicals [10], phytosterols [10], soluble dietary fibers [10] and are proposedly associated with CVD risk reduction in aspects of blood pressure [14], body weight [14] and cholesterol-lowering effects [14]. Foods rich in polyphenols, a key bioactive group, are reportedly protective against CVD due to their antioxidant or anti-inflammatory properties or their role in nitric oxide production [15].

The *Opuntia spp.* cacti components of PP and cladode (cactus pad; CLD) have been used in traditional medicines of the Central and North Americas [16-18]. The PP is considered favourable based on its palatability along with its high fiber, particularly pectin, high mineral and phytochemical content [19]. The consumption of PP is reported to lower the risk of some atherosclerotic pathologies [7, 16-18, 20] and their potentially beneficial effects (PP and CLD) are often confused with one another, or used interchangeably within the literature [19, 21] in spite of being considerably different in their composition and proposed effects upon consumption [7, 16-19, 22]. This systematic review aims to examine the current evidence on the effects of the consumption of *Opuntia spp.* cacti components (PP and CLD) on blood lipids in human and help clarify some of the issues.

2. Materials and Methods

This review was registered with the international register of systematic reviews, PROSPERO (CRD42018110643). The searches were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 (PRISMA) statement [23]. The literature searches were conducted in six electronic databases: Food Science and Technology Abstracts (EBSCO), Medline, Scopus, CINAHL, Web of Science, and Cochrane databases using specific free-word search terms detailed in Section 2.1. Database outputs and reference lists were screened for relevance by title, abstracts and full text (Figure 1).

Figure 1. PRISMA Flow chart of database output exclusion.

2.1 Search Terminology and Selection Criteria

The following search terminology was used to produce the database outputs: *"(Opuntia OR "Prickly Pear" OR "Cactus Fruit" OR "Tuna Fruit" OR "Indian Fig" OR Cladode OR Stems OR Nopal OR "Cactus pad" OR "Cactus Stem" OR "Cactus Leaf") AND (Dyslipid*mia OR Hyperlipid*mia OR Hypercholesterol*mia OR 'Cholesterol' OR 'HDL' OR 'LDL' OR 'Triglycerides')".* The results were limited to (included on the basis of) quantitative, human, intervention control-trials investigating the effects of *Opuntia spp.* fruit or stem/leaf consumption on blood/serum lipids in humans, since journal inception until September 2019. Additionally, the included results were limited to original peer-reviewed full-text articles published in English. The included articles' reference lists were also searched for any additional relevant studies.

The exclusion criteria included: 1) participants were out of the 18-65 years age range, 2) research not conducted in humans, or 3) research was observational or did not contain a control, 4) involved the consumption of a different cactus species (not *Opuntia spp.*), or 5) included the consumption of other cactus products (not fruit or leaf or their commercial products), or 6) the consumed components were unidentified, or 7) the publication type was one of conference proceedings, abstracts, opinion papers, editorials, guidelines, commentaries, case reports, or various forms of review articles.

2.2. Data Extraction and Outcomes of Interest

Two reviewers (C. A. G and R. M) independently screened titles and abstracts of the search results for their relevance. Any disagreements were resolved via discussion. The data extraction from the included articles was undertaken by C. G. and RM. EndNote® citations software (v8, Clarivate Analytics) was used in the process.

2.3. Data Analysis

The included studies were evaluated using the '*Cochrane Risk of Bias Tool'* [24] and compared by statistically significant differences by means, defined by the initial article analysis ($p<0.05$ or $p<0.001$). The forms of bias considered included; selection, performance, detection, attribution, reporting and '*other*' biases, scored either '*low*', '*high*' or '*unclear*' and are defined within the tool [25].

3. Results

3.1. Literature Search

The search strategy produced 5003 references (Figure 1) for consideration. After removal of duplicates (*n*=786), 4217 references were screened for relevance by title and then by the abstract. A total of 17 articles were relevant when considering only the titles and abstracts. However, only 11 articles [7, 26-36] met the inclusion criteria. The four studies excluded on different grounds are identified in Figure 1. Out of the 11 included articles, six investigated the PP fruit (Table 1) [26-30, 37], four, the CLD (Table 2) [31-35] and one, used formulated *Opuntia spp.* products (Table 3) [36]. The included studies did not feature mixed PP fruit and CLD products or *'unspecified'* products.

Table 1. Summary of the effects of *Opuntia spp*. fruit consumption on blood lipids in human trials [7, 26-30].

Table 2. Summary of the effects of *Opuntia spp.* Cladode consumption on blood lipids in human trials [31-35].

Table 3. Summary of the effects of *Opuntia spp.* fruit and Cladode product consumption on blood lipids in human trials [36].

3.2 Risk of Bias

Using the Cochrane Risk of Bias Tool [24], the included studies were scored for bias by C. A. G. and R. M. Investigations into *Opuntia spp.* components (Table 4), shared unclear or unreported selection, performance and detection bias. Overall attribution and reporting biases were generally categorised as *'low'*. Studies including the *'high'* bias ratings were mainly orientated towards the; *"selection bias",* typically a result of health condition screening [28, 29, 31], *"performance bias"* due to of blinding such as *'un-blinded'* or 'un-matched' treatments [26, 30, 32, 36], and lastly recognition of selective reporting [30].

Table 4. Risk of bias summary information for studies included in this systematic review [7, 26-36].

3.3 The effect of *Opuntia spp.* cactus product consumption

3.3.1 Results of the effect of *Opuntia spp.* Prickly Pear Fruit consumption

The included studies investigating the effects of PP consumption (Table 1) shared similar dietary interventions but varied in length of intake (2-8 weeks), population characteristics; gender (Male: *n*=83; Female: *n*=26) and health status ('*healthy*', hyperlipidemic, familial heterozygous hypercholesterolemia, metabolic syndrome (MetS), and Type II Diabetes). The included studies [7, 27, 28] used different PP fruit preparations; PP flesh (250 g) as a dietary fiber replacement (50 %; w/w) of a prescribed and standardized diet [7, 27, 28]; PP juice (150 ml) [26] and lastly, fruit peel (250 g) [30].

The use of PP, as a fiber substitute, was investigated in a study by Budinsky et al. (2001) [7] in males (*n*=8) and females (*n*=7) with heterozygous hypercholesterolemia, and later, in similar studies by Wolfram *et al.* (2002) [28] and Palumbo *et al.* (2003) [27]. The results of the study by

Budinsky *et al.* (2001) [37] indicated a significant increase in total cholesterol (TC; p=0.02; 293.3±22.4 to 299.1±27.0) in the intervention group following four weeks of PP consumption (despite that, the authors reported, in the text, a significant decrease in total cholesterol levels). The levels of LDL-C went down significantly in the treatment group (p=0.04; 223.0±23.6 to 208.0±20.3). No significant changes in High-density lipoprotein cholesterol (HDL-C; p>0.05) or triglycerides (TG) levels (p>0.05) were seen [7]. Palumbo *et al.'s* (2003) [27] initial findings were also replicated by Wolfram *et al.* (2002) [28] in a parallel control trial with a longer intervention period in i) hypercholesterolemic and ii) hyperlipidemic populations for TC (i. and ii.; p<0.005), LDL-C (i. and ii.; p<0.005) and HDL-C (ii. p<0.01) [28]. Again, no effect was reported in HDL-C (i. p>0.05) and TG (i. and ii.; p>0.05) [28]. Following a similar study design, Palumbo *et al.* (2003) also included the consumption of PP based on dietary fiber supplementation (50 %; w/w) following a similar duration (4 weeks) in participants with familial isolated hypercholesterolemia. The findings of this study reported significant reductions in groups; i) males, ii) females and iii) all participants, in; TC (iii. p<0.0001; i. p<0.0014) and LDL-C (iii. p<0.001; i. p<0.0022; ii. p<0.0001) [27]. Furthermore, the control measures (*'regular diet' vs. 'treatment'*) were again found to alter comparisons, in that it also had a reducing effect, on the following measures; LDL-C (ii. p=0.0001; iii. p=0.0001) and HDL-C (iii. p=0.0026) [27].

A separate intervention also considered the effect of PP pulp using a similar study design to that of Wolfram *et al.* (2002) [28] and Palumbo *et al.* (2003) [27], where treatment was replaced with an isocaloric diet, rather than a fiber replacement [29]. The intervention reported significant reductions in TC (p=0.04) and LDL-C (p=0.03) in both males and females with heterozygous hypercholesterolemia after eight weeks of a controlled diet, followed by four weeks of PP pulp (250 g/ day) consumption [29].

Investigating the effect of a separate component, and associated waste product of the PP, Pimienta-Barrios *et al.* (2008) [30] considered the effects of PP peel consumption on blood lipids in healthy males undergoing an Oral Glucose Tolerance Test (OGTT). The study found significant reductions in TC at 60 and 180 minutes (p<0.05), in healthy males with OGTT induced hyperglycemia, but not other time intervals. No effect was reported on TG (p>0.05), and lipoproteins were not investigated [30].

Another study investigated the consumption associated effects of PP, as a juice, in *'healthy'* males (*n*=22) in addition to an exercise intervention (yo-yo intermittent recovery test; parallel) [26]. The consumption of PP juice was reported to reduce serum TC, TG and LDL-C (All p's<0.05) after the consumption of juice but not HDL-C (p>0.05) for comparisons; i) between control and treatment, post-exercise; and ii) before and after consumption [26].

3.3.2 Results of the effect of *Opuntia spp.* Cladode consumption

Studies which examined CLD consumption on blood lipids (Table 2), administered the treatment as boiled vegetable [31, 32] or capsules [33]. In a study by Frati-Munari *et al.* the broiled CLD (100 g; 3 x day before meals) was tested in three populations; *'healthy'* (*n*=8), obese (*n*=14) and T2DM participants (*n*=7) [31]. In this study, when compared to a *'normal diet'* (control; 10 days; parallel design), significant reductions were reported in *'healthy'* populations for TC (p<0.01), and in both i) obese and ii) T2DM for; TC (i. p<0.001; ii. p<0.05), LDL-C (i. p<0.001; ii. p<0.05) and TG (ii. p<0.05). A study by Pignotti *et al.* (2016) also considered the effects of CLD (boiled) consumption using cucumber as a control [32]. The findings of this study reported that in the hypercholesterolemic group (*n*=16), there were no significant differences between the CLD and cucumber consumption for TC (p=0.440), HDL-C (p=0.687), LDL-C (p=0.341) and TG (p=0.09) between the CLD and cucumber consumption [32].

Although there was no reported effect of CLD consumption on blood lipids overall, Pignotti *et al.* (2016) did report changes in cholesterol content of lipoproteins (LDL and HDL) after consumption [32]. In addition cholesterol content of large HDL, significant reductions in cholesterol incorporation were measured in large LDL (p=0.037) but not in small LDL [32]. This may indicate that CLD consumption may reduce CVD risk [32, 38].

In a placebo-controlled monocentric double-blind, randomized control trial, 68 female participants diagnosed with metabolic syndrome, with a body mass index (BMI) between 25 and 40 kg/m^2, were randomly allocated into two groups and the intervention groups received a patented fiber powder (made from dried CLD) for 42 days (1.6 g powder/meal in capsules) with the other group receiving placebo capsules [35]. The study reported an average increase of 0.0217 g/L (HDL-C; no *p*-value provided) in the intervention group while this increase was significant in the over 45 years of age subgroup (0.049 g/L; p=0.029) of the intervention group. In addition, the latter subgroup indicated a measurable but not significant decrease in serum TG level of 154 g/L (*p* = 0.103) [35].

A study by Linarés et al. (2007) used the commercially available 'NeOpuntia©' capsules (3 x 1.6 g/day; dehydrated CLD) in females with MetS (*n*=59) [33]. In this population sample, supplementation was found to have no effect on TC (p=0.156), LDL-C (p=0.673), HDL-C (p=0.090) or TG (p=0.388) at 14 days. At 42 days there were no differences in TC (p=0.429), LDL-C (p=0.256), HDL-C (p=0.082) and TG (p=0.435) [33]. However, the participants consuming placebo capsule (contents not reported) exhibited significant reductions in TC (p=0.041) at 14 days, and TC (p=0.035) and LDL-C (p=0.05) at 42 days [33].

3.3.3 Results of the effect of *Opuntia spp.* fruit and cladode product consumption

Only one of the included studies in this systematic literature review investigated the effects of both PP and CLD on the lipid responses in healthy participants (Table 3) [36]. The *Opuntia spp.* cactus products were formulated as either bar-snacks or tortillas to examine the consumption associated effect on blood lipids, in *'healthy'* participants (*n*=28) over three weeks [36]. The effects of consumption were studied as fortified or unfortified bars (PP jam) or tortillas (CLD). The observed results indicated significant differences in TC ($p<0.05$), LDL-C ($p<0.05$) and TG ($p<0.05$) between placebo and treatment (CLD) tortillas; where the only difference between treatment bars containing PP jam and corresponding placebo bar-snacks was found in LDL-C ($p<0.05$) [36]. The effect of both active treatments (PP and CLD) together was not investigated.

4. Discussion

The hypolipidemic actions associated with fruit and vegetable consumption have consistently been proposed due to fiber content [5] and associations with altered rates of fat absorption, in addition to its phytochemical composition, reducing oxidative stress [15], amongst other mechanisms [6, 7, 26-34, 36].

4.1. Opuntia spp. fruit

Studies reporting the effects of PP consumption indicate that PP consumption (PP flesh, peel and juice) can cause significant reductions in TC in hyperlipidemic populations [7, 27, 28] (Tables 1 and 3). Khouloud *et al.* (2018) reported significant decreases in TC, TG and LDL-C in *'healthy'* males after two weeks of juice supplementation (150 ml per day), after exercise post-exercise (yo-yo intermittent recovery test), although such results were unclear, as significant increases were reported in the controls [26]. An overall reduction in LDL-C was observed in all included studies investigating the PP (pulp, juice and bar) in *'healthy'* and hyperlipidemic participants [7, 26-28]. Additionally, in one of the included studies, there was a significant reduction in HDL-C in participants with heterozygous hypercholesterolemia with participants that did not follow a controlled diet within the *'pre-running'* or *'lead-in'* period [27]. Furthermore, in two studies the TC levels increased in the control groups potentially due to the introduced *'control diets'* [26, 28]. Overall, it could be seen that the consumption of PP products might suppress the rise of lipid measures through factors such as inhibiting fat absorption, rather factors inducing lipid-lowering effects.

The consistent reduction in TC and LDL-C is suggestive of an effect via one or more of the cholesterol regulatory pathways, such as modulation of dietary fat absorption, increase in bile secretion or up-regulation of LDL receptor activity (LDL-R) [4]. The modulation relationship is regulated by factors including the rate of very-low-density lipoprotein (VLDL)/LDL conversion, LDL-C production and transport rate [4]. The PP fruit's lipid-lowering effects have been proposed to be a result of its high fiber content resulting in the altered rate of absorption that perhaps interrupts the entero-hepatic circulation of lipids [7, 27, 28]. The reductions in TC and LDL-C in the included articles [27, 28, 37] investigating the effect via dietary supplementation with PP (fiber replacement), maybe due to the PPs high pectin content [7, 27, 28].

Pectin consumption is associated with an increase in fecal bile acid and up-regulation of LDL-R via promotion of chenodeoxycholic (bile) acid synthesis, and hepatic uptake resulting in reduced serum cholesterol concentrations [6]. Similar studies [7, 27, 28] showing significant reductions in TC and LDL-C after consumption of PP are limited by unquantified dietary fiber or pectin composition in the diet of participants during i) baseline and ii) controlled diet. Within these investigations, bile acid clearance was also not reported. Based on the reviews findings, despite the limited number of studies available, the lipid-lowering effects of PP identifies its potential as a functional food ingredient that may assist in the reduction of CVD risk factors, due to its compositional characteristics with particular reference to fiber and phytochemical content [10].

4.2. Opuntia spp. Cladode (leaf)

The included studies (Table 2 and 3) investigating CLD consumption, provided conflicting results concerning its efficacy in modifying blood lipid levels [31-33, 35]. Significant decreases were observed for TC in *'healthy'*, obese, T2DM participants simultaneously [9, 31]. One study [35] showed a significant increase in the average serum HDL levels for the age group of >45 years, following 42 days consumption of a patented CLD powder (NeOpuntia®), with a smaller increase for the whole intervention group (*p*-value not reported). The remainder of the included studies in this group did not report any significant effects on the lipid profile (all p's>0.05). The variability in the studies' components (treatment and control groups, types of interventions, and variation in design and intervention length) may also account for the conflicting results.

Two studies included in this review reported no significant differences in blood lipid parameters between CLD and controls (cucumber [32] or placebo capsules [35]). The capsule-based studies were conducted on participants with MetS (all females) and were associated with contradicting results about the observed HDL-C level. In one of the studies [35], consumption of the control capsules resulted in significant reductions in TC which could be due to the combined effect of dietary changes in response to a *'healthy balanced diet'* and changes in participants' physical activity (minimum 30 minutes). When CLD was consumed as a vegetable (280 g; control: cucumber) over two weeks, there were no differences in blood lipid markers [32]. In another study, the consumption of CLD powder for 42 days caused significant increases in serum HDL levels with an insignificant decrease in the average serum TG level for the +45 year of age sub-group for the intervention group [35].

Therefore, the findings suggest that there is inconsistent evidence about the effect of *Opuntia spp.* CLD consumption on blood lipids. Future studies of CLD consumption as a potential lipid-lowering food product should consider the consumption of treatments at higher doses (>280 g per day) for more extended periods (>8 weeks) with cautions towards gastrointestinal discomfort when consuming fiber-rich foods. The potential for an effect at either higher dose or extended period is supported by similar investigations into CLD fiber powder consumption, finding significant increases in fat binding capacity, and an increase in fecal fat excretion ($p<0.001$) upon consumption of much smaller dose (500 mg) in *'healthy'* humans [39]. Such effects are widely proposed to be the underlying mechanisms of bodyweight reduction provided by *Opuntia spp.* products [14].

5. Conclusions

In conclusion, PP and CLD do not share equivalent hypolipidemic and hypocholesterolemic effects. The consumption of the PPs flesh as a fiber replacement consistently demonstrated a significant reduction in TC in hyperlipidemic participants. Similarly, PP consumption is reported to reduce LDL-C in *'healthy'* and hyperlipidemic participants. The CLD did not share the same effects, possibly due to compositional variations. Nevertheless, the CLD, when consumed as a vegetable, did indicate the potential for a more substantial impact with an increased dose or served as a vegetable (>280 g) over a longer period in hyperlipidemic participants. Further research into the lipid-lowering properties of the PP should consider standardization of the fiber in the provided food products (study foods) to assist in determining the underlying mechanisms of action. Nonetheless, the PP appears to be a good source of phytochemicals, and their consumption-associated effects should be investigated.

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Consent for publication: All authors have reviewed the final manuscript and have agreed to submit for publication.

Ethics Approval: Not required for this study.

Figure 1. PRISMA Flow chart of database output exclusion

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Table 3. Summary of the effects of *Opuntia spp*. fruit and cladode product consumption on blood lipids in human trials.

Table 4. Risk of bias summary for included studies in this systematic review

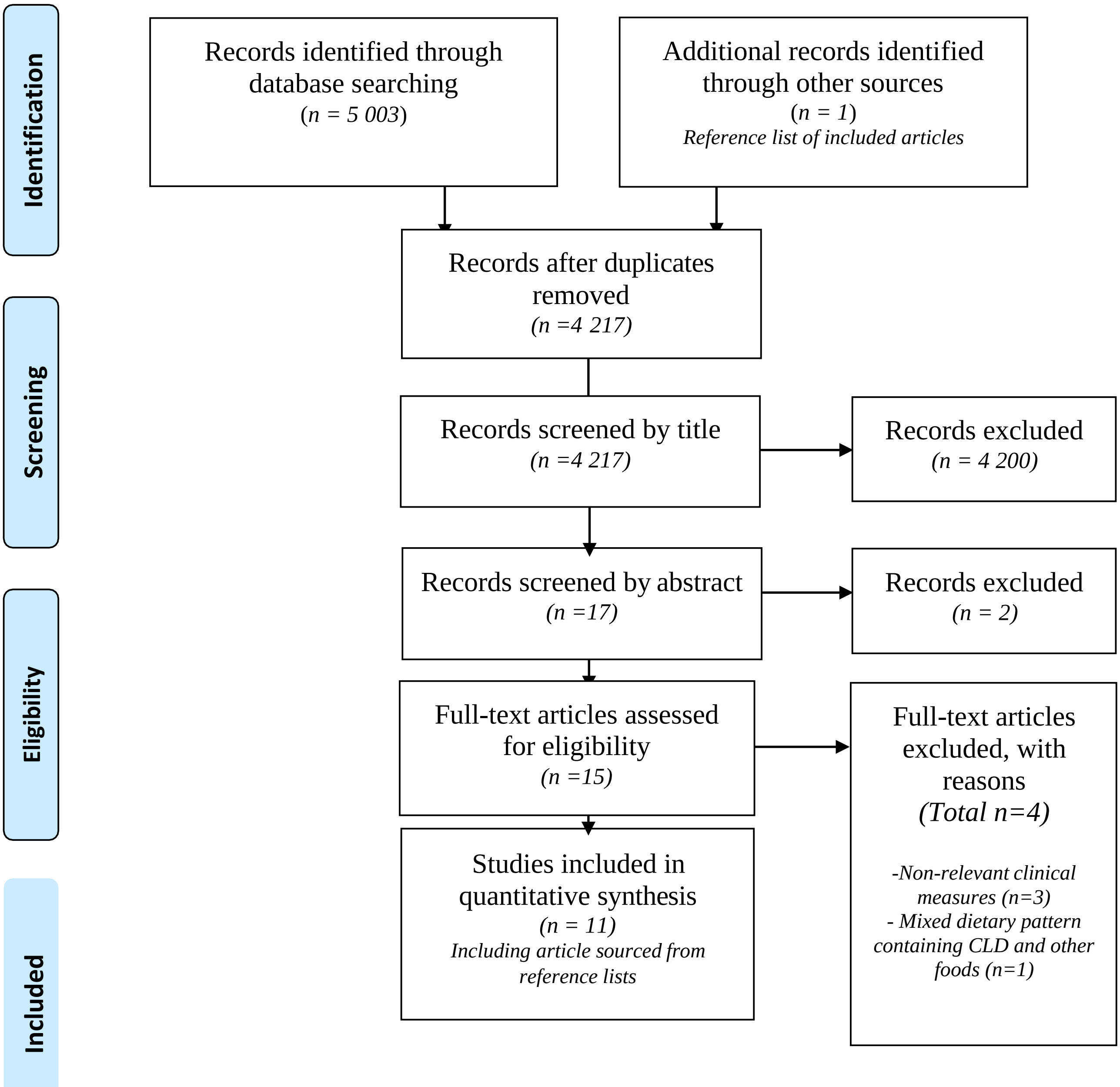

Figure 1. PRISMA Flow chart of database output exclusion

Table 1. Summary of the effects of *Opuntia spp.* Prickly Pear fruit consumption on blood lipids in human trials [7, 26-30].

Author (Year) Country	Participants, Sample Size, Gender and Age.	Aim	Intervention	Outcomes	Results (T vs C)
Khouloud *et al.* (2017) [26] Tunisia	*'Healthy'* Males (*n*=22)	Effect of PP juice supplementation on oxidative stress, CVD parameters and biochemical markers following a Yo-Yo intermittent recovery test	Duration: 2 weeks T: 3 x 50 ml of PP juice/day; 3,000 kcal diet C: 3,000 kcal diet Randomized Cross-over Controlled Trial	Pre vs. Post Exercise (fasted, serum) TC LDL-C HDL-C TG	C: ↑ TC ($p<0.01$), TG ($p<0.05$), HDL-C ($p<0.01$) and LDL ($p<0.01$) T: ↓ TC ($p<0.05$), TG ($p<0.05$) and LDL-C ($p<0.05$) ND on HDL-C ($p>0.05$)
Budinsky *et al.* (2001) [7] Austria	Familial heterozygous isolated hypercholesterolemic participants (*n*=15) Male (*n*=8) Age: 35±6.3 yrs. Female (*n*=7) Age: 31.6±6.3 yrs.	Effect of PP ingestion on oxidative injury	Duration: Phase i: Baseline (4 weeks) Phase ii: Dietary counselling (4 weeks), Phase iii: T(PP) (4 weeks)	Pre vs. Post supplementation (fasted, serum): TC LDL-C HDL-C	Males vs Females: HDL-C ($p=0.03$). Phase i) vs. ii): Males and females: ND in TC ($p>0.05$), LDL-C

			T: Fiber replacement (625 kJ; 50% of fiber replaced with 250 g/day broiled) C: Dietary counselling (7506 kJ diet) Parallel Control-trial	TG	(p>0.05) or HDL-C (p>0.05). Phase ii) vs iii): Males: ↓ TC (p=0.01) and LDL-C (p=0.05). Females: ND on TC (p>0.05), LDL-C (p>0.05), HDL-C (p>0.05), TG (p>0.05). Phase i) vs iii): Males: ↓ TC (p=0.04) and LDL-C (p=0.04). ND on HDL-C (p>0.05) or TG (p>0.05). Females:

					↓ TC (p=0.01) and LDL-C (p=0.04). ND on HDL-C (p>0.05) or TG (p>0.05).
Palumbo *et al.* (2003) [27] Austria	Familial heterozygous hypercholesterolemic participants *(n*=10) Male: *(n*=6) Age: 27-46 yrs. Female: *(n*=4) Age: 25-40 yrs.	Effect of PP on liver LDL binding in familial heterozygous hypercholesterolemia	Duration: 4 weeks Phase i: Baseline (4 weeks) Phase ii: Dietary counselling (4 weeks), Phase iii: T(PP) (4 weeks) T: (625 kJ; 50% of fiber replaced with 250 g/day broiled) C: Dietary counselling (7506 kJ diet) Parallel-Controlled trial	Pre vs. Post supplementation (Fasted, serum): TC LDL-C HDL-C	Phase i) vs ii): ND on TC (p>0.01), LDL-C (p>0.01), HDL-C (p>0.01) overall, females or males. Phase ii) vs iii): ↓ Overall TC (p<0.0001) LDL-C (p<0.001). ↓Male TC (p<0.0014), LDL-C (p=0.0022). ↓ Female LDL-C (p<0.0001). Phase i) vs iii):

					↓ Female LDL-C (P=0.0001). ↓ Overall HDL-C (p<0.0026).
Wolfram *et al*. (2002) [28] Austria	Primary isolated hypercholesterolemic and hyperlipidemic participants Male (*n*=24) Age: 37-55 yrs. Group A: Hypercholesterolemia (*n*=12) Group B: Hyperlipidemia (*n*=12)	Effect of PP pectin on blood glucose and lipids in hypercholesterolemic and hyperlipidemic patients	Duration: 8 weeks Dietary counselling (8 weeks), T(PP) (8 weeks) T: (625 kJ; 50% of fiber replaced with 250 g/day) C: Dietary counselling (7506 kJ diet) Parallel-Controlled trial	Pre vs. Post supplementation (Fasted, serum): TC LDL-C HDL-C TG	Group A vs B Baseline: ↑ Group A in LDL-C (p<0.0001). ↑ Group B in TG (p=0.0001). Phase i) vs ii): Group A: ↓ TC (p<0.005), LDL-C (p<0.005) and HDL-C (p<0.01). ND on TG (p>0.01). Group B: ↓ TC (p<0.005), LDL-C (p<0.005). ND on TG (p>0.01) or HDL-C (p>0.01).

Oguogho *et al*. (2010) [29] Austria	Familial heterozygous hypercholesterolemic participants *(n*=14) Male: *(n=9*) Female: *(n=5*) Mean Age: 22.29 yrs.	The effect of PP consumption on TC, HDL, LDL and TG	Duration: 8 weeks Dietary counselling (8 weeks, once a week) T(PP): 250 g/day *Opuntia lidheimerii* fruit pulp *(*4 weeks) C: Isocaloric diet (7, 500 kJ; 4 weeks) Control trial	TC TG HDL LDL	T vs C: ↓ TC (p=0.04) ↓ LDL-C (p=0.03) ND on TG and HDL-C.
Pimienta-Barrios *et al.* (2008)[30] Mexico	Phase 1: 'Healthy' Male (*n*=14) Age: 22.4±3.2 yrs Phase 2: 'T2DM participants' Female (*n*=10) Age: 42.4±3.3 yrs	The effects of yellow PP peel on health males (single consumption) and diabetic females (Chronic; 5 weeks)	Phase 1: Single consumption T: 250 g fruit peel and GLU solution C: 75 g GLU (solution) Control trial Phase 2: Duration: 5 weeks Fasted; 3 x 50 g PP peel/week	OGTT (12 hr. fasted) Time -20, 0, 20, 30, 60, 80, 100, 120, 140, 160, 190, 200 min Phase 1 and 2: TC TG	Phase 1: ↓TC: at 60 min and 180 min (p>0.05). ND on other time points. ND on TG (p<0.05). Phase 2: TC and TG were not reported.

			Control: Baseline measurements Control Trial		

[1] BMI: Body Mass Index; Yrs.: Years; PP: Prickly Pear; C: Control; T: Treatment; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglycerides; GLU: Glucose; ND: No Difference; ↓: Decrease; ↑: Increase.

Table 2. Summary of the effects of *Opuntia spp*. Cladode consumption on blood lipids in human trials [31-33, 35].

Author (Year) Country	Participants, Sample Size, Gender and Age.	Aim	Intervention	Outcomes	Results (T vs C)
Frati-Munari *et al.* (1983) [31] Mexico	Males (*n*=11) and Females (*n=18*) Group 1: *'Healthy'* (*n=8*) Group 2: Obese (*n=14*) Group 3: Diabetic (*n=7*)	Effect of CLD consumption on blood lipids	Duration: 10 days T: 100 g broiled CLD, before meals, 3 x day C: Normal diet Parallel-Controlled trial	Pre vs. Post supplementation (serum): TC LDL-C (β-cholesterol) HDL-C (α-Cholesterol)	Group 1: ↓TC (p<0.01), ND in LDL-C (p>0.05), HDL-C (p>0.05) and TG (p>0.05) Group 2: ↓TC (p<0.001), LDL-C (p<0.001) and TG (p<0.001).

				TG	ND in HDL-C ($p>0.05$). Group 3: ↓TC ($p<0.05$), LDL-C ($p<0.05$) and TG ($p<0.05$). ND in HDL-C ($p>0.05$).
Pignotti *et al.* (2016) [32] Italy	Hypercholesterolemic participants (*n=16*) Males (*n*=5) Females (*n*=11) Age: 46±14 yrs. BMI: 31.4±5.7 kg/m^2	Effects of CLD leaf on lipoprotein profiles in hypercholesterolemic adults.	Duration: 2 weeks. 2-3 weeks wash-out. T: 280 g CLD/day (Boiled) C*:* 266 g Cucumber/day Randomized Cross-over Controlled Trial	Pre vs. Post supplementation (Fasted, serum): TC LDL-C HDL-C TG	T vs C: ND for TC ($p=0.440$), HDL-C ($p=0.687$), LDL-C ($p=0.341$) and TG ($p=0.09$) between treatments. Lipoprotein subfractions: ↓Cholesterol in large LDL-C ($p=0.037$) in T. ND Cholesterol in small LDL-C ($p=0.573$). ND in Cholesterol in small ($p=0.455$), intermediate

					(p=0.980) or large (p=0.481) HDL-C.
Linares *et al.* (2007) [33] France	MetS Females (*n=59*) Age: 20-55 yrs. BMI: 24-40 kg/m^2		Duration: 6 weeks T: 3 x 1.6 g NeOpuntia© (Dehydrated CLD leaf)/day C*:* Placebo capsule Randomized double-blind placebo-controlled trial	Day 0, 14 and 42 (Fasted, serum): TC LDL-C HDL-C TG	Day 0 vs Day 14 T: ND in TC (p=0.156), LDL-C (p=0.673), HDL-C (p=0.090) and TG (p=0.388). C: ↓TC (p=0.041). ND in LDL-C (p=0.060), HDL-C (p=0.346) and TG (p=0.767). Day 0 vs. Day 42 T: ND in TC (p=0.429), LDL-C (p=0.256), HDL-C (p=0.082) and TG (p=0.435). C: ↓TC (p=0.035) and LDL-C (p=0.05). ND in HDL-C (p=0.137) and TG (p=0.963).

Lecareux, C. (2008) [35] France	Females with MetS (*n=68*) Age: 47.3± 10.1 yrs BMI: 25-40 kg/m^2	The effects of a patented powder of leaves of *Opuntia ficus-indica* (NeOpuntia ®) on blood lipids	Duration: 6 weeks Treatment: 1.6 g CLD powder/meal in capsules Control: Placebo capsule Both treatments: 2000 Kcal diet, limited lipid intake, no more than 30 minutes exercise for both groups A monocentric placebo-controlled, randomized, double-blind trial	Measurement of blood lipids on Day 14 and 42: TC TG HDL-C LDL-C	T vs. C ↑ in HDL (Day 42; by 0.0217 g/L; no *p*-value provided). T vs. C of subgroup (>45 yrs) ↑ in HDL (Day 42; increase by 0.049 g/L; *p = 0.029)* ND in TG (decrease of 154 g/L; *p*=0.103)

[1] MetS: Metabolic Syndrome; BMI: Body Mass Index; Yrs.: years; CLD: Cladode; C: Control; T: Treatment; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglycerides; ND: No Difference; ↓: Decrease; ↑: Increase.

Table 3. Summary of the effects of *Opuntia spp*. fruit and cladode product consumption on blood lipids in human trials [36].

Author (Year) Country	Participants, Sample Size, Gender and Age.	Aim	Intervention	Outcomes	Results (T vs C)
Guevara-Arauza *et al.* (2011) [36] Mexico	'Healthy' *n*=12 Males *n*=16 Females (*n*= 28)	To determine bio-functional effects of nopal (CLD) and PP products	Length: 3 weeks Treatment: Supplement diet with 40 g Bars: Control-bar vs 'Nopal (32 %) with PP pulp Jam' bar (15 g); and 100 g Tortillas vs. Tortillas with Nopal (48 %). Dose: Twice a day, three-weeks. Control trial	Fasted (8 hrs.) blood samples TC HDL LDL TG	T (PP pulp jam bars) vs. C: ↓ LDL ($p<0.05$) ND on TC, HDL, TG ($p>0.05$). T (Tortilla) vs C: ↓ TC ($p<0.05$), LDL ($p<0.05$) and TG ($p<0.05$). ND on HDL ($p>0.05$)

[1] MetS: Metabolic Syndrome; BMI: Body Mass Index; Yrs.: years; CLD: Cladode; C: Control; T: Treatment; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglycerides; ND: No Difference; ↓: Decrease; ↑: Increase.

Table 4. Risk of bias summary for included studies in this systematic review [7, 26-36].

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
Prickly Pear fruit							
Budinsky *et al.* (200) [7]	Unclear	Unclear	Unclear	Unclear	Low	High	Low
Palumbo *et al.* (200) [27]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Wolfram *et al.* (2002) [28]	High	Unclear	Unclear	Unclear	Low	Low	Low
Khouloud *et al.* (2017) [26]	Unclear	Unclear	High	Unclear	Low	Low	Low
Oguogho *et al.* (201) [29]	High	Unclear	Unclear	Unclear	Low	Low	Low
Pimienta-Barrios *et al.* (2008)[30]	Unclear	Unclear	High	Unclear	Unclear	High	Low
Cladode							

Pignotti *et al.* (2016) [32]	Unclear	Unclear	High	Unclear	Low	Low	Low
Linares *et al.* (2007) [33]	Unclear	Unclear	Low	Unclear	Low	Low	Low
Frati-Munari *et al.* (1983) [31]	High	Unclear	Unclear	Unclear	Low	Low	Low
Lecareux, C. (2008) [35]	Unclear	Unclear	Low	Low	Low	Low	Low
Opuntia spp. Products							
Guevara-Arauza *et al.* (2011) [36]	Unclear	Unclear	High	Unclear	Low	Low	Low

[1] The forms of bias considered included; selection, performance, detection, attribution, reporting and ‘other’ biases, scored either ‘low’, ‘high’ or ‘unclear’.

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