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Effects of blueberry and cranberry consumption on type 2 diabetes glycemic control: a systematic review

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The authors state that they have no conflict of interest.

ABSTRACT

The metabolic effects of cranberry and blueberry consumption on glycemic control have been evaluated *in vitro* and in animal models as well as in human studies, although findings have not

been systematically reviewed yet. Therefore, a systematic review was carried out of relevant randomized clinical trials (RCTs) in order to assess the effect of berries (blueberry and cranberry) consumption on type 2 diabetes (T2DM) glycemic control. Some evidences were also discussed on the anti-diabetic mechanisms exerted by berries polyphenols. Studies were identified by searching electronic databases: LILACS, PubMed/MEDLINE, Scopus, The Cochrane Library and Web of Science. Three authors independently searched and extracted RCTs in which the effect of berries (cranberry or blueberry) consumption on T2DM glycemic control was assessed. A total of 7 RCTs, involving 270 adults with type 2 diabetes were included. Despite the heterogeneity of the administration forms (*in natura*, dried, extract, preparations – juice), dosage, duration of the intervention and type of population of the studies involving these two berries some studies highlight the potential benefit of berries, especially of blueberry, on glucose metabolism in T2DM subjects. Daily cranberry juice (240 mL) consumption for 12 weeks and blueberry extract or powder supplementation (9.1 to 9.8 mg of anthocyanins, respectively) for 8 to 12 weeks showed a beneficial effect on glucose control in T2DM subjects. Those results indicate a promising use of these berries in T2DM management; although more studies are required to better understand the mechanisms involved.

Keywords: anthocyanins; glucose control; glycemic response; nutraceuticals; polyphenols

1. INTRODUCTION

Diabetes mellitus is a complex and chronic metabolic disease characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association 2017). Type 2 diabetes mellitus (T2DM) is the most prevalent category of diabetes, accounting for 90% of all cases of diabetes (Scully 2012). The global prevalence of diabetes worldwide has been rising, largely due to the increasing prevalence of T2DM (World Health Organization 2016). In 2014, there were approximately 422 million adults with diabetes in the world. In addition, diabetes directly caused 1.5 million deaths in 2012 and high blood glucose itself caused another 2.2 million of deaths, by increasing the risks of cardiovascular and other types of diseases (World Health Organization 2016). Nevertheless, diabetes has serious adverse consequences for health and well-being and impose substantial economic costs on patients and their families, and the economies of nations (World Health Organization 2016; Zhou et al. 2016a). The estimated global cost of diagnosed diabetes in 2014 was 825 billion dollars per year (Zhou et al. 2016b). Therefore, diabetes prevention and disease management may be particularly worthwhile.

In recent years, growing attention has been focused on bioactive and nutraceuticals compounds to prevent chronic diseases (Jurikova et al. 2017; Mouhid et al. 2017; Rasines-Perea & Teissedre

2017). In this context, berries are good sources of bioactive compounds (Skrovankova et al. 2015). Blueberry and cranberry (*Vaccinium* spp.) are a species from the family Ericaceae, which includes approximately 450 species (Skrovankova et al. 2015; Michalska & Łysiak 2015). Both plants from *Vaccinium* genus are dated back to the Cretaceous period, more than 100 million years ago, and were domesticated in the 20th century (Routray & Orsat 2011; Michalska & Łysiak 2015). Since then, their popularity and commercial value has been increasing over the past years (Hancock et al. 2008; Michalska & Łysiak 2015), due to various phenolic compounds (i.e. phenolic acids, flavonoids, anthocyanidins) and their health benefits (Li et al. 2013; Federation of American Societies for Experimental Biology. et al. 2015). The benefit of cranberry and blueberry on glycemic control and other metabolic effects were demonstrated *in vitro* and in animal models (Grace et al. 2009; Khanal et al. 2010; Anhê et al. 2015; Elks et al. 2015; Nachar et al. 2017). Also, the effects of berries consumption on T2DM glucose control in humans have been investigated (Wilson, S.L.L. Meyers, et al. 2008; Lee et al. 2008; Wilson et al. 2010; Shidfar et al. 2012a; Hoggard et al. 2013; Kianbakht et al. 2013; Mirfeizi et al. 2016). Therefore, the aim of the present study was to perform a systematic review of randomized clinical trials (RCTs) in order to assess the effect of berries (blueberry and cranberry) consumption on T2DM glucose control. Some evidences were also discussed on anti-diabetic mechanisms exerted by berries polyphenols.

2. METHODS

2.1. Protocol and Registration

This systematic review was carried out and reported according to PRISMA Statement (Liberati et al. 2009) (see Appendix Checklist). The review has been registered at the PROSPERO (www.crd.york.ac.uk/prospero/): registration number CRD42017063941.

2.2. Eligibility Criteria

Type of studies: Randomized controlled trials (RCTs).

Type of subjects: Subjects aged 18 years old or above with T2DM. Due to differences in the metabolic parameters evaluated, adult subjects have been chosen for the selection criteria and excluded children and adolescents subjects.

Type of intervention: Any dose and form of berries (cranberry or blueberry) in oral administration. Studies assessing the effect of treatments containing either both berries or combinations with other berries at the same time were excluded, although studies in which the simultaneous administration of either one of those with insulin, oral hypoglycemic agents or both were included (but when there is already a constant use of these drugs). Control: non-exposed control group; placebo; no treatment.

Types of outcome measures: Primary outcomes: blood glucose concentrations. Secondary outcomes: blood insulin concentrations, insulin sensitivity was evaluated using homeostasis model assessment of insulin resistance (HOMA-IR) calculated by the following formula:
$$\text{HOMA-IR} = [\text{fasting glucose (nmol/L)} \cdot \text{fasting insulin } (\mu\text{U/mL})] \div 22.5$$
, glycosylated hemoglobin A1c (HbA1c), and other metabolic markers related to glucose homeostasis.

2.3. Literature Search

Studies have been identified by searching electronic databases: LILACS (Latin American and Caribbean Center on Health Sciences Information), PubMed/MEDLINE, Scopus, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science (Science and Social Science Citation Index). The following search terms were used to search databases: (diabetes OR diabetic OR "glucose intolerance") AND (blueberry OR blueberries OR cranberry OR cranberries OR vaccinium). Filters were used, if available, for human studies. The validated filter was also used to search for randomized controlled trials at PubMed database, as recommended by Cochrane Handbook (Lefebvre et al. 2011). The search strategies had no date restrictions. June 11th, 2017 was the date of our last search.

2.4. Study Selection and Data Collection Process

Eligibility assessment of original RCTs assessing the effect of the consumption of berries (cranberry or blueberry) on T2DM glycemc control was performed independently by three authors (APSC, BPS and DMUPR). Any discrepancies among the reviewers were resolved through consensus. For studies that fulfilled the inclusion criteria, three review authors (APSC, BPS and DMUPR) independently extracted relevant information: subjects (sample size, mean age, mean fasting glucose concentrations and HbA1c, mean body mass index – BMI, calculated as body weight in kilograms divided by height in meters squared) and intervention design (including type of study, type of intervention, outcome measures). This information was then summarized in a standard data extraction template.

2.5 Risk of Bias Assessment

The methodological quality was assessed of the included trials and the risk of bias checked by using elements of the Cochrane collaboration tool for assessing risk of bias (Higgins et al. 2011). Included studies were assessed for the following risk of bias domains: (1) selection, (2) performance, (3) detection, (4) attrition and (5) reporting bias (Higgins et al. 2011). Each domain was judged ('Low risk' of bias; 'High risk' of bias, or 'Unclear risk' of bias) independently by three authors (APSC, BPS and DMUPR), based on the available information in the study. The outcomes reported in published reports were compared to their study protocol, if available. For each domain, 'Unclear' risk of bias was applied when experimental details were not enough for judgment. Our evaluation of 'Risk of bias' was recorded in Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre 2014). Studies were classified as having a low risk of bias when >80% questions were answered as "yes (low risk)", a moderate risk of bias when 50 to 79% of the questions were answered as "yes (low risk)" and a high risk of bias when <50% questions were answered as "yes (low risk)" (Gomes et al. 2017).

3. RESULTS

3.1 Study Selection

A total of 459 records were initially identified through database searching in CENTRAL, LILACS, MEDLINE/PubMed, Scopus and Web of Science. About half (205 records) duplicates were removed resulting in 254 unique records. The remaining studies were screened based on their titles and abstracts. Then, 240 of them were excluded because they did not meet the

inclusion criteria. Therefore, 14 studies were assessed for eligibility through full-text reading. From these, 7 studies met all the criteria for the systematic review and were included in the review. The most common reasons for study exclusion were animal studies, *in vitro* or characterization studies, lack of a comparison group (healthy control), lack of subjects with diabetes or insulin resistance, presence of subjects with multiple diseases (**Fig. 1**). Study selection was performed independently in an unblinded standardized manner by 3 reviewers (APSC, BPS and DMUPR). Disagreements in studies selection were resolved by consensus.

3.2 Study Characteristics

3.2.1 Methods

All the seven selected studies were blind randomized clinical trials published in English. Four trials had a parallel design (Lee et al. 2008; Shidfar et al. 2012a; Kianbakht et al. 2013; Mirfeizi et al. 2016) and three showed a crossover design (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010; Hoggard et al. 2013). There was a multicenter study (Mirfeizi et al. 2016). There were three acute studies (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010; Hoggard et al. 2013) and four intervention studies (8 to 12 weeks) (Lee et al. 2008; Shidfar et al. 2012a; Kianbakht et al. 2013; Mirfeizi et al. 2016). Three studies evaluated the blueberries consumption effect (Hoggard et al. 2013; Kianbakht et al. 2013; Mirfeizi et al. 2016) and four studies assessed the cranberries consumption effect (Wilson, S.L.L. Meyers, et al. 2008; Lee et al. 2008; Wilson et al. 2010; Shidfar et al. 2012a) on blood glucose concentrations.

3.2.2 Subjects

The included studies involved 270 subjects with T2DM, taking hypoglycemic agents but not insulin, none reported changes in the medication used during the intervention period. The majority of the studies involved men and women (Wilson, S.L.L. Meyers, et al. 2008; Lee et al. 2008; Wilson et al. 2010; Kianbakht et al. 2013; Mirfeizi et al. 2016) and two studies involved only men (Shidfar et al. 2012a; Hoggard et al. 2013). The mean age of the subjects ranged from 53.6 to 66.0 years. The mean body mass index (BMI) at baseline ranged from 25.9 to 34.7 kg/m² (Table 1).

3.2.3 Interventions

The studies were based on oral blueberries or cranberries in capsules (Lee et al. 2008; Hoggard et al. 2013; Kianbakht et al. 2013; Mirfeizi et al. 2016), in raw or dried form (Wilson et al. 2010) or juice (Wilson, S.L.L. Meyers, et al. 2008; Shidfar et al. 2012a). The species of blueberry tested were *Vaccinium myrtillus* L. (Hoggard et al. 2013) and *Vaccinium arctostaphylos* L. (Kianbakht et al. 2013; Mirfeizi et al. 2016), but the cranberries species were not declared by authors (Wilson, S.L.L. Meyers, et al. 2008; Lee et al. 2008; Wilson et al. 2010; Shidfar et al. 2012a). The ingredients in the control varied among the studies, and they included mineral water with strawberry flavor (Shidfar et al. 2012a), white bread (Wilson et al. 2010), microcrystalline cellulose (Hoggard et al. 2013), starch (Mirfeizi et al. 2016), dextrose (Wilson, S.L.L. Meyers, et al. 2008) and toast powder (Kianbakht et al. 2013). However, this information was not declared in one study (Lee et al. 2008).

3.2.4 Outcomes

Fasting blood glucose was measured in 4 studies (Lee et al. 2008; Shidfar et al. 2012a; Kianbakht et al. 2013; Mirfeizi et al. 2016), 2-hour postprandial glucose was measured in 2 studies (Kianbakht et al. 2013; Mirfeizi et al. 2016), glycemic response during 120 min following cranberry consumption was assessed in 2 studies (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010) and one study evaluated the glycemic response to blueberry consumption followed by a glucose load over a 300 min postprandial period (Hoggard et al. 2013).

Secondary outcomes included HbA1c, which was measured in 3 studies (Lee et al. 2008; Kianbakht et al. 2013; Mirfeizi et al. 2016), insulin concentrations, assessed in five studies (Wilson, S.L.L. Meyers, et al. 2008; Lee et al. 2008; Wilson et al. 2010; Hoggard et al. 2013; Mirfeizi et al. 2016), and HOMA-IR in two studies (Lee et al. 2008; Mirfeizi et al. 2016).

3.3 Risk of Bias within Studies

The 7 RCTs could be classified by their quality into one with moderate risk of bias (Mirfeizi et al. 2016) and six with high risk of bias (Wilson, S.L. Meyers, et al. 2008; Lee et al. 2008; Wilson et al. 2010; Shidfar et al. 2012a; Hoggard et al. 2013; Kianbakht et al. 2013). Kianbakht et al. (2013) claimed to have carried out a triple-blind study, but the person assessing the outcomes was not blind to intervention, being then classified as 'High' risk for detection bias. One study was classified with 'High' risk for reporting bias due to possible omission of primary outcomes described in the clinical trial (fasting blood glucose before the 1 ½ month of intervention) (Mirfeizi et al. 2016). Two studies were classified as having 'High' risk of bias, for others bias, since the study design was not adequate for the assessed effectiveness of berry consumption over glucose response. This was attributed to selection of control group, which was not equivalent to

intervention (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010). The results of the risk of bias assessments were graphically summarized (**Fig. 2 and 3**).

3.4 Results of Individual Studies

3.4.1 Acute Response Studies

Glucose Metabolism

The effect of cranberries consumption on blood glucose concentrations was assessed in two acute crossover studies (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010). According to Wilson et al (2008) the acute consumption of an unsweetened low-calorie cranberry juice (19 kcal/240 mL) was associated with lower glycemic response than the consumption of a normal calorie dextrose sweetened cranberry juice (130 kcal/240 mL). However, blood glucose concentration responses were similar when the response obtained after both juices was compared to the one obtained after their controls (normal calorie control and low-calorie control, respectively) (Wilson, S.L.L. Meyers, et al. 2008). In another study, Wilson et al. (2010) evaluated the effect of the consumption of sweetened dried cranberries (40 g), low-sugar dried cranberries (40 g) and raw cranberries (55 g) on postprandial glucose response. The area under curve (AUC) for glucose was lower after raw cranberry consumption, compared to the control group (57 g of white bread). The glycemic response after dried cranberry and the control was not different (Wilson et al. 2010).

In a double-blinded crossover study involving men, the blueberry extract consumption (169 mg of anthocyanins) followed by a glucose load (75 g) intake reduced 18% the incremental AUC (iAUC) compared with placebo (Hoggard et al. 2013).

Secondary outcomes

Among the acute studies, the insulin was the only secondary outcome assessed (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010; Hoggard et al. 2013). In a study involving subjects with T2DM consuming a normal calorie cranberry juice (130 kcal/240 mL – 45.7 mg of polyphenols), the insulin response was not affected in the 60 and 120 min postprandial period compared with the control group (140 kcal/240 mL) (Wilson, S.L.L. Meyers, et al. 2008). In another study, the consumption of raw cranberry (55 g) and of sweetened dried cranberry less-sugar (40 g) reduce insulin AUC compared to control (57 g of white bread).

The consumption of blueberry extract (169 mg of anthocyanins) followed by a glucose load (75 g), insulin iAUC reduced 18% compared to placebo (Hoggard et al. 2013).

3.4.2 Interventions Studies

Glucose Metabolism

The effect of the consumption of blueberry (Kianbakht & Hajiaghaee 2013; Mirfeizi et al. 2016) or cranberry (Lee et al. 2008; Shidfar et al. 2012a) on glucose concentration was assessed in four long-term studies.

Shidfar et al. (2012) performed a study focusing on the consumption of cranberry on the lipid profile, in men. Cranberry juice (240 mL) improved fasting glucose concentrations after 12 weeks of intervention, compared to a placebo drink (flavored water) (Shidfar et al. 2012a). However, fasting glucose was not affected after 12 weeks of cranberry extracts consumption compared with placebo (Lee et al. 2008).

Kianbakht et al. (2013) showed that the consumption of blueberry extract (9.1 mg of anthocyanins/day), for 8 weeks, reduced fasting glucose concentrations compared with placebo (Kianbakht et al. 2013). Mirfeizi et al. (2016) showed that daily blueberry powder (1 g with 9.8 mg of anthocyanins) supplementation reduced fasting blood glucose concentrations after 3 months of intervention, compared with baseline but not with the placebo treatment (Mirfeizi et al. 2016).

Secondary outcomes

The secondary outcomes assessed in the intervention studies with berries were 2-hour postprandial glucose concentrations (Kianbakht & Hajiaghaee 2013; Mirfeizi et al. 2016), HbA1c (Lee et al. 2008; Kianbakht & Hajiaghaee 2013; Mirfeizi et al. 2016), insulin (Lee et al. 2008; Mirfeizi et al. 2016) and HOMA-IR (Lee et al. 2008; Mirfeizi et al. 2016). One study did not assess any secondary outcome (Shidfar et al. 2012a).

Cranberry extract exhibited a neutral effect on glucose homeostasis, since the concentrations of glucose, HbA1c, fasting insulin, and HOMA-IR did not change after 12 weeks of intervention (Lee et al. 2008). Shidfar et al. (2012), on the other hand did not assess any secondary outcome.

In another study, the blueberry extract consumption (9.1 mg of anthocyanins/day), during 8 weeks, improved 2-hour postprandial glucose concentration and HbA1c in comparison to placebo group (Kianbakht et al. 2013). On the other hand, Mirfeizi et al. (2016) observed consumption of blueberry powder improved 2-hour postprandial glucose, HbA1c, insulin concentrations and HOMA-IR, compared with baseline values but not with the placebo group (Mirfeizi et al. 2016).

4. DISCUSSION

In the 7 RCTs selected for this systematic review, the effect of berries (blueberry and cranberry consumption) in raw, dried, juice or supplement (capsules) forms on glycemic response was assessed in 270 adults with type 2 diabetes. While the acute glycemic response of cranberry (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010) and of blueberry (Hoggard et al. 2013) was evaluated in three of these studies, the long-term effect after the consumption of cranberry (12 weeks) (Shidfar et al. 2012a; Park et al. 2013) and of blueberry (8 to 12 weeks) (Kianbakht et al. 2013; Mirfeizi et al. 2016) was assessed in four studies.

The acute effect of the cranberry consumption (single day) was assessed in two studies (Wilson, S.L.L. Meyers, et al. 2008; Wilson et al. 2010). Wilson et al. (2008) showed that cranberry juice (unsweetened or dextrose sweetened) consumption did not change glucose or insulin responses, when compared to their respective controls. On the other hand, Wilson et al. (2008) emphasized that consumption of unsweetened low-calorie cranberry juice (19 kcal/240 mL) has led to a lower glycemic response than a normal calorie dextrose sweetened cranberry juice (130 kcal/240 mL). However, the sweetened beverage had higher carbohydrate content than unsweetened one.

Thus, the obtained result could be related to carbohydrate content of the treatments. In another study, there was a lower area under the glucose and insulin curves after raw cranberry (55 g) consumption compared with the control group (57 g of white bread)(Wilson et al. 2010). Once again, the available carbohydrate content of these treatments was not comparable (3.8 g vs 29 g of available carbohydrate, respectively). Therefore, due to these methodological problems no conclusions could be drawn regarding the efficacy of cranberry on glucose and insulin response.

Although cranberry extract supplementation has had neutral effect on glucose homeostasis (fasting glucose, HbA1c, insulin and HOMA-IR) (Lee et al. 2008), cranberry juice (240 mL) reduced fasting glucose concentrations, after 12 weeks of intervention (Shidfar et al. 2012a). The authors of both studies did not provide phenol concentrations of the treatments, being difficult to compare the obtained results. In healthy subjects, the consumption of low-calorie cranberry juice (80 kcal/480 mL per day), during 8 weeks, reduced glucose concentrations and HOMA-IR, improving glucose control and insulin sensitivity (Novotny et al. 2015).

The acute effect of blueberry intake (169 mg of anthocyanins) followed by a glucose load (75 g) on glucose response improved postprandial glucose response (glucose iAUC) and reduced insulin iAUC (Hoggard et al. 2013). This was the only acute study that evaluated the impact of blueberry intake on glucose homeostasis in T2DM subjects.

The impact of blueberry supplementation on glucose control was assessed for at least 8 weeks (Kianbakht et al. 2013; Mirfeizi et al. 2016). Mirfeizi et al. (2016) reported reduction of fasting blood glucose, 2-hour postprandial glucose, insulin and HOMA-IR after 3 months of daily blueberry supplementation (1g/day) compared with baseline but not with the placebo group.

However, according to the data shown in the table, there was a significantly greater reduction on fasting blood glucose (154 ± 39 mg/dL vs 166 ± 59 mg/dL, respectively; $P = 0.024$) and 2-hour postprandial glucose (209 ± 65 mg/dL vs 246 ± 88 mg/dL, respectively; $P = 0.019$) after blueberry supplementation than placebo. After adjusting for baseline values, the authors applied analysis of covariance (ANCOVA) to test differences among post-intervention groups. In case of significant differences ($P < 0.05$), Turkey's post hoc test indicated significant difference in pairwise comparison among the groups ($P < 0.05$). Thus, for interpretation purposes we considered the data presented in the table. Then, both long-term blueberry interventions reduced fasting glucose, after supplementation with blueberry extract or powder (containing 9.1 to 9.8 mg of anthocyanins, respectively) (Kianbakht et al. 2013; Mirfeizi et al. 2016).

Although blood glucose measurement is essential to assess acute glycemic response, HbA1c is an important proxy indicator of long term blood glucose control in the previous two to three months (Sherwani et al. 2016). Thus, along with fasting glucose, HbA1c assessment is the test of choice for monitoring the chronic effect of a given diabetes treatment (Sherwani et al. 2016). Blueberry consumption led to controversial effects on HbA1c (Kianbakht et al. 2013; Mirfeizi et al. 2016), and did not affect insulin and HOMA-IR concentrations after 12 weeks of intervention (Mirfeizi et al. 2016). Despite of that, 2-hour postprandial glucose concentrations decreased in both studies (Kianbakht et al. 2013; Mirfeizi et al. 2016). Altogether, these results indicate that blueberries consumption may reduce immediately glucose response, in T2DM, but effect would be not maintained in the long-term basis.

Berries Polyphenols: Possible Anti-Diabetic Mechanism of Berries

Polyphenols are secondary plants metabolites, mainly in fruits, vegetables, cereals and beverages (red wine, tea and coffee). They present antioxidant properties associated with potential health benefits, including reduced risk for cancer, cardiovascular diseases, diabetes and others non-communicable diseases (Pandey & Rizvi 2009). Polyphenols are divided into flavonoids, phenolic acids, stilbenes, and lignans (Pandey & Rizvi 2009). Flavonoids comprise the most studied group of polyphenols, and it includes flavones, flavanols, flavanones, isoflavones, and anthocyanins (Pandey & Rizvi 2009; Y. Kim et al. 2016). The most prevalent flavonoids found in blueberries and cranberries are described in **Table 2**.

The results of the studies included in this review highlight the potential of blueberries as an adjuvant for T2DM management. Blueberries and cranberries have similar nutritional composition of macronutrients and fiber, but blueberry polyphenol concentration is 2 times greater (**Table 2**). Growing evidence indicates that dietary polyphenols also influence blood glucose and lipid metabolism (Chen et al. 2014; Heber et al. 2014; Wang et al. 2015; Wu et al. 2016). Therefore, since blueberries are rich in polyphenols, specifically in flavonoids, some possible anti-diabetic mechanisms exerted by these compounds are proposed, which should be investigated in future research.

Digestion and Absorption of Glucose

Carbohydrate digestion and absorption are key targets for T2DM therapy. α -Amylase, produced and secreted by salivary glands and pancreatic cells, catalyzes starch α -1, 4-glucosidic linkages breakage producing maltose and other oligosaccharides (McDougall & Stewart 2005; Williamson 2013). In the small intestine, the membrane border enzyme, α -glucosidase, continues

catalyzing the oligosaccharides into absorbable monosaccharides (Y. Kim et al. 2016). The digestive enzymes suppression (α -amylase and α -glucosidase) regulates intestinal glucose digestion and absorption, decreasing the postprandial rise in blood glucose (Y. Kim et al. 2016). Those strategies could delay the diabetic complications onset.

Acarbose and voglibose are known anti-diabetic drugs that inhibit digestive enzymes (α -amylase and α -glucosidase) (McDougall & Stewart 2005; Nyambe-Silavwe et al. 2015). However, there are side effects of the use of these drugs such as liver disorders, abdominal pain, flatulence, diarrhea, and nausea (Zhang et al. 2014). Berries, on the other side, seems to promote similar benefits without these undesirable effects (Nyambe-Silavwe et al. 2015). However, the absence of side effects after berries consumption is not well elucidated. Cranberries have shown to be a potential α -amylase inhibitor (Pinto et al. 2010; Barrett et al. 2013). This effect was dependent on tannin concentration, which is present in a greater proportion in cranberries (Barrett et al. 2013). Besides, blueberry suppresses α -glucosidase better than it inhibits α -amylase (McDougall & Stewart 2005; McDougall et al. 2005). That effectiveness is related to its anthocyanins and proanthocyanins content, in a dose-dependent manner (McDougall & Stewart 2005; McDougall et al. 2005). One of the proposed mechanisms is a competitive inhibition of α -glucosidase activity on its usual substrate (maltose), due to chemical structure similarities (McDougall & Stewart 2005).

Glucose is a hydrophilic molecule that cannot cross biological membranes. Hence, intestinal transporters in small intestine, predominantly sodium/glucose cotransporter member 1 (SGLT1) and glucose transporter type 2 (GLUT2), are essential for glucose absorption into the blood

stream(Kellett et al. 2008; Williamson 2013). SGLT1 is a sodium-dependent glucose cotransporter found in the small intestine brush border, on the apical side of enterocytes(Kellett et al. 2008; Williamson 2013). GLUT2 is a facilitated glucose transporter, independent of sodium, activated at high glucose concentrations (Kellett et al. 2008; Williamson 2013).

Polyphenols found in berries have demonstrated to have a competitive inhibitory effect on those intestinal glucose transporters(Coe & Ryan 2016). Cermak et al. (2004) have showed that quercetin reduced dependent sodium glucose transporters and independent sodium glucose transporters, via SGLT1 and GLUT transporters(Cermak et al. 2004).However, quercetin and myricetin reduce only glucose uptake through GLUT2 transporters, but do not affect active transporters of glucose, like SGLT1 in a similar study (Johnston et al. 2005).

Like α -amylase and α -glucosidase digestive enzymes, SGLT1 and GLUT2 expression are enhanced in T2DM. Also, GLUT2 in T2DM is permanently located at the enterocytes apical membrane (Williamson 2013). Thus, polyphenols found in berries could inhibit glucose uptake, by reducing glucose digestion and absorption, favoring glucose homeostasis in T2DM.

Enhanced glucose uptake

Blueberry and cranberry extract restores glucose uptake in muscle cells and adipose tissue by stimulating the recruitment of glucose transporter type 4 (GLUT4), in a T2DM model (Collin et al. 2017). Additionally, blueberry extract (10 g of anthocyanins/kg diet) enhanced GLUT4 expression in skeletal muscle and white adipose tissue of male adults T2DM mouse. Increased GLUT4 expression was accompanied by AMPK phosphorylation in both tissues, suggesting that

GLUT4 translocated from cytoplasm to membrane through insulin-dependent mechanisms. That evidence corroborates with the improvement observed in glucose and insulin concentrations after 3-5 weeks of intervention (Takikawa et al. 2010). However, in a study performed by Vendrame et al. (2015) no effect on abdominal adipose and liver tissues GLUT4 expression was observed in obese Zucker rats consuming a 110-time lower amount of blueberry anthocyanins (0.12 g of anthocyanins/kg diet) during 8 weeks (Vendrame et al. 2015). Possibly the absence of the effect was associated with the lower blueberry consumption, which also did not show improvement in glycemia or insulinemia, like the first study (Takikawa et al. 2010; Vendrame et al. 2015).

Gut Microbiota

Obesity is associated with increased Firmicutes/Bacteroidetes ratio as well as a reduction in microbial diversity (Aoki et al. 2017). Gut microbiota plays a role on obesity-related disorders (Anhê et al. 2013). Therefore, gut microbiota modulation has been considered as an emerging strategy for body weight control and prevention of metabolic inflexibility, including dyslipidemia, fasting glucose impairment and insulin resistance (Kim et al. 2014; Aoki et al. 2017).

Blueberry anthocyanins and proanthocyanins rises *Bifidobacterium* and *Lactobacillus* populations in humans and animal models (Molan et al. 2009). In streptozotocin (STZ)-induced diabetes obese mice (C57BL/6J), the *Bifidobacterium* spp. supplementation reduced glucose concentrations and enhanced insulin signaling through increased expressions of insulin receptor beta (IR- β), insulin receptor substrate 1 (IRS-1), protein kinase B (Akt/PKB) (Le et al. 2015). Anti-diabetic effect was also observed in obesity induced mice and *ob/ob* mice treated with

Bifidobacterium animalis ssp. *lactis* GCL2505. *B. lactis* GCL2505 consumption improved glucose tolerance and adiposity, raised glucagon-like peptide-1 (GLP-1) concentrations, but plasma insulin concentrations remained unchanged (Aoki et al. 2017). In addition, in T2DM model (*in vitro* and *in vivo*) treatment with *Bifidobacterium lactis* HY8101 exerted a beneficial impact on glucose metabolism, decreasing glucose concentrations by augmenting GLUT4 translocation to plasma membrane, and enhancing insulin sensitivity (Kim et al. 2014). *Lactobacillus reuteri* DSM 17938 daily supplementation for 12 weeks did not affect fasting blood glucose or HbA1c, in T2DM subjects (Mobini et al. 2017). In diet-induced obese mice, *Lactobacillus casei* Shirota administration improved insulin resistance and glucose intolerance (Naito et al. 2011). Also, *Lactobacillus reuteri* L3 decreased glucose and insulin concentrations associated with body weight loss in high-fat diet-induced obese mice model (Qiao et al. 2015).

Bifidobacterium and *Lactobacillus* spp. are representative examples of probiotic microorganisms (Aoki et al. 2017). Recently, the results of a meta-analysis study showed that probiotic supplementation, including *Lactobacillus* spp. and *Bifidobacterium*, improved T2DM glycemic control (Li et al. 2016). Another similar meta-analysis evaluated the effect of probiotics in some metabolic risk factors in T2DM subjects. Controversially, they did not verify any significant effect on glucose concentration. But, HbA1c and HOMA-IR were improved (Kasińska & Drzewoski 2015). These results suggest that probiotic supplementation might modulate glucose homeostasis in T2DM subjects. Hence, modification of the gut microbiota by berry consumption could have beneficial effect on T2DM glucose management.

Inflammation and Oxidative Stress

Inflammation and oxidative stress are associated to diabetes and its associated complications, such as insulin-resistance, and could precede T2DM development (Vikram et al. 2014; Odegaard et al. 2016). Diabetes-associated complications result from a positive feedback cycle of chronic systemic inflammation, oxidative stress and insulin resistance progression (Vikram et al. 2014). Hence, controlling of inflammatory response and antioxidant capacity could be a potential target in T2DM management. Blueberries and cranberries are excellent sources of polyphenols and natural antioxidants (Li et al. 2013; Federation of American Societies for Experimental Biology. et al. 2015). These food compounds may lead to benefits to human health and could be useful for development of adjuvant clinical therapy for metabolic disorders such as T2DM (Stull et al. 2010; Cherniack 2011).

Blueberry and cranberry showed anti-inflammatory and antioxidative activities in mice (Grace et al. 2013). Cranberry polyphenols showed a dose-dependent anti-inflammatory activity by suppressing *IL-1 β* expression in LPS-stimulated murine RAW 264.7 macrophage model (Grace et al. 2013). Anthocyanins from blueberry decreased cellular reactive oxygen species in LPS-treated macrophages. Also, blueberry anthocyanins diminished *IL-1 β* and *TNF* gene expression, in a dose-dependent manner, probably due to inhibition of NF- κ B p65 translocation to the nucleus, upon LPS stimulus (Lee et al. 2014). Esposito et al. (2014) showed that crude extract and fractions of blueberry suppress inflammatory mRNA biomarkers, such as *COX-2*, *iNOS* and *IL-1 β* . The most prevalent phenolic compounds (malvidin-3-glucoside, epicatechin and chlorogenic acid) were associated with the modulation of acute inflammatory response in murine

RAW 264.7 macrophages (Esposito et al. 2014). However, the inflammatory response and antioxidant activity remained unchanged in diet-induced obese mouse model fed with a high fat diet supplemented containing frozen blueberry (5%) during 12 weeks (B. Kim et al. 2016).

In humans, the outcomes also are scarce and controversial. Regular consumption of 250 mL of blueberry drink (6 weeks) did not affect inflammatory biomarkers or enzymatic oxidant activity in subjects presenting at least one cardiovascular risk factor. Despite of that blueberry drink consumption reduced oxidized purines and improved the resistance against H₂O₂ induced DNA damage in blood mononuclear cells (Riso et al. 2013). However, the authors of that study considered smokers/ex-smokers as subjects with cardiovascular risk. That may have been a bias for the outcomes observed for oxidative stress and inflammation. Furthermore, although the consumption of low-calorie cranberry juice (480 mL with 80 kcal/day) during 8 weeks did not affect inflammatory cytokines (IL-6, IL-10, IL-1b, and TNF-a), there was reduction on serum C-reactive protein in non-diabetic adults (Novotny et al. 2015). However, in a similar intervention, daily consumption of 480 ml of blueberry beverage for 8-week, did not affect postmenopausal women CRP was not (Johnson et al. 2015).

Final Considerations

The beneficial mechanisms attributed to berries consumption are quite difficult to assess *in vivo* since polyphenols are poorly absorbed (within 1–3 h) and quickly metabolized and excreted within 12–24 h after consumption (Riso et al. 2013). Also, their absorption may be influenced by dosage, administration vehicle, prior diet, food matrix and differences in the gut microbial populations (Anhê et al. 2013). Further, berries chemical composition could be affect by soil

conditions, temperature, humidity, light besides growing location and conditions (da Silva et al. 2016).

We have found that there is considerable variability among the comorbidities associated with diabetes in the studies (also, lacking information in some studies) and that they may affect their outcome. It is also believed that some studies outcomes must be prudently considered since they were not properly designed (inappropriate selection of control groups) to assess the effect of berries consumption on glucose control.

Berries were tested in different forms (*in natura*, dried, extract, preparations – juice). Also, dose range varied among the trials. Therefore, the evidence is insufficient to establish an ideal dosage and/or the best administration form of berries (cranberry or blueberry) to improve glucose control. However, regardless of these limitations the results of some studies (Shidfar et al. 2012b; Hoggard et al. 2013; Kianbakht & Hajiaghaee 2013; Mirfeizi et al. 2016) highlight the potential benefit of berries, especially of blueberry, on glucose metabolism in T2DM subjects.

5. CONCLUSIONS

According to the results obtained in the studies included in this review, a beneficial effect on glucose control was observed in response to the consumption of blueberry extract or powder supplementation (9.1 to 9.8 mg of anthocyanins, respectively) for 8 to 12 weeks as well as to daily consumption of cranberry juice (240 mL) for 12 weeks. Altogether, outcomes indicate a promising use of these berries in T2DM management; although more studies are required to better understand the mechanisms involved.

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Table 1. Characteristics of the eligible randomized clinical trials

Author, year	Study Design	Subjects *	Berry (Specie)	Phenolic Compounds	Dietary Interventions	Duration	Washout	Glucose Assessment	Main Results †
Wilson et al., 2008	Crossover, randomized, controlled	n: 12	Cranberry (specie N/A)	45.7 mg of phenolics	- Normal calorie cranberry juice (240mL)	Single day trial (acute response)	1 week §	Venous blood analyzed immediately	↔ Postprandial glucose ↔ Postprandial insulin
		F/M: 6/6			- Normal calorie control (240mL)				
		Age: 65.3 ± 8.0 y			- Low calorie cranberry juice (240mL)				
		BMI: 34.7 ± 5.5 kg/m ²			- Low calorie control (240mL)				
		Glucose: 126.1 ± 25.0 mg/dL							
		HbA1c: 6.7 ± 0.3 %							
Wilson et al., 2010	Crossover, randomized, controlled	n: 13	Cranberry (specie N/A)	131 mg of phenolics ** (Sweetened dried cranberry) 163 mg of phenolics ** (Sweetened dried with less sugar cranberry)	- Raw cranberry (55 g)	Single day trial (acute response)	N/A	Plasma samples stored until analyses (-80°C)	↓ Glucose AUC (raw cranberry) ↓ Insulin AUC (raw and sweetened dried less sugar cranberry)
		F/M: 6/7			- Sweetened dried cranberry (40 g)				
		Age: 61.6 ± 8.3 y			- Sweetened dried with less sugar cranberry (40 g)				
		BMI: 33.2 ± 4.4 kg/m ²			- Control (white bread) (57 g)				
		Glucose: ≈ 117 mg/dL †							
		HbA1c: 6.2 ± 0.6 %							
Hoggard et al., 2013	Double-blind, crossover, randomized	n: 8 F/M: 0/8 Age: 62.1 ±	Blueberry (<i>Vaccinium myrtillus</i> L.)	169 mg of anthocyanins	- Hydroalcoholic extract of blueberry	Single day trial (acute response)	2 weeks	Venous plasma samples stored until	↓ Glucose iAUC ↓ Insulin iAUC

	ed, placebo-controlled	4.5 y BMI: 30.3 ± 4.4 kg/m ² Glucose: 129.0 ± 25.4 mg/dL HbA1c : N/A			y; 0.47 mg/capsule; 1 capsules/day (Mirloselect ®; Indena S.p.A.) - Placebo (capsule microcrystalline cellulose)	e)		analyses (-70°C)
								Both were added to a glucose load (75 g of Polycal)
Lee et al., 2008	Double-blind, parallel, randomized, placebo-controlled	n: 30 F/M: 14/16 Age: 65.5 ± 7.6 y BMI: 26.0 ± 3.3 kg/m ² Glucose: 154.9 ± 31.5 mg/dL HbA1c : 8.0 ± 0.8 %	Cranberry (specie N/A)	N/A	- Cranberry extract powder; 500 mg/capsule; 3 capsules/day (Triarco Industries Inc., USA) - Placebo (N/A)	12 weeks	-	N/A ↔ Fasting Glucose ↔ HbA1c ↔ Insulin ↔ HOMA-IR
Shidfar et al., 2012	Double-blind, parallel, randomized, placebo-controlled	n: 58 F/M: 0/58 Age: 54.8 ± 9.1 y BMI: 28.8 ± 3.6 kg/m ²	Cranberry (specie N/A)	N/A	- Cranberry juice (240 mL) - Placebo (mineral water with strawberry)	12 weeks	-	Serum samples from venous blood ↓ Fasting Glucose

		Glucose: 137.9 ± 9.3 mg/dL HbA1c : < 9 %						flavor) (240 mL)	
Kianbakht et al., 2013	Double-blind, parallel, randomized, placebo-controlled	n: 74 F/M: 35/39 Age: 55.1 ± 9.6 y BMI: 29.1 ± 7.9 kg/m ² Glucose: 185.7 ± 31.2 mg/dL HbA1c : 7.4 ± 1.0 %	Blueberry (<i>Vaccinium arctostaphylos</i> L.)	9.1 mg of anthocyanins	-	8 weeks	-	Hydro alcoholic extract of blueberry; 350 mg/capsule; 3 capsules/day Placebo (capsule – toast powder)	N/A ↓ Fasting Glucose ↓ 2-hour Postprandial Glucose ↓ HbA1c
Mirfeizi et al., 2016	Triple-blind, parallel, randomized, placebo-controlled	n: 102 F/M: 79/23 Age: 53.8 ± 11.7 y BMI: 28.7 ± 3.9 kg/m ² Glucose: 186.3 ± 66.9 mg/dL HbA1c : 8.6 ± 1.4 %	Blueberry (<i>Vaccinium arctostaphylos</i> L.)	9.8 mg of anthocyanins	-	12 weeks	-	Blueberry powder; 500 mg/capsule; 2 capsules/day Cinnamon; 500 mg/capsule; 2 capsules/day Placebo (starch); 500 mg/capsule; 2 capsules/day	Blood samples stored until analyses (-70°C) ↓ Fasting Glucose ↓ 2-hour Postprandial Glucose ↔ HbA1c ↔ Insulin ↔ HOMA-IR

n: number of subjects; F/M: male/female; y: years; N/A: not available; DNA: does not apply;

HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment of insulin resistance;

AUC: area under the curve; iAUC: incremental AUC; * data are expressed as mean \pm SD; † extrapolated data from the graphic showed in the study; ‡ result compared to the control/placebo group; § subject assignment to interventions occur on 4 of 5 semi consecutive weeks according to the author; ** phenolic (flavonols and proanthocyanidin) content identified only in sweetened dried cranberries at the study of Wilson et al. (2010).

Table 2. Chemical characterization of blueberry and cranberry ($\text{g} \cdot 100^{-1}$).

Characteristics	Blueberry	Cranberry
Energy (kcal)	57	46
Carbohydrate (g)	14.49	11.97
Protein (g)	0.74	0.46
Lipid (g)	0.33	0.13
Fiber (g)	2.4	3.6
Anthocyanidins		
Cyanidin (mg)	8.46	46.43
Peonidin (mg)	20.03	49.2
Delphinidin (mg)	35.4	7.7
Petunidin (mg)	31.5	0
Malvidin (mg)	67.6	0.4
Flavonols		
Quercetin (mg)	7.7	14.8
Myricetin (mg)	1.3	6.6
Proanthocyanidins		
Proanthocyanidin dimers (mg)	6.4	17.7
Proanthocyanidin trimers(mg)	4.9	16.4
Proanthocyanidin 4-6mers (mg)	20.5	56.8
Proanthocyanidin 7-10mers(mg)	14.3	46.2
Proanthocyanidin polymers(mg)	136.0	217.6
Total polyphenols (mg)	656.0	315.0

Sources: US Department of Agriculture Nutrient Data Base.

<http://ndb.nal.usda.gov/ndb/foods/list> (accessed in March 21, 2017) and Phenol-Explorer 3.0.

Data base on polyphenol content in foods. <http://www.phenol-explorer.eu> (accessed in March 21, 2011).

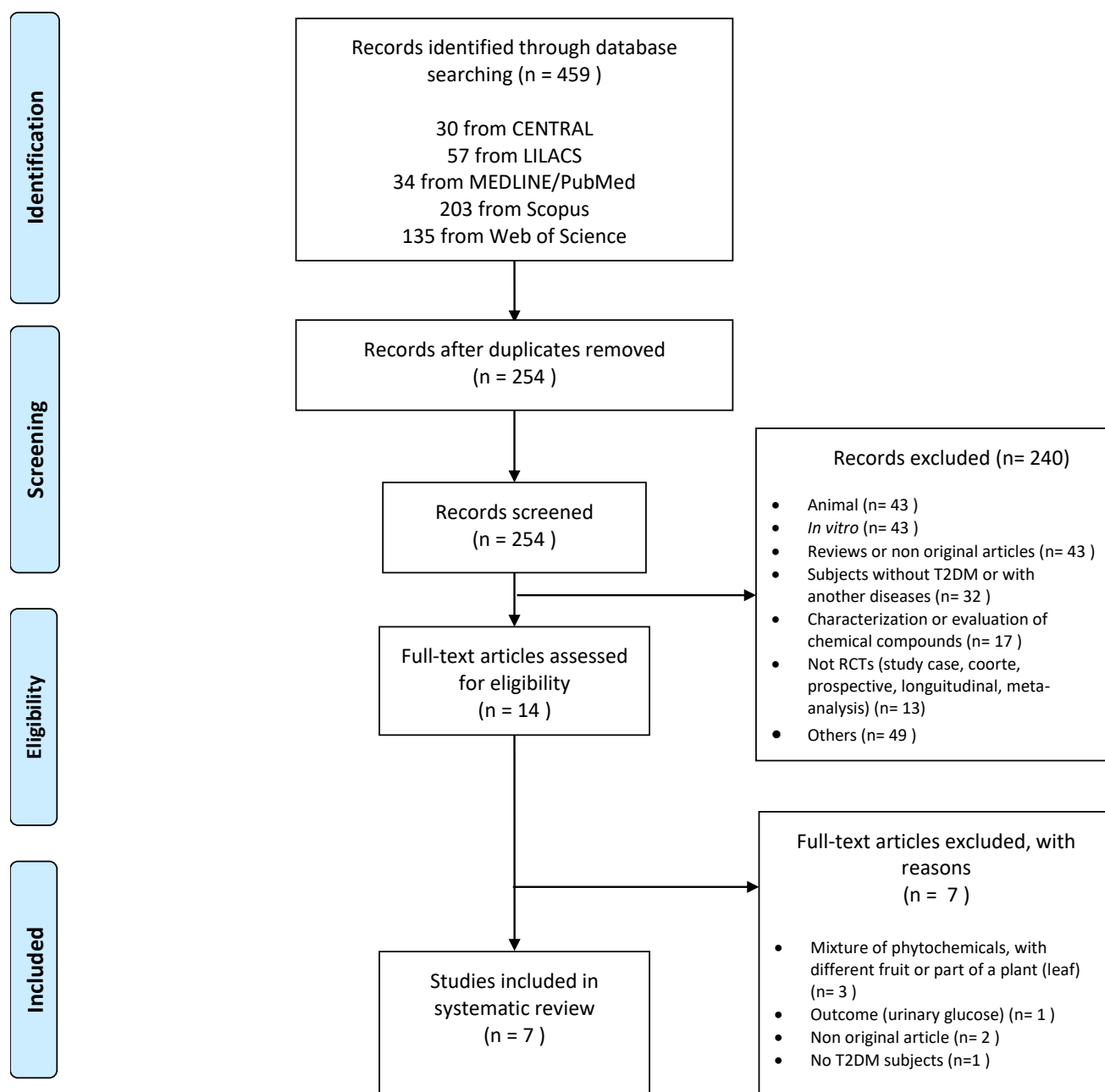


Figure 1. Flowchart of studies selection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hoggard et al. 2013	?	?	+	?	?	+	?
Kianbakht et al. 2013	+	?	+	-	?	+	?
Lee et al. 2008	?	?	+	?	+	?	?
Mirfeizi et al. 2016	+	+	+	+	?	-	?
Shidfar et al. 2012	?	?	+	?	?	+	?
Wilson et al. 2008	?	?	?	?	?	+	-
Wilson et al. 2010	?	?	?	?	?	+	-

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

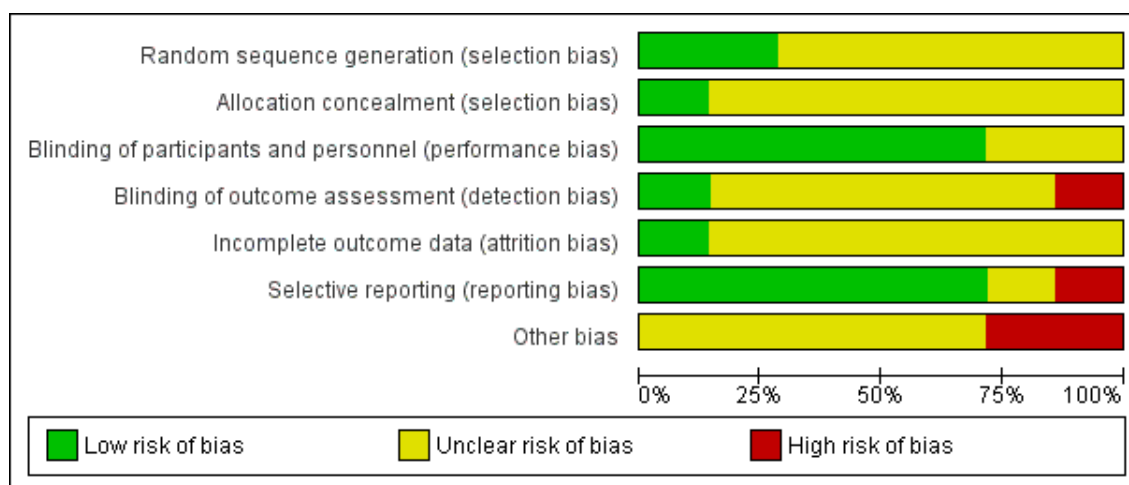


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.