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Systematic Review Article

Title:

A tale of two cinnamons: a comparative review of the clinical evidence of *Cinnamomum verum* and *C. cassia* as diabetes interventions

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Abstract

Objective: This review investigates the effectiveness of two cinnamon species, *Cinnamomum verum* and *C. cassia*, in diabetes management; their impact on related health conditions and relevant parameters in healthy individuals and safety issues.

Methods: PubMed, Cochrane Library, and ScienceDirect were searched from 2000 up to April 2018 for clinical trials using either *C. verum* or *C. cassia* in controlling blood glucose and other diabetes-related parameters and conditions.

Results: A total of twenty-five studies (n=997) were included for reviewing clinical evidence. Among these trials, fifteen studies investigated the effects on type II diabetes mellitus

(T2DM) patients (n=831), four investigated subjects with related clinical conditions (n=82), and six investigated healthy individuals (n=84). Nineteen studies used *C. cassia* and six used *C. verum*. Results suggested *C. cassia* helped manage diabetes at 3-6g, while the effectiveness of *C. verum* remained inconclusive. In addition, the chemical properties of *C. cassia* and *C. verum* differ considerably. Of note, *C. cassia* contains high levels of the potentially hepatotoxic constituent coumarin. A skin rash was the only adverse event reported.

Conclusion: While evidence supports the therapeutic benefit of *C. cassia*, interchangeability of *C. cassia* and *C. verum* remains inconclusive. Further research is warranted to address the effectiveness and safety of these cinnamon species. Given the potential hepatotoxicity of *C. cassia*, RCTs that include liver function tests are required. Robust RCTs on *C. verum* are recommended to establish if its efficacy can match its safety profile.

Keywords: cinnamon, *Cinnamomum verum*, *Cinnamomum cassia*, diabetes

1. Introduction

The number of diabetes sufferers has been increasing. In 2014, globally, 422 million people were living with diabetes, compared with 108 million in 1980, according to the World Health Organization (WHO, 2016). Diabetes is a metabolic disorder affecting blood glucose levels, which can have serious consequences, including cardiovascular disease, nephropathy, retinopathy, peripheral neuropathy and diabetic foot (Struijs et al., 2006; WHO, 2016). The majority of diabetes patients are affected by type II diabetes mellitus (T2DM), which mainly occurs among adults and is associated with insulin resistance, metabolic syndrome and obesity (Kahn et al., 2006). Growing evidence suggests the association between insulin resistance and several clinical conditions, including polycystic ovarian syndrome (PCOS) (Pauli et al., 2011), non-alcoholic fatty liver disease (NAFLD) (Ballestri et al., 2016), various cancers (Malaguarnera et al., 2017; Vona-Davis et al., 2007) and their complications (e.g. muscle wasting cachexia (Honors and Kinzig, 2012)). In addition, epidemiological evidence

suggests that people with diabetes are at an increased risk for cognitive decline, vascular dementia, and Alzheimer's disease (Gudala et al., 2013; Ninomiya, 2014; Ojo and Brooke, 2015), indicating the importance of diabetes management in the ageing population.

Due to the increasing prevalence and chronic nature, T2DM is a global health issue of significant economic importance. According to American Diabetes Association (ADA), the direct medical cost in 2012 was $176 billion in the United States, and average medical expenditure on a diabetes patient was about $13,700 per year: approximately 2.3 times higher than the estimate in the absence of diabetes (ADA, 2013). In Europe, a study comprising 8 countries (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom) revealed the cost of T2DM to be € 29 billion a year (1999 values) and the estimated average yearly cost € 2834 per patient (Jönsson B and Board., 2002). In Germany alone, average annual direct cost of medical care was € 5,262, approximately 1.9 times higher compared with costs of age- and sex-matched non-diabetic control subjects (Köster et al., 2006). Although some of the top-selling medications such as metformin are modestly priced and drug costs for managing T2DM are relatively low (7% of the total healthcare costs for T2DM) (Jönsson B and Board., 2002), the exploration of blood glucose management using traditional herbal medicines is warranted as it could help prevent the development of T2DM and comorbidities, thereby reducing the direct and indirect costs. Current anti-diabetic drugs such as sulfonylureas and α-glucosidase inhibitors help manage blood glucose levels. However, due to potential side effects such as nausea, dyspepsia and weight gain (Sola et al., 2015; van de Laar, 2008), it is important to find effective and safer alternatives.

The medicinal properties of cinnamon have been acknowledged since antiquity (De Vos, 2010). The genus *Cinnamomum* (Lauraceae) includes more than 250 species, among which *Cinnamomum verum* J.Presl (synonym: *C. zeylanicum* Blume, Ceylon cinnamon or true cinnamon) and *C. cassia* (L.) J.Presl (synonym: *C. aromaticum* Nees, cassia cinnamon or Chinese cinnamon) are most commonly used as medicines (Nabavi et al., 2015). The inner bark is used as a circulatory stimulant, a digestive aid, diaphoretic, and antitussive (Bone and

Mills, 2013; Klein and Rister, 1993). Historically, *C. cassia* is among the top 14 'simples' (plants that can be used on their own for medicinal purposes, rather than as part of a formula) listed in 12 important texts including *Hippocratic Corpus* (5^{th} -4^{th} century BC), *De Materia Medica* by Dioscorides (1^{st} century AD), The Canon of Medicine (volume 2) by Avicenna (980 – 1037 AD), and *Farmacopea Espanola* (1865), while *C. verum* is one of the top 26 simples, listed in 11 out of the 12 texts (De Vos, 2010). In The Canon of Medicine, *Cinnamomum spp*. was among 18 plants that protect the liver from injuries or diseases, and recent studies confirmed the hepatoprotective effect of *Cinnamomum spp*. using animal models (Shamsi-Baghbanan et al., 2014). In a 15th-century French herbal '*Le Livre des Simples Medecines*', cinnamon was among the six medicinal spices (pepper, ginger, cinnamon, cloves, nutmeg, and mace). The text states that cinnamon is used 'for weakness of the stomach and liver and to help digestion weakened by cold', 'to restore appetite', 'for recently cracked lips and other sores', and 'for heart ailments and syncope' (Nam, 2014). In fact, the use of cinnamon to treat digestive tract ailments has continued throughout history (De Vos, 2010). The European Medicine Agency (EMA) endorses the traditional use of *C. verum* for symptomatic treatment of mild, spasmodic gastro-intestinal complaints (EMA, 2011b). At present, cinnamon is on the market as a prophylactic supplement for metabolic syndrome, insulin resistance, T2DM, hyperlipidaemia, and arthritis (Medagama, 2015; Rafehi et al., 2012).

The major constituents of cinnamon include cinnamaldehyde, cinnamyl acetate, eugenol, catechin, epicatechin, and proanthocyanidins (Chen et al., 2012; Chen et al., 2014; Kaul et al., 2003; Vallverdú-Queralt et al., 2014). A number of potential mechanisms for cinnamon have been suggested (Rafehi et al., 2012), including activation of phosphorylation of insulin receptors β-subunits; increased expression of GLUT 4, increase in GLUT 1 mediated glucose uptake, increase in GLP-1, increase in PPAR, inhibition of intestinal α-glucosidase and pancreatic α-amylase, inhibition of gluconeogenesis, and delay of gastric emptying. Preclinical studies demonstrated hypoglycaemic and hypolipidaemic properties of

cinnamon extract and the active constituents (Medagama, 2015). *In vivo* studies found improved insulin sensitivity and lowered intestinal carbohydrate absorption after the treatment with cinnamon extract in T2DM model mice (Kim et al., 2006), a reduction of plasma glucose levels by cinnamaldehyde via insulin secretion from pancreatic β-cells (Subash Babu et al., 2007), insulin-like activity of cinnamon polyphenols (trimers and tetramers of catechin and epicatechin) (Anderson et al., 2004), blood glucose-lowering effects of polyphenol-enriched *C. verum* extract (IM et al., 2014b) and polyphenol-enriched de-coumarinated *C. cassia* extract (IM et al., 2014a), and lowered triglyceride and total cholesterol levels after treatment with cinnamon extract in T2DM model mice (Kim et al., 2006). PPAR-γ and α activation in adipocytes (Sheng et al., 2008) and up-regulation of anti-inflammatory factors such as tristetraprolin and glucose transporter (GLUT1) in macrophages were also suggested *in vitro* (Cao et al., 2008). Using *C. verum*, Kadan *et al*. demonstrated a significant gain in GLUT4 on the cell surface of muscle cells, suggesting that *C. verum* could facilitate glucose uptake into skeletal muscle (Kadan et al., 2013). Considering that glycemic fluctuations and hyperglycemia trigger endothelial dysfunction and inflammation (Mannucci et al., 2013), controlling hyperglycemia is likely to reduce the risk of atherogenesis and cardiovascular events. In addition, hyperglycemia and abnormal insulin levels are related to an increased risk of Alzheimer's disease as well as vascular dementia (Gudala et al., 2013; Matsuzaki et al., 2010; Rönnemaa et al., 2008; Young et al., 2006). Therefore, the hypoglycaemic property of cinnamon may protect against diabetes-related comorbidities such as cardiovascular diseases and dementia.

The EMA states that cinnamon bark contains up to 4% of essential oil consisting primarily of cinnamaldehyde (60-75%) (EMA, 2011a). Herbal preparations equivalent to 2-4g cinnamon per day, or 50-200mg of essential oil, are indicated for symptomatic treatment of mild spasmodic gastrointestinal complaints including bloating and flatulence (EMA, 2011b). *C. cassia* has traditional use similar to *C. verum*, however the two species have differences in their constituents as summarised elsewhere (Ranasinghe et al., 2013): *C. verum* bark oil

contains 49.9–62.8% trans-cinnamaldehyde while *C. cassia* contains almost 95% cinnamaldehyde. In addition, it is notable that *C. cassia* contains coumarin up to 1% (Krieger et al., 2013), whereas *C. verum* contains coumarin only at trace or undetectable levels (Krieger et al., 2013; Ranasinghe et al., 2013). Considering that *o*-hydroxyphenylacetaldehyde (o-HPA), a metabolite of coumarin, is hepatotoxic, long-term consumption of *C. cassia* may pose a health risk (Abraham et al., 2010; Ranasinghe et al., 2013), while *C. verum* would likely be free of this particular risk (Medagama, 2015). Therefore it has been suggested that *C. verum* should be used in preference to *C. cassia* in treating T2DM (Medagama, 2015).

Five reviews have examined the efficacy of cinnamon species for diabetes (Table 1). A systematic review and meta-analysis conducted in 2012 (Leach and Kumar, 2012) assessed ten RCTs published between 2003 and 2010. The authors concluded that there is insufficient evidence to support the use of cinnamon as an anti-diabetes mellitus treatment. On the other hand, systematic review and meta-analysis by Akilen *et al*. (2012) found a significant decrease in HbA1c and fasting blood glucose levels (Akilen et al., 2012). A year later, In 2013, a meta-analysis (Allen et al., 2013) found significant improvement in fasting blood glucose levels as well as in lipid parameters, although no significant effect was found on HbA1c levels. Another meta-analysis (Alanazi and Khan, 2015) reflected the findings of Allen *et al.* (2013). Medagama (2015) found improved glycaemic control in T2DM patients without other medications as well as those with pre-diabetes and high pre-treatment HbA1c. Medagama concluded that cinnamon is potentially useful as an adjuvant therapy in managing T2DM. The difference in conclusions between those reviews is interesting, ranging from insufficient evidence to a useful add on treatment. Of note, none of these reviews separately assessed the different cinnamon species. Overall this suggests the evidence for effective intervention in T2DM is growing, but provisional, given the heterogeneity of cinnamon species, preparations, and dosages.

The herbal CONSORT statement (Gagnier et al., 2006) considers it “imperative that reports of RCTs provide clear and complete descriptions of the herbal intervention”,

including the Latin binomial name together with botanical authority and family name in addition to common names for each herbal ingredient. If the species is unspecified it is difficult to establish causality. Given the potential confusion, substitution or adulteration of herbal products, (Fong, 2002; Posadzki et al., 2012), this review focuses on interventions using two named cinnamon species: *C. cassia* and *C. verum.*

While Medagama discussed the safety issue of high coumarin content in *C cassia,* suggesting *C. verum syn zeylanicum* as a safer alternative, none of the five reviews evaluated the differential efficacy of the two main medicinal cinnamon species and their dosages as a T2DM intervention and whether the coumarin content of these species is a cause for concern. Furthermore, these reviews did not assess the differential evidence for the suitability of the two cinnamon species for related clinical conditions, nor the effect of the two cinnamon species on blood sugar related parameters in healthy populations. Hence, this study seeks to review the current evidence for *C. cassia* and *C. verum* in the treatment of T2DM and metabolically related conditions, their effects on blood sugar related parameters in healthy populations, and their safety profile.

2. Methods

2.1 Database searching for clinical evidence

The current review focuses on trials investigating the effects of *C. verum* and *C. cassia* on the levels of blood glucose and other relevant parameters in diabetes management. To consider prophylactic benefits and effectiveness in the management of diabetes, trials on T2DM patients, as well as subjects with other related clinical conditions and healthy individuals, were reviewed.

Search strategy

To find clinical evidence for the anti-diabetic effects of *C. verum* and *C. cassia,* searches were conducted using databases, namely PubMed/Medline, Cochrane Library, and ScienceDirect. Studies were included in the current review if they were published between 2000 up to April 2018 and met the inclusion criteria below. PubMed/Medline searches were conducted for

article type 'Clinical Trial', using search terms '*Cinnamomum verum*' and its botanical synonym '*Cinnamomum zeylanicum*', '*Cinnamomum cassia*', and its botanical synonym '*Cinnamomum aromaticum*'. The same terms were used for searching in Cochrane Library, and ScienceDirect. For ScienceDirect, searches were refined by selecting 'Abstract, Title, Keywords' and categories of 'Nursing and Dentistry', 'Nursing and Health Professions', 'Pharmacology', and 'Toxicology and Pharmaceutical Science'.

Inclusion criteria:

1. Original study
2. Focusing on the effect of either *C. verum* or *C. cassia* (not in combination with other herbs or nutrients) in controlling blood glucose levels or other parameters relevant to diabetes management or related clinical conditions
3. Published in English
4. Controlled

Publications not meeting the above criteria, as well as studies using unspecified or different cinnamon species, or combination products, were excluded. Each author assessed the final selection of studies independently, before final agreement on inclusion.

2.2 Coumarin content and safety issues

To assess coumarin contents and potential toxicity of cinnamon species, database searches were conducted for journal articles using the combination of 2 keywords, namely coumarin and either *C. verum* or *C. cassia*. PubMed searches were conducted using the following search terms: (1) (*Cinnamomum zeylanicum*) AND coumarin, (2) (*Cinnamomum verum*) AND coumarin, (3) (*Cinnamomum cassia*) AND coumarin, and (4) (*Cinnamomum aromaticum*) AND coumarin, for publication from 1971 to November 2017. For ScienceDirect, the same term combinations were searched in abstract, title, and keywords. Searches were conducted on 2017 Dec 1-3. Papers were screened by title and abstract, and then selected for reviewing if it contained quantitative information about the contents of coumarins or safety issues of either *C. verum* or *C. cassia*.

3. Results and Discussions

There are 3 most common ways to detect diabetic and prediabetic conditions: fasting blood glucose, HbA1c levels, and glucose tolerance (ADA, 2010; Patel and Macerollo, 2010). HbA1c test is a blood test that provides the average blood glucose over the past 3 months. Oral Glucose Tolerance Test (OGTT) measures glucose tolerance by measuring blood glucose after fasting and after glucose intake. Trials reviewed in this study assessed the effectiveness of cinnamon in T2DM patients using these and related parameters, as well as the effect of *C. cassia* and *C. verum* on related conditions and healthy populations.

3.1 Cinnamon for diabetes management

A total of 12 database searches (4 for each database: PubMed, ScienceDirect, and Cochrane Library) were conducted using the 4 search terms, and 308 results were obtained. There were 67 results (39 from PubMed, 21 from ScienceDirect, and 7 from Cochrane Library) for '*Cinnamomum verum*, 121 results (38 from PubMed, 37 from ScienceDirect, and 46 from Cochrane Library) for '*Cinnamomum zeylanicum*', 100 results (10 from PubMed, 78 from ScienceDirect, and 12 from Cochrane Library) for '*Cinnamomum cassia*', and 20 results (7 from PubMed, 6 from ScienceDirect, and 7 from Cochrane Library) for '*Cinnamomum aromaticum*'. After removing duplicates and screening from title and abstract, 32 articles remained. Seven studies were removed, three due to the lack of information on the cinnamon species used in the trials (Altschuler et al., 2007; Khan et al., 2010; Mirfeizi et al., 2016); three using a different species: *C.burmanii* as the formulation CinSulin (Anderson et al., 2016; Roussel et al., 2009; Ziegenfuss et al., 2006); one using a combination product including zinc gluconate (Wainstein et al., 2011). The remaining 25 studies of 997 participants were selected for reviewing (Table 1). The selection process is presented in a flowchart (Figure 1).

Fifteen studies were conducted on T2DM patients, among which twelve trials used *C. cassia* (Akilen et al., 2010; Blevins et al., 2007; Crawford, 2009; Gullapalli et al., 2013;

Hasanzade et al., 2013; Khan et al., 2003; Lu et al., 2012; Mang et al., 2006; Sengsuk et al., 2016; Soni and Bhatnagar, 2009; Suppapitiporn et al., 2006; Vanschoonbeek et al., 2006) (n=730) and three trials used *C. verum* (Azimi et al., 2014; Azimi et al., 2016; Vafa et al., 2012) (n=123). Dosages were 1-3g per day, and durations of the trials ranged from 30 days to four months. Reduction in fasting blood glucose or other diabetes-related parameters were demonstrated in ten studies (*C. cassia* 1.5-6g per day for 40 days - four months, or *C. verum* 3g per day for 8 weeks) (Akilen et al., 2010; Azimi et al., 2014; Azimi et al., 2016; Crawford, 2009; Gullapalli et al., 2013; Khan et al., 2003; Lu et al., 2012; Mang et al., 2006; Sengsuk et al., 2016; Soni and Bhatnagar, 2009), and a study showed postprandial blood glucose decrease after 40-day administration of *C. cassia* (2g per day) (Soni and Bhatnagar, 2009). On the other hand, four studies found no significant effect on fasting blood glucose levels after 1-1.5g *C. cassia* administration for 30 days – three months (Blevins et al., 2007; Hasanzade et al., 2013; Suppapitiporn et al., 2006; Vanschoonbeek et al., 2006). Four studies (n=82) were conducted on subjects with other clinical conditions such as impaired glucose tolerance (IGT), high fasting or postload blood glucose levels and obesity. Among these studies, three trials used *C. cassia* (Gutierrez et al., 2016; Magistrelli and Chezem, 2012; Wickenberg et al., 2014) (n=72) and one trial used *C. verum* (Wickenberg et al., 2012) (n=10). Three trials were conducted on postprandial glucose levels using an oral glucose tolerance test with cinnamon intake at the test (Gutierrez et al., 2016; Wickenberg et al., 2012; Magistrelli and Chezem, 2012). Intake of *C. cassia* 5-6g reduced postprandial glucose levels in obese individuals (Gutierrez et al., 2016; Magistrelli and Chezem, 2012), while *C. verum* 6g had no effect in IGT patients (Wickenberg et al., 2012). Twelve-week oral administration of 12g of *C. cassia* had no effect on insulin sensitivity, fasting blood glucose or HbA1c (Wickenberg et al., 2014). Six studies were conducted on 84 healthy subjects, among which four trials used *C. cassia* (Hlebowicz et al., 2009; Mettler et al., 2009; Solomon and Blannin, 2007, 2009) and two trials used *C. verum* (Beejmohun et al., 2014; Markey et al., 2011). Five OGTT studies were conducted with *C. cassia* or *C. verum* (Beejmohun et al., 2014; Hlebowicz et al., 2009; Markey et al., 2011; Mettler et al., 2009; Solomon and Blannin,

2007) and one study looked at postprandial glucose and insulin levels after 14-day administration of *C. cassia* (Solomon and Blannin, 2009). Positive outcomes were obtained in the trials using *C. cassia* (3-5g) (Hlebowicz et al., 2009; Mettler et al., 2009; Solomon and Blannin, 2007, 2009), and 1g alcoholic extract of *C. verum* (Beejmohun et al., 2014). However, *C. verum* 3g had no effect on postprandial glucose and lipid levels after a high fat meal (Markey et al., 2011).

3.1.1 T2DM: *C. cassia* and *C. verum* compared (Table 2-1)

Out of 15 studies on T2DM patients, 12 used *C. cassia* and three used *C. verum*. Of these 15 studies, ten reported significant improvements with a variety of outcome measures including HbA1c, fasting blood glucose, postprandial blood glucose and insulin as well as the patho-metabolically related parameters of blood pressure. Eight of these ten positive outcomes were from the 12 *C. cassia* studies (Akilen et al., 2010; Blevins et al., 2007; Crawford, 2009; Gullapalli et al., 2013; Hasanzade et al., 2013; Khan et al., 2003; Lu et al., 2012; Mang et al., 2006; Sengsuk et al., 2016; Soni and Bhatnagar, 2009; Suppapitiporn et al., 2006; Vanschoonbeek et al., 2006) and the remaining positive outcomes were two of the three *C. verum* studies (Azimi et al., 2014; Vafa et al., 2012). Furthermore, *C. cassia* 1.5-6g per day, aqueous extract 120-360 mg per day for 40 days – three months, or *C. verum* 3g per day for eight weeks reduced triglyceride and LDL levels in T2DM patients (Khan et al., 2003; Lu et al., 2012; Sengsuk et al., 2016). Considering that body fat is a significant diabetes-associated risk factor for cardiovascular disease (Howard et al., 2000), *C. cassia* and *C. verum* may help prevent the development of vascular comorbidity in T2DM. Five studies (Azimi et al., 2016; Blevins et al., 2007; Hasanzade et al., 2013; Suppapitiporn et al., 2006; Vanschoonbeek et al., 2006) reported no improvements in the analysed outcome measures including fasting glucose levels and HbA1c. Four of these were *C. cassia* studies (Blevins et al., 2007; Hasanzade et al., 2013; Suppapitiporn et al., 2006; Vanschoonbeek et al., 2006) and one was a *C. verum* study (Azimi et al., 2016). The dosages for three of *C. cassia* studies were 1g per day (Blevins et al., 2007; Hasanzade et al., 2013), and 1.5g per day (Suppapitiporn et al., 2006;

Vanschoonbeek et al., 2006). These dosages are low compared to the most commonly used dosage of 3g per day. In addition, the duration in the Hasanzade study was 30 days (Hasanzade et al., 2013), which is likely too short to meaningfully assess changes in HbA1c levels, an outcome measure used in the study. Administration of 3g per day for eight weeks showed no improvement in a study (Azimi et al., 2016), which measured blood pressure and endothelial function in T2DM rather than direct blood glucose parameters. This is relevant considering the relationship between poor blood glucose control and hypertension via the development of atherosclerosis may take longer to modify than eight weeks that was provided in the trial. Interestingly, when the same authors reported fasting blood glucose as the outcome measure on this study, a decrease was found (Azimi et al., 2014), suggesting it is easier to modify this parameter with *C. verum* than its downstream effects. Both publications (Azimi et al., 2014; Azimi et al., 2016) refer to different datasets within the same study of four individual herbal interventions, including *C. verum* 3g/day.

3.1.2 Related Clinical Conditions: *C. cassia* and *C. verum* compared (Table 2-2)

Four studies were conducted on subjects with clinical conditions other than T2DM: IGT (Wickenberg et al., 2012; Wickenberg et al., 2014) as a pre-diabetic condition, and obesity (Gutierrez et al., 2016; Magistrelli and Chezem, 2012), which is a risk factor for diabetes. In obese subjects, ingestion of *C. cassia* 5g and 6g suppressed postprandial glucose rise (Gutierrez et al., 2016; Magistrelli and Chezem, 2012).. In a study with IGT participants, Wickenberg *et al*. found no impact of *C. cassia* 12g per day for 12 weeks on the fasting glucose and insulin levels (Wickenberg et al., 2014). These findings suggest the potential effectiveness of *C. cassia at* 5g-6g per day, but not as high as 12g per day for the prevention of T2DM development in individuals with high risk.

Turning to *C. verum*, Wickenberg also authored a study on *C. verum,* and found no effect of *C. verum* 6g on postprandial blood glucose and insulin levels (Wickenberg et al., 2012).

3.1.3 Healthy: *C. cassia* and *C. verum* compared (Table 2-3)

A study on healthy subjects found that postprandial insulin rise was suppressed by 3g *C. cassia* but not by 1g (Hlebowicz et al., 2009), suggesting that the critical dosage of *C. cassia* lies between 1 and 3 g per day. Single administration of *C. cassia* (3g or 5g) (Hlebowicz et al., 2009; Solomon and Blannin, 2007) and *C. cassia* (3g) for 14 days (Solomon and Blannin, 2009) led to decrease in postprandial glucose response. Mettler *et al*. reported that *C. cassia* 4g had a significant impact on postprandial glucose levels only when taken in combination with acetic acid (Mettler et al., 2009). Interestingly, in the historical text '*Le Livre des Simples Medecines*', combination of cinnamon with vinegar is suggested for its effectiveness (Nam, 2014). These data suggest that *C. cassia* powder 3g or *C. cassia* taken with vinegar, could help control blood glucose levels and associated parameters, which may be of benefit to T2DM patients.

In two *C. verum* studies in healthy populations, ingestion of an alcoholic extract (1g) of *C. verum* led to a reduction in postprandial glucose and insulin levels (Beejmohun et al., 2014), while ingestion of a dose of *C. verum* 3g with a high fat meal (Markey et al., 2011) did not influence postprandial changes in glucose and triacylglycerol levels.

Overall, *C. cassia* (≥ 3g) in healthy individuals had positive outcomes in postprandial glucose control, while evidence supporting *C. verum* is insufficient.

3.2 Safety issues

3.2.1 Adverse events in the clinical trials

Ten studies positively reported no adverse events. Fourteen studies did not report whether or not any adverse events occurred during the studies. One study reported a subject developing a rash (Crawford, 2009). Another study (Wickenberg et al., 2014), using 12g/day *C .cassia* for 12 weeks, whilst not actively reporting adverse events, did measure liver enzymes, and found no change in serum transaminases.

3.2.2 Coumarin and safety (Table 3)

Due to the high coumarin content of *C. cassia*, *C. verum* has been suggested to be a safe alternative intervention for diabetes (Medagama, 2015). Coumarin (2*H*-chromen-2-one) is a naturally occurring constituent of many plants, and long term use of cinnamon as a flavouring agent is generally considered safe (Leach and Kumar, 2012). It was first isolated from tonga beans *Dipteryx odorata* (Aubl.) Willd. in 1820 and chemically synthesized coumarin had been marketed as a food flavouring agent for a long time until its hepatotoxic potential was discovered in laboratory animals in the middle of the 20th century. From the 1970s, coumarin was approved as a medicine to treat oedemas as well as tumours in several countries. However some patients developed severe hepatotoxicity, which led to the withdrawal of products from the market in 1990s (Abraham et al., 2010). Coumarin is metabolized via two major pathways: detoxification by 7-hydroxylation and the formation of 3,4-epoxide intermediate, the latter of which leads to the generation of a hepatotoxic metabolite *o*-HPA. As the 7-hydroxyation pathway is predominant in primates including humans, humans are less susceptible to coumarin hepatotoxicity compared to rodents. However, clinical data revealed that a human population subgroup reacts sensitively to coumarin (Loprinzi et al., 1999; Schmeck-Lindenau et al., 2003), although the underlying mechanism is unknown (Abraham et al., 2010).

To evaluate the coumarin-related safety issues of the two cinnamon species, database searches were conducted. The search retrieved a total of 19 results (18 results for PubMed, 1 for ScienceDirect), of which five articles are selected and summarised in Table 3. Abraham *et al*. (2011) compared the absorption of coumarin after oral administration of isolated coumarin and *C. cassia* in different preparations (capsules, tea, and rice pudding) (Abraham et al., 2011). They found that coumarin in isolation and in *C. cassia* were equally absorbed, and that *C. cassia* tea exhibited the fastest and highest coumarin absorption, compared to capsules and rice pudding. Data on the coumarin contents in different cinnamon species confirmed higher coumarin levels in *C. cassia* compared to *C. verum* (Table 3). Three independent studies conducted on the coumarin levels of *C. cassia* reported considerably different values: 2.57±0.08g/kg (2.512–2.628 g/kg) (Krieger et al., 2013), 0.201±0.104 g/kg (0.085-0.310g/kg)

(Wang et al., 2013), and 1.60±1.70g/kg (0.33-6.5 g/kg) (Lv et al., 2010), which could be due to several factors including extraction methods, analytical methods, and the sources of plant materials. In fact, those studies were conducted using different extraction and analytical methods, namely 80% methanol extraction without heat or sonication and LC-MS and DIP-APCI-MS analyses (Krieger et al., 2013), methanol extraction with sonication and UPLC-UV/MS (Wang et al., 2013), and pressurized liquid extraction with ethyl acetate at 160°C and and GC-MS (Lv et al., 2010), which could underlie the variability in these studies. Furthermore, plant materials were obtained from different sources, such as German retail market (Krieger et al., 2013), commercial source in China and the United States (Wang et al., 2013), and different regions of China (Lv et al., 2010). As demonstrated by Lv *et al*., coumarin contents of *C. cassia* could considerably vary (from 0.33 to 6.50 mg/g) depending on the geographical origins (Lv et al., 2010), which is likely due to different climatic conditions, plant age, and harvest timings. In addition, coumarin levels could vary depending on which plant parts were used. A study compared the levels of coumarin and other constituents in the bark, shaved bark (without cork layer), and twig of *C. cassia*, both used in traditional East Asian medicines, and found that coumarin in cinnamon twig was less than one-third compared to cinnamon bark, and shaved cinmmamon bark contained the highest levels of coumarin (Chen et al., 2016). Importantly, a study showed that a de-coumarinated polyphenol-enriched *C. cassia* extract, prepared using a novel procedure, was effective in lowering blood glucose levels in T2DM rats (IM et al., 2014a), indicating that the selection of extraction procedure could significantly enhance the safety of *C. cassia*. Of note, *C. burmannii* (Nees & T. Nees) Blume, commonly also known as ‘cassia’ cinnamon (Avula et al., 2015), has characteristically high coumarin levels, which is distinct from *C. cassia* (Avula et al., 2015; Chen et al., 2014; Wang et al., 2013), and *C. burmannii* was likely referred to as ‘cassia’ cinnamon in some reports. Importantly, Wang *et al*. reported that *C. cassia* contains higher levels of cinnamaldehyde: *C. cassia* (18.5±2.9 g/kg, n=4) > *C. verum* (11.2±5.5 g/kg, n=17) (Wang et al., 2013). Considering that anti-diabetic actions of cinnamon is at least partly mediated by cinnamaldehyde (Li et al., 2012), the dosage of *C. verum* should be carefully

considered as a replacement for *C. cassia*. In fact, short-term administration (≤ 14days) of *C. verum* (3g and 6g) were ineffective (Markey et al., 2011; Wickenberg et al., 2012), while *C. cassia* 3 - 6 g were effective (Hlebowicz et al., 2009; Magistrelli and Chezem, 2012; Mettler et al., 2009; Solomon and Blannin, 2007), suggesting that *C. cassia* has higher potency compared to *C. verum*. Overall, it is important to identify botanical origin, geographical origin, plant parts, and extraction procedures, in using and reporting analytical as well as clinical trial data.

In addition to liver damage caused by coumarin, allergic reactions should be considered as a possible adverse effect, as several cases of contact dermatitis have been reported (Ackermann et al., 2009; Calapai et al., 2014; Isaac-Renton et al., 2015). In fact, a subject developed a rash after consuming *C. cassia* 1g per day in a trial (Crawford, 2009), however this was the only adverse reaction reported in any of the trials considered in this review. In fact, no case reports of interactions were identified therefore it was considered unlikely that it would affect the effectiveness of conventional drugs (Edwards et al., 2015). However, pharmacovigilance is important for any potential interactions and additive effects. Both *C. verum* and *C. cassia*, in therapeutic doses, should be avoided during pregnancy (Edwards et al., 2015; Gardner and McGuffin, 2013).

3.3 Limitation of the study

Due to the scarcity of available data, this study included both randomised placebo-controlled and open-label trials. In addition, compared to *C. cassia*, only a few trials have been conducted with *C. verum*. This is limiting as the discussion is based on evidence supported by a small number of studies with less vigorous study designs. More robust studies are needed in the future.

3.4 Concluding remarks

Most clinical studies were conducted using *C. cassia*, which was originally used as an anti-diabetic medicine and listed as the unique origin of 'Cortex cinnamomi' in the Chinese pharmacopoeia (Lv et al., 2010). Evidence suggests that oral administration of *C. cassia* 3-6g per day could improve glucose metabolism in T2DM patients and healthy individuals, while effectiveness was inconsistent below 1.5g. However, heterogeneity in the methods used in the trials as well as quality issues including lack of botanical authentication compromise the evidence for the efficacy and safety.

Therapeutic potency depends on the levels of active constituents. Considering that medicinal plants in general contain a number of bioactive compounds, the levels of which could be affected by many factors such as geographical origin, plant parts, and crude drug processing, it is important to assess the chemical properties of botanical medicines before using and evaluating the therapeutic potency and safety. In addition, due to the high coumarin content of *C. cassia*, future trials should be designed taking into account the assessment of potential hepatotoxicity by including liver function tests over suitable trial durations. These efforts would allow a more reliable safety and efficacy evaluation of *C. cassia.* as a diabetes intervention.

On the other hand, data are scarce and inconclusive for the effectiveness of *C. verum*. It should be noted that the interchangeability of the two cinnamon species as a diabetes intervention is not established and there is currently no standardisation method for quality control. It is important for practitioners to consider possible differences in the potency between the two species as well as within the same species, and potential risk associated with coumarin consumption. Given the low coumarin content of *C. verum* there is an opportunity for more robust RCTs, of longer duration and larger participant numbers giving greater power, to investigate whether this species has potential for this growing patient group. The effective and safe dosage practices for different species should be built on scientific data through careful examination and comparison, as well as drawing on long-standing traditional usages. Key to this is clarity about the intervention including establishing botanical authenticity. Such work could not only benefit T2DM patients and those diagnosed as pre-

diabetic, but also the growing number of diseases that are related to insulin resistance, and hence favourably ameliorate the personal, social and economic costs of these conditions.

Conflict of Interest

The authors declare no conflicts of interest associated with this manuscript.

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Figure 1. Flowchart illustrating the selection process.

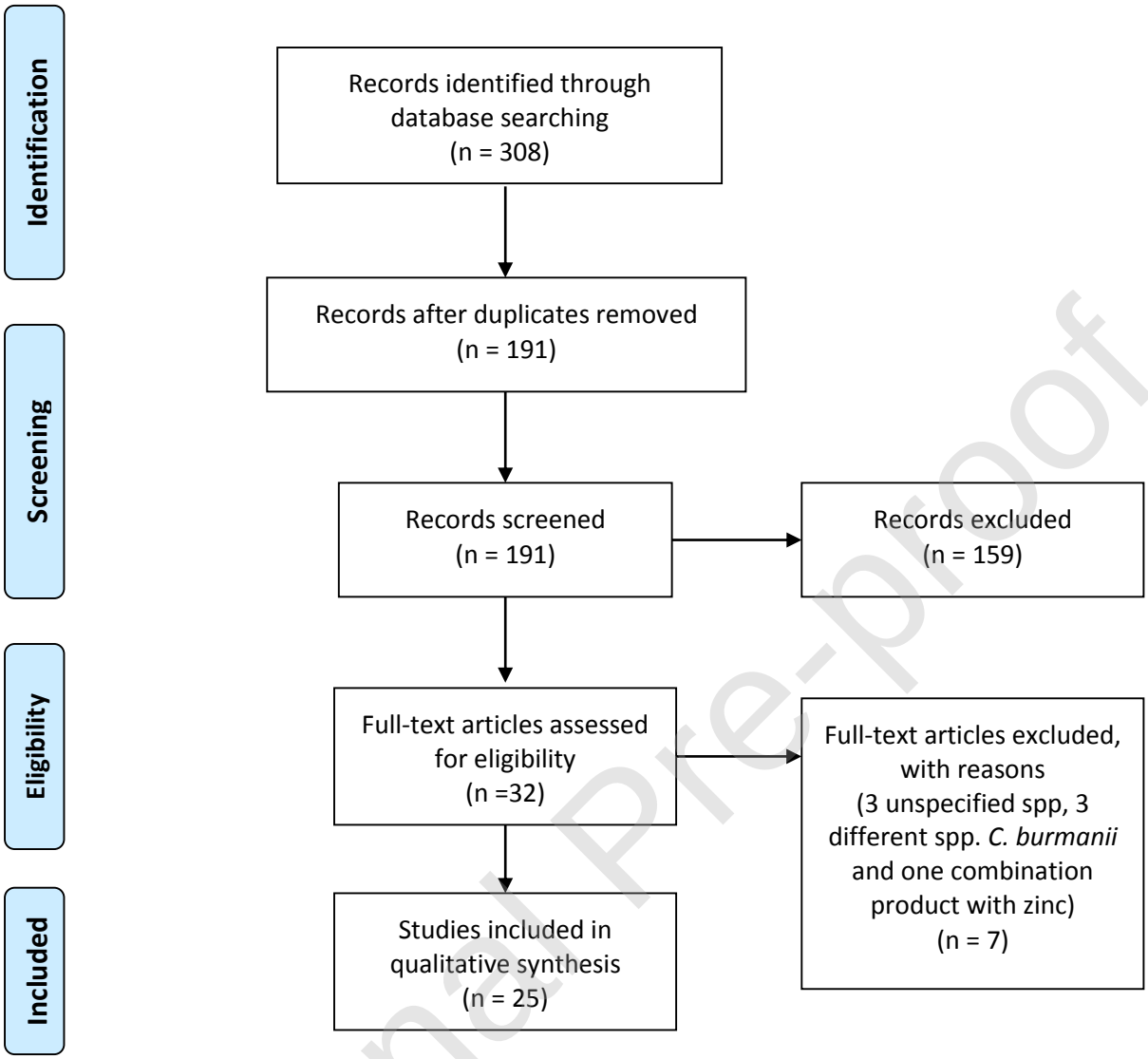

Table 1. Trials included in five previous reviews and current study

	Previous reviews					Current study
	Akilen et al. (2012)	Leach & Kumar (2012)	Allen et al. (2013)	Alanazi and Khan 11 trials but 16 datasets used from the 11	Medagama (2015)	
Number of trials	6	10	10	11	8	25
C. cassia						
T2DM						
Khan *et al.* (2003)	√	√	√		√	√
Mang *et al.* (2006)	√	√	√	√	√	√
Suppapitiporn *et al.* (2006)		√	√	√	√	√
Vanschoonbeek *et al.* (2006)	√	√	√	√	√	√
Blevins *et al.* (2007)	√	√	√	√	√	√
Crawford (2009)	√	√	√	√	√	√
Akilen *et al.* (2010)	√	√	√	√	√	√
Lu *et al.* (2012)			√	√		√
Hasanzade *et al.* (2013)				√		√
Gullapalli *et al.* (2013)				√		√
Sengsuk *et al.* (2015)						√
Soni and Bhatnagar (2009)						√
Related clinical conditions						
Magistrelli & Chezem (2012)						√
Wickenberg *et al.* (2014)						√
Gutierrez *et al.* (2016)						√
Healthy						
Solomon & Blannin (2007)						√
Hlebowicz *et al.* (2009)						√
Solomon & Blannin (2009)						√
Mettler *et al.* (2009)						√
C. verum						
T2DM						
Vafa *et al.* (2012)				√		√
Azimi *et al.* (2014)						√
Azimi *et al.* (2016)						√
Related clinical conditions						
Wickenberg *et al.* (2012)						√
Healthy						
Beejmohun *et al.* (2014)						√
Markey *et al.* (2011)						√
Not *C. cassia* / *C. verum*, unidentified species or combined with other substances						
Altschuler *et al.* (2007)		√				
Khan *et al.* (2010)		√	√			
Rosado *et al.* (2010)		√				
Wainstein *et al.* (2011)			√	√		
Anderson *et al.* (2016)					√	
Conclusion	Effective (significant decrease in HbA1c and fasting blood glucose levels)	Insufficient evidence (only inconclusive evidence on fasting blood glucose; no significant effect on HbA1c, serum insulin and postprandial glucose)	Effective (improved fasting blood glucose, total cholesterol, LDL cholesterol, and triglycerides. No significant effect on HbA1c)	Effective (improved fasting blood glucose, total cholesterol, LDL cholesterol, and triglycerides)	Potentially useful as an adjuvant.	*C. cassia*: effective at 3-6g *C. verum*: insufficient evidence

Table 2-1. Trials with T2DM patients

1st Author	Population	Intervention	Source of cinnamon bark	Study design	Outcome	Safety	Limitation
C. cassia							
Sengsuk *et al*. 2015	Population: T2DM patients aged 57.2±1.1 (treatment) and 56.9±1.2 (control) Sample size: n=99 (treatment: 49, control: 50)	*C. cassia* 1.5g per day (after each meal, 0.5g each), for 60 days	Purchased from Government Pharmaceutical Organization of Thailand	Study design: randomised, double-blind Control: placebo	Reduction in glucose, triglycerides, and HbA1c levels. Increase in HDL and eGFR	No adverse reactions	No voucher specimen number
Gullapalli et al. (2013)	Population: T2DM patients Sample size: n = 60 (treatment: 30, control: 30)	*C. cassia* 1g, 3g or 6g per day, for 40 days.	Certified by Spice Board, Kochi, Kerala	Study design: randomized Control: placebo (wheat flour)	1g, 3g and 6g all reduced mean fasting serum glucose, triglyceride, LDL and total cholesterol. No significant changes in HDL.	No adverse reactions	No voucher specimen number
Hasanzade *et al*. (2013)	Population: T2DM patients aged 53.7±9.7 (treatment) and 54.7±8.1 (control) Sample size: n= 71 (treatment: 35, control: 36)	*C. cassia* 1g per day (after breakfast and dinner 0.5g each), for 30 days	Prepared by collage of pharmacy (Mashhad University of Medical Science)	Study design: randomised, double-blind Control: placebo	No significant effect on fasting blood glucose and HbA1c levels	Not mentioned	No voucher specimen number
Lu *et al*. (2012)	Population: Chinese patients with T2DM, taking sulfonylurea, aged around 60 Sample size: n=66 (placebo: 20, low-dose: 23, high-dose: 23)	*C. cassia* aqueous extract 120 mg (from 2.8g of *C. cassia*) or 360 mg per day for 3 months.	Produced by Shanghai Jinsijia Health-Care Food Co, Ltd (Shanghai, China), batch number 20090901	Study design: randomised, double-blind Control: placebo	Decrease in HbA1c and fasting glucose levels (120mg and 360mg extract). Decrease in triglyceride treatment group (120mg).	No adverse reactions	
Akilen *et al*. (2010)	Population: T2DM patients taking oral hypoglycaemic agents, multi-ethnic, aged 54.9±9.8 Sample size: n=58 (treatment: 30, control: 28)	*C. cassia* 2g per day for 12 weeks	Certified (reference: HBL14020NB)	Study design: randomised, double-blind, parallel Control: placebo	Decrease in HbA1c, Systolic and diastolic blood pressure.	Safe and well tolerated	
Crawford (2009)	Population: T2DM patients, multi-ethnic, aged around 60 Sample size: n=109 (treatment: 55, control: 54)	*C. cassia* 1g each day with meal, for 90 days	Puritan's Pride, Oakdale, NY	Study design: stratified randomisation, parallel Control: usual management care	Significant reduction in HbA1c levels in the treatment group, compared to moderate reduction in control group.	One subject in the treatment group reported developing a rash.	Not blinded
Soni & Bhatnagar (2009)	Population: T2DM male patients aged 40-60 Sample size: n=30 (treatment: 15, control: 15)	*C. cassia* 2g per day (after breakfast, lunch, evening tea, and dinner, a quarter each), for 40 days	No information	Study design: controlled Control: no supplementation	Decrease in fasting and postprandial blood glucose levels	Not mentioned.	The source of *C. cassia* is unknown.
Blevins *et al*. (2007)	Population: T2DM patients Sample size: n=57 (treatment: 29, control: 28)	*C. cassia* 1g per day (2x 0.5g capsules, one with breakfast one with dinner), for 3 months	No information	Study design: stratified randomisation, double-blind Control: placebo capsules containing wheat flour	No effect on fasting glucose, lipid, and insulin levels.	Not mentioned.	The source of *C. cassia* is unknown.
Suppapitiporn *et al*. (2006)	Population: T2DM patients Sample size: n = 60 (treatment: 20; control 40)	*C. cassia* 1.5g per day, for 12 weeks.	No information	Study design: randomized, single blind	No decrease in HbA1c, lipid profile, fasting plasma glucose.	No adverse reactions	The source of *C. cassia* is

					Reduction in SGOT (AST).		unknown.
Mang *et al.* (2006)	Population: T2DM patients (not on insulin therapy), aged 31.1±2.0 Sample size: n=65 (treatment: 33, control: 32)	*C. cassia* aqueous extract 336mg (equivalent to 3g of *C.cassia*) daily (capsules 1g x 3 times a day), for 4 months	Cinnamon extract TC112 prepared by Finzelberg (Andernach, Germany)	Study design: randomised, double-blinded. Control: placebo capsules with microcrystalline cellulose	Decrease in fasting plasma glucose levels.	No adverse reactions.	
Vanschoonbeek *et al.* (2006)	Population: postmenopausal patients with T2DM, aged 62.9±1.5. Sample size: n=25 (treatment: 13, control: 12)	*C. cassia* 1.5g per day (0.5g x 3 times a day after each meal), for 2 and 6 weeks	Verstegen brand	Study design: stratified randomisation, double-blinded. Control: placebo (wheat flour)	No effect on postprandial glucose and insulin levels, fasting lipid levels, at 2 weeks and 6 weeks.	Not mentioned.	Small sample size
Khan *et al.* (2003)	Population: T2DM patients, taking sulfonylurea, average age 52.0 Sample size: n=30 (10 per group)	*C. cassia* 1g, 3g, or 6g per day, after lunch and dinner, for 40 days	Certified by the Office of the Director, Research and Development/Non-Timber Forest Products, NWFP Forest Department, Peshawar, Pakistan	Study design: randomised. Control: placebo (wheat flour)	Decrease in fasting serum glucose, triglyceride, and LDL cholesterol levels, at 20, 40, and 60 days.	Not mentioned.	Small sample size
C. verum							
Azimi *et al.* (2016)	Population: T2DM patients Sample size: n=79 (treatment: 40, control: 39)	*C. verum* 3g with black tea for 8 weeks	Approved by the Ministry of Health (License No. 16/13777)	Study design: randomised, single-blind, parallel. Control: black tea only	No effect on blood pressure and endothelial function.	No adverse reactions	Processed cinnamon
Azimi *et al.* (2014)	Population: T2DM patients Sample size: n=79 (treatment: 40, control: 39)	*C. verum* 3g with black tea, for 8 weeks	Approved by the Ministry of Health (License No.16/13777)	Study design: randomised, single-blind, parallel. Control: black tea only	Decrease in fasting blood glucose. No effect insulin and HbA1c but only 8 weeks	No adverse reactions	Processed cinnamon
Vafa *et al.* (2012)	Population: T2DM patients, sample size: n=44 (treatment: 22, control: 22)	*C. verum* 3g per day for 8 weeks	No information	Study design: double blind, randomized. Control: placebo (wheat flour)	Outcome: decrease in fasting blood glucose, HbA1c, triglyceride, weight, BMI and body fat mass	No adverse reactions	

Table 2-2. Trials with related clinical conditions

1st Author	Population	Intervention	Source of cinnamon bark	Study design	Outcome	Safety	Limitation
C. cassia							
Gutierrez *et al.* (2016)	Population: sedentary and obese females aged 22.7±4 Sample size: n=10	*C. cassia* 5g (capsules) with OGTT	Nature's Bounty, Bohemia, NY	Study design: crossover Control: placebo (placebo)	Lower response to oral glucose tolerance test. No difference in insulin resistance and sensitivity.	Not mentioned.	Small sample size
Wickenberg, J. *et al.* (2014)	Population: IGT, aged around 72 Sample size: n=17 (treatment: 8, control: 9)	12g *C. cassia* per day, for 12 weeks.	Svampbutiken, Mediapoint AB, Västerås, Sweden	Study design: stratified randomised, double-blind, parallel Control: placebo (cellulose)	No effects on fasting-insulin, glucose, HbA1c, cholesterol levels, triglycerides, and liver enzymes.	Not mentioned. No change in serum transaminases.	Small sample size
Magistrelli & Chezem (2012)	Populations: normal (BMI 21.1±1.1, aged 21.0±2.5) and obese (BMI 33.1±4.6, aged 22.1±2.4) Sample size: n=45 (normal: 30, obese: 15)	Cereal prepared with *C. cassia* 6g	Swagger Foods, Vernon Hills, IL	Study design: randomised, cross-over Control: plain cereal	Slower postprandial blood glucose rise	Not mentioned.	Not blinded
C. verum							
Wickenberg *et al.* (2012)	Population: IGT, aged 29-73 Sample size: n=10	*C. verum* 6g with OGTT	Svampbutiken, Mediapoint AB, Västerås, Sweden	Study design: randomised, cross-over (at intervals of 1 week) Control: placebo capsules (lactose)	No effect on postprandial plasma glucose and insulin.	Not mentioned.	Small sample size

Table 2-3. Trials with healthy populations

1st Author	Population	Intervention	Source of cinnamon bark	Study design	Outcome	Safety	Limitation
C. cassia							
Hlebowicz *et al.* (2009)	Population: healthy, aged between 20-27 Sample size: n=15	Rice pudding mixed with 1 or 3g *C. cassia.* Single administration	Santa Maria AB, Mölndal, Sweden	Study design: randomised, cross-over Control: plain rice pudding	Decrease in postprandial insulin rise. Increase in the release of glucagon like peptide 1 (GLP-1) (3g *C. cassia* group only)	Not mentioned.	Not blinded.
Mettler *et al.* (2009)	Population: healthy Sample size: n=27	Sugar drink and milk rice meal with: 1. *C.cassia* 4g in the meal 2. vinegar in the sugar drink 3. *C.cassia* + vinegar Single administration.	Gewürzmühle Brecht GmbH, Eggenstein, Germany	Study design: randomised, cross-over Control: sugar drink and plain milk rice meal	(1) No difference for *C.cassia* alone. (2) Postprandial glucose levels lower for *C.cassia* + vinegar.	Not mentioned.	Not blinded.
Solomon & Blannin (2009)	Population: healthy, aged 25±1 Sample size: n=8	*C. cassia* 3g per day, for 14 days	Everythingcinnamon.com, Essex, UK	Study design: randomised, single blind, placebo controlled, cross-over Control: placebo (wheat flour)	Decrease in postprandial glucose levels and insulin levels.	Not mentioned.	Small sample size
Solomon & Blannin (2007)	Population: healthy male volunteers, aged 26±1 Sample size: n=7	(1) OCTT supplemented with 5g *C.cassia* (2) 5g *C.cassia* capsules 12h before OCTT. Single administration	Everythingcinnamon.com, Essex, UK	Study design: randomised, cross-over, placebo controlled Control: placebo capsules with 5g wheat flour	Decrease in postprandial plasma glucose. Increase in insulin sensitivity by one index (Matsuda) but not in another index (HOMA).	Not mentioned.	Small sample size
Beejmohun *et al.* (2014)	Population: healthy, aged 29.9±1.8 Sample size: n=18	Single administration. *C. verum* hydro-alcoholic (50/50) extract 1g after a standardised meal	MealShape trademark	Study design: randomised, double-blind, placebo-controlled, cross-over Control: placebo	Decrease in postprandial hyperglycaemia.	No adverse reaction.	
C. verum							
Markey *et al.* (2011)	Population: healthy, aged 26.2±3 Sample size: n=9	A high-fat meal, with *C. verum* 3g. Single dose.	Schwartz, UK	Study design: randomised, placebo-controlled, single-blinded, cross-over Control: placebo (wheat flour)	No effect on the postprandial levels of triacylglycerol, glucose, oxidative stress, arterial function, or appetite, in response to a high-fat test meal.	Not mentioned.	Small sample size

Table 3. Coumarin contents of cinnamon species

1st Author (year)	Aim of the study	Materials	Method	Coumarin contents	Notes	Source of plant materials
Coumarin levels						
Krieger *et al*. (2013)	Methodological study on the detection of coumarins using DIP-APCI-MS and LC-MS	*C. verum* and *C. cassia* powder from different origins (n=5 for *C. verum* and n=2 for *cassia*)	Extraction: 80% methanol (0.5g/40mL) Analysis: LC-MS and DIP-APCI-MS analyses	*C. verum*: 0.092-0.427 g/kg *C. cassia*: 2.512–2.628 g/kg	*C. cassia* contains considerably higher levels of coumarin.	No information
Wang *et al*. (2013)	To analyse coumarin and other compounds in different cinnamon species and cinnamon containing foods and supplements	*C. verum*, *C. cassia*, *C. loureiroi*, and *C. burmannii* from different origins (n=16 for *C. verum*; n=3 for *C. cassia*; n=1 for *C. loureiroi*; n=7 for *C. burmannii*)	Extraction: Methanol (0.5g/2.5mL, sonication for 30min, 3 times) Analysis: UPLC-UV/MS	*C. verum*: 0.007-0.090 g/kg *C. cassia*: 0.085-0.310 g/kg *C. loureiroi*: 1.06-6.97 g/kg *C. burmannii*: 2.14-9.30 g/kg	(1) Coumarin contents: *C. burmannii* > *C. loureiroi* > *C. cassia* > *C. verum* (2) Cinnamon aldehyde contents: *C. cassia* > *C. verum*	National Center for Natural Products Research codes: *C. verum* 3997, 3974 - 3987, 4895, 7545; *C. burmannii* 3995, 4881, 4887, 4892, 4896, 4897, 4898, 5605; *C. loureiroi* 3996, 5227; *C. cassia* 5227, 5336, 4893, 4899
Blahová & Svobodová (2012)	To determine the coumarin content of ground cinnamon in the Czech retail markets	Powder of unknown cinnamon species (n=12)	Extraction: Hot water Analysis: HPLC-UV	2.65–7.02 mg/kg		Purchased from supermarkets and a specialized spice market
Lv *et al.* (2010)	To develop a reliable quantification method for the constituents in cinnamon	*C. cassia* powder of different origins (n=15)	Extraction: Pressurised liquid extraction, ethyl acetate, 160°C Analysis: GC-MS	0.33 – 6.50 g/kg (1.70 ± 0.44 g/kg, n=15)	*C. cassia* contains cinnamaldehyde: 16.11 – 38.61 g/kg (25.6 ± 1.5 g/kg, n=15)	Authenticated voucher specimens (CC01-CC15) obtained from local herbal drug stores in different parts of China (deposited at the Institute of Chinese Medical Sciences, University of Macau, Macao, China).