

From type 2 diabetes to antioxidant activity: a systematic review of the safety and efficacy of common and cassia cinnamon bark¹

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Abstract: Common (*Cinnamomum verum*, *C. zeylanicum*) and cassia (*C. aromaticum*) cinnamon have a long history of use as spices and flavouring agents. A number of pharmacological and clinical effects have been observed with their use. The objective of this study was to systematically review the scientific literature for preclinical and clinical evidence of safety, efficacy, and pharmacological activity of common and cassia cinnamon. Using the principles of evidence-based practice, we searched 9 electronic databases and compiled data according to the grade of evidence found. One pharmacological study on antioxidant activity and 7 clinical studies on various medical conditions were reported in the scientific literature including type 2 diabetes (3), *Helicobacter pylori* infection (1), activation of olfactory cortex of the brain (1), oral candidiasis in HIV (1), and chronic salmonellosis (1). Two of 3 randomized clinical trials on type 2 diabetes provided strong scientific evidence that cassia cinnamon demonstrates a therapeutic effect in reducing fasting blood glucose by 10.3%–29%; the third clinical trial did not observe this effect. Cassia cinnamon, however, did not have an effect at lowering glycosylated hemoglobin (HbA1c). One randomized clinical trial reported that cassia cinnamon lowered total cholesterol, low-density lipoprotein cholesterol, and triglycerides; the other 2 trials, however, did not observe this effect. There was good scientific evidence that a species of cinnamon was not effective at eradicating *H. pylori* infection. Common cinnamon showed weak to very weak evidence of efficacy in treating oral candidiasis in HIV patients and chronic salmonellosis.

Key words: cinnamon, cassia, diabetes, antioxidant, *Cinnamomum verum*, *Cinnamomum zeylanicum*, *Cinnamomum aromaticum*, systematic review.

Résumé : La cannelle de Ceylan (*Cinnamomum verum*, *C. zeylanicum*) et la cannelle de Chine (*C. aromaticum*) sont utilisées depuis longtemps comme épices et aromatisants. De plus, leur utilisation est associée à de nombreux effets pharmacologiques et cliniques. Nous avons eu pour objectif de faire une revue systématique de la littérature scientifique concernant les preuves précliniques et cliniques de l'innocuité, de l'efficacité et de l'activité pharmacologique de la cannelle de Ceylan et de Chine. Nous avons utilisé les principes de la médecine factuelle et effectué une recherche dans 9 bases de données, puis compilé les données en fonction du niveau de preuve obtenu. La littérature a révélé une étude pharmacologique

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sur l'activité antioxydante et sept études cliniques sur divers états de santé, à savoir le diabète de type 2 (3), l'infection à *Helicobacter pylori* (1) l'activation du cortex olfactif (1), la candidose buccale chez les patients VIH (1) et la salmonellose chronique (1). Sur trois essais cliniques aléatoires, deux ont indiqué, à partir de preuves scientifiques solides, que la cannelle de Chine a démontré un effet thérapeutique en réduisant le glucose sanguin à jeun de 10,3 % à 29 % ; le troisième essai n'a pas observé cet effet. La cannelle de Chine, toutefois, n'a pu diminuer l'hémoglobine glycosylée (HbA1c). Un essai clinique aléatoire a indiqué que la cannelle de Chine a diminué le cholestérol total, le cholestérol HDL et les triglycérides ; les deux autres essais, toutefois, n'ont pas observé cet effet. Des données probantes indiquent qu'un type de cannelle n'a pu éradiquer l'infection à *H. pylori*. La cannelle de Ceylan a démontré une efficacité faible à très faible dans le traitement de la candidose chez les patients VIH et dans celui de la salmonellose chronique.

Mots-clés : cannelle, cassia, diabètes, antioxydant, *Cinnamomum verum*, *Cinnamomum zeylanicum*, *Cinnamomum aromaticum*, revue systématique.

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Introduction

Cinnamon bark is widely used as a spice and flavouring agent. There are reports of cinnamon being imported to Egypt from China as early as 2000 BC. Cinnamon is mentioned in the Bible (Exodus and Proverbs) and in Chinese texts written 4000 years ago (Leung and Foster 1996; Toriizuka 1998).

Cinnamon is a small evergreen tree, approximately 10–15 m tall, native to Sri Lanka and Southern India. The name cinnamon comes from the Greek *kinnámōmon*, ultimately from the Malaysian and Indonesian *kayu manis*, which means “sweet wood.” Common cinnamon correctly refers to “true cinnamon,” or its synonym Ceylon cinnamon (*Cinnamomum verum*, *C. zeylanicum*) (Jellin 2006a). In addition, the related species cassia cinnamon (*C. aromaticum*), also known as Chinese cinnamon, is sometimes sold labelled as cinnamon (Jellin 2006a, 2006b).

Common and cassia cinnamon have been shown to be generally safe when ingested and to have many pharmacological properties, such as antioxidant activity and antimicrobial effects (Mancini-Filho et al. 1998; Lopez et al. 2005; Shan et al. 2005; Jellin 2006a, 2006b). On the basis of preclinical and clinical data, common and cassia cinnamon are well known for their pharmacological properties in the treatment of type 2 diabetes (Khan et al. 2003; Verspohl et al. 2005). In rats, glucose tolerance tests have shown that both common and cassia cinnamon reduce blood glucose, with cassia found to be superior to common cinnamon (Verspohl et al. 2005). It has also been proposed that the antioxidant properties of common and cassia cinnamon may influence diabetic complications (Anderson et al. 2004). In humans, 3 randomized controlled trials have been conducted on cassia and its effects on fasting glucose, glycosylated hemoglobin (HA1c), and lipid profile markers (Khan et al. 2003; Mang et al. 2006; Vanschoonbeek et al. 2006). Often misrepresented in the media and scientific literature, the cinnamon bark used in these studies was in fact cassia and not common cinnamon. The authors did not specify in their scientific abstracts the cinnamon species used, although they do so within the works themselves (Khan et al. 2003; Mang et al. 2006; Vanschoonbeek et al. 2006).

Given the variety of preclinical and clinical evidence on common and cassia cinnamon and the fact that people with diabetes are taking natural health products (NHPs), there is a need to determine safety, efficacy, and pharmacological ac-

tivity of the NHPs. Therefore, we systematically reviewed the scientific literature pertaining to common and cassia cinnamon for evidence of their safety, efficacy, and pharmacological activity.

Materials and methods

Search strategy

In keeping with the principles of evidence-based practice, we endeavoured to identify and analyse all relevant preclinical and clinical medical literature that provides information on the safety, efficacy, and pharmacology of common and cassia cinnamon. Our strategy employed systematic searches of the following databases from their inception to August 2006:

- MEDLINE (1966–)
- OLDMEDLINE (1950–65)
- Cumulative Index to Nursing & Allied Health Literature (CINAHL) (1982–)
- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- DARE (Database of Abstracts of Reviews of Effectiveness)
- Allied and Complementary Medicine (AMED) (1985–)
- EMBASE (1980–)
- AltHealthWatch

To ensure that all reports, trials, and other key areas of evidence were not overlooked, the following additional databases were consulted: Complete German Commission E Monographs by the American Botanical Council, Natural Database, and Natural Standard. In addition, we conducted hand searches of all relevant review papers as well as the reference lists of original research publications.

The MeSH (medical subject headings) terms used for searching included “cassia,” “cinnamon,” and “cinnamomum.” Studies in which common and (or) cassia cinnamon were not studied on their own, that is, combination products such as traditional Chinese medicine patents, were excluded. Given the limited amount of evidence on NHPs in the scientific literature, the search strategy employed for evaluating therapeutic efficacy was designed to capture all human preclinical and clinical studies. To properly evaluate toxicology, adverse effects, and pharmacology, animal and in vitro studies were also included in our search strategy.

Data extraction

Each relevant journal article was collected and referenced in our database. The nature of the findings and the grade of evidence were then extracted and compiled in our final report. For evaluation of therapeutic efficacy, each study was rated and assigned a grade of evidence as outlined in Table 1. Special consideration was given for safety during pregnancy and lactation and this is emphasized through the additional assignments on evidence level for harm as outlined in Table 2. The evidence grades used are standardized and have been described in more detail in previous publications (Dugoua et al. 2006a, 2006b, 2006c; Perri et al. 2006).

Results

Therapeutic efficacy

As part of our search strategy on the therapeutic efficacy of common and cassia cinnamon, we identified 8 studies involving humans. One pharmacological study on antioxidant activity and 7 clinical studies on various medical conditions were reported in the scientific literature, including type 2 diabetes (3), *Helicobacter pylori* infection (1), activation of the olfactory cortex of the brain (1), oral candidiasis in HIV (1), and chronic salmonellosis (1). These studies are discussed in further detail below and summarized in Table 3.

Type 2 diabetes

Mang et al. (2006) (Grade B1) conducted a randomized controlled trial ($n = 79$) of type 2 diabetics in which they observed a significantly higher reduction in fasting glucose in the group taking cassia cinnamon (10.3%) versus the placebo group (3.4%) (Mang et al. 2006). Patients received an aqueous cassia extract corresponding to 3 g of cassia cinnamon powder per day or placebo for 4 months. No significant difference was observed in glycosylated hemoglobin A1c (HbA1c), total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), or triacylglycerol concentrations.

Khan et al. (2003) (Grade B1) conducted a randomized controlled trial ($n = 60$) in which they demonstrated that patients randomized to the cassia intervention experienced statistically and clinically significant improvements in blood glucose control and reductions in established cardiovascular risk factor biomarkers (Khan et al. 2003). This study demonstrated that intake of 1, 3, or 6 g of cassia cinnamon per day reduced serum glucose, triglycerides (TG), LDL-C, and total-C in people with type 2 diabetes. After 40 days of treatment, daily doses of 1, 3, and 6 g of cassia cinnamon reduced fasting serum glucose by 18%–29%, TG by 23%–30%, LDL-C by 7%–27%, and total-C by 12%–26%. No significant changes were noted in the placebo group. The fasting glucose values at baseline were quite high (11.4–16.7 mmol/L), and unfortunately, HbA1c values were not investigated.

Vanschoonbeek et al. (2006) (Grade B2) conducted a small randomized controlled trial ($n = 25$) of postmenopausal patients with type 2 diabetes in which they found that supplementation with 1.5 g/day (500 mg, 3 times/day) of cassia cinnamon over 6 weeks did not significantly improve fasting glucose, plasma insulin, total-C, or LDL-C in comparison with the control group (Vanschoonbeek et al.

2006). A reduction of HbA1c, HDL-C, and TG values after cassia administration was not observed; rather, the trend of these measurements was either unchanged or very slightly increased after 6 weeks. Although the methodological quality of this study was good overall, the trial was underpowered to detect a difference in outcomes assessed. It is of note that the dosage used was 50% higher than the lowest dose by Khan et al. (2003) and should, in theory, have been sufficient to demonstrate a therapeutic effect.

Helicobacter pylori infection

Nir et al. (2000) (Grade B2) conducted a small randomized controlled pilot study ($n = 23$) of human patients infected with *H. pylori* in which cinnamon extract was shown to be ineffective in eradicating *H. pylori* (Nir et al. 2000). Subjects were randomized in a study:control ratio of 2:1 to receive either 40 mg of an alcoholic cinnamon extract twice daily for 4 weeks or placebo. The amount of *H. pylori* colonization was measured by the ^{13}C -urea breath test before and after therapy. The mean urea breath test counts in the treatment and control groups before and after therapy were 22.1 and 23.9 versus 24.4 and 25.9, respectively. Although the authors discussed the trend in their data, statistical significance was not achieved. Seven patients were excluded from the final analysis owing to antibiotic use, poor compliance, or negligible urea breath test at baseline. Given the small sample and number of data points excluded from final analysis, the authors may have underpowered this study; also, the authors did not report whether they used intention-to-treat analysis. The cinnamon extract was well tolerated and side effects were minimal. The researchers did not specify which cinnamon species (i.e., cassia or common) was administered.

Activation of the olfactory cortex of the brain

Gonzalez et al. (2006) (Grade C) conducted an observational study on 23 human subjects to determine the effect of abstract linking of linguistic and odour information in the brain using functional magnetic resonance imaging (fMRI) (Gonzalez et al. 2006). Odour-related terms, such as reading the word “cinnamon,” elicited activation in the primary olfactory cortex, which include the piriform cortex and the amygdala.

Oral candidiasis in HIV

Quale et al. (1996) reported a case series of 5 patients with HIV infection and oral candidiasis that received a commercially available common cinnamon preparation (*Cinnamomum zeylanicum*) for 1 week (Quale et al. 1996). After 1 week, 3 of the 5 patients demonstrated improvements of their oral candidiasis.

Chronic salmonellosis

A case (Grade E) was reported of an infant chronic carrier of *Salmonella enteritidis* that improved after the consumption of ground cinnamon bark (*Cinnamomum zeylanicum*) mixed with fruit 3–4 times daily for 1 month (Rosti and Gastaldi 2005). The infant contracted salmonellosis from his mother and he became a chronic carrier, indicated by repeated positive stool tests for *S. enteritidis*. One month after consumption of cinnamon bark, stool culture results showed no growth of pathogens. The stool tests remained negative

Table 1. Levels of evidence for efficacy.

Grade	Level of evidence	
A	Very strong scientific evidence	Statistically significant evidence of benefit from one or more systematic reviews and (or) meta-analysis
B1	Strong scientific evidence	Statistically significant evidence of benefit from one or more properly conducted RCTs
B2	Good scientific evidence	Statistically significant evidence of benefit from one or more RCTs. The RCTs, however, are either of small sample size or have discrepancies in their methodologies
C	Fair scientific evidence	Statistically significant evidence of benefit from one or more cohort studies or outcome studies or case control studies
D	Weak scientific evidence	Evidence from case series
E	Indirect and (or) clinical evidence	Evidence from case reports or expert opinion or laboratory studies
F	Historical or traditional evidence	Historical or traditional use by medical professionals, herbalists, scientists, or aboriginal groups

Note: RCTs, randomized controlled trials.

after testing at both 2- and 3-month follow-ups. Cinnamon has demonstrated antimicrobial effects in in vitro studies, lending support to this clinical observation (Yuste and Fung 2004).

Pharmacological study of antioxidant status

Ranjbar et al. (2006) (Grade B2) conducted a comparative cross-sectional pharmacological study on 54 subjects (Ranjbar et al. 2006). Individuals consuming cinnamon tea had increased total serum antioxidant status, increased thiols, and decreased lipid peroxidation when compared with individuals consuming water or regular tea. Subjects were randomly divided into 3 groups: water (control), regular tea, or common cinnamon (*Cinnamomum zeylanicum*) tea and were instructed to consume the beverages for 2 weeks. Blood samples were obtained at baseline and after 2 weeks and analyzed for lipid peroxidation levels, total antioxidant power, and total thiol groups.

Toxicology and adverse effects

A randomized controlled trial ($n = 60$) of cassia cinnamon demonstrated that intake of up to 6 g daily over 40 days did not have any significant adverse effects (Khan et al. 2003). Two other trials ($n = 25$ and $n = 79$) of cassia cinnamon dosed at 1.5 g/day over 6 weeks and 3 g/day over 4 months, respectively, did not report any significant adverse effects (Mang et al. 2006; Vanschoonbeek et al. 2006). The remaining human studies identified in the previous section did not report any clinically significant adverse effects (Quale et al. 1996; Nir et al. 2000; Rosti and Gastaldi 2005; Gonzalez et al. 2006; Ranjbar et al. 2006).

Two textbooks on herbal medicines reported that cinnamon is safe when used in medicinal amounts, but may be of concern when used in excessive amounts or in the long term (Newall et al. 1996; McGuffin et al. 1997). One of these texts reported that cinnamaldehyde consumption should not exceed 700 µg/kg (Newall et al. 1996). A case was reported in which a child ingested 60 mL of cinnamon oil had serious side effects, including vomiting, diarrhea, dizziness, and loss of consciousness (Pilapil 1989).

According to the United States Food and Drug Administration (USFDA), *Cinnamomum* spp., including common and cassia cinnamon, are generally recognized as safe

(GRAS) when used in amounts commonly found in food (USFDA 2006). The adverse reaction database maintained by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) at Health Canada was searched from January 1965 to August 2006 and revealed no entries for common or cassia cinnamon (CADRMP 2006).

Low-level evidence from case reports and case series indicate that common and cassia cinnamon in excessive amounts may be of concern. The likely source of these adverse effects may be the volatile oil content of common and cassia cinnamon, which may irritate skin and mucous membranes (Pilapil 1989; Newall et al. 1996; McGuffin et al. 1997; Jellin 2006a, 2006b). The most common adverse effects reported with common and cassia cinnamon were related to contact irritation or allergic reaction with skin or mucus membranes. Examples of adverse reactions include the following:

- Contact dermatitis (Leifer 1951; Calnan 1976; Drake and Maibach 1976; Goh and Ng 1988; De Benito and Alzaga 1999; Sanchez-Perez and Garcia-Diez 1999; Hartmann and Hunzelmann 2004; Garcia-Abujeta et al. 2005; Nadiminti et al. 2005).
- Stomatitis (Drake and Maibach 1976; Bousquet et al. 2005; Endo and Rees 2006)
- Oral lichen planus (Hoskyn and Guin 2005)
- Oral leukoplakia (Mihail 1992)
- Mouth-burning syndrome (Zukervar et al. 2005)
- Sunscreen dermatitis (Fisher 1992)
- Urticaria (Ludera-Zimoch 1981)
- Perioral dermatitis (Farkas 1981)
- Oral erythema multiforme-like sensitivity reaction (Cohen and Bhattacharyya 2000)

Less frequent but more severe adverse effects observed in case reports include the following:

- A case of a 24-year-old woman who developed squamous cell carcinoma of the tongue after persistent and prolonged exposure to cinnamon-flavoured chewing gum (Westra et al. 1998). Cinnamon gum-chewing was discontinued by the patient and the lesion was surgically removed (Westra et al. 1998).
- A case of an 11-year-old boy who presented at a pediatric clinic with a 10 cm × 12 cm second-degree burn on his posterior thigh (Sparks 1985). The blistered area was

Table 2. Levels of evidence for harm.

Level	Evidence	
1a	Very strong scientific evidence	Statistically significant evidence from one or more systematic reviews or RCTs
1b	Strong scientific evidence	Statistically significant evidence from one or more outcome studies or cohort studies or case control studies
1c	Good scientific evidence	Evidence from one or more case series
2	Fair scientific evidence	Evidence based on case reports
3	In vitro scientific evidence	Evidence based on scientific studies conducted on animals, insects, or microorganisms or laboratory studies on human cells
4	Indirect evidence	Evidence based on scientific theory or expert opinion
5	Unknown	No available information

Note: RCTs, randomized controlled trials.

surrounded by a 3- to 4-centimetre first-degree burn (Sparks 1985). The injury was the result of a cinnamon oil spill from a broken vial in his rear pants pocket (Sparks 1985). The area had remained unwashed for 48 h and smelled strongly of cinnamon (Sparks 1985).

- A series of 32 cases of cinnamon oil abuse were reported within a 5-month period at the Pittsburgh Poison Center (Perry et al. 1990). All cases involved males aged 11–16 years (Perry et al. 1990). Sucking on toothpicks or fingers, which had been dipped in cinnamon oil was the primary method of abuse (Perry et al. 1990). A rush or sensation of warmth, facial flushing, and oral burning were the experiences reported by the users (Perry et al. 1990). Some children complained of nausea or abdominal pain, but no systemic effects were reported (Perry et al. 1990).
- A clinical trial reported that topical administration of a herbal preparation, SS-cream, containing common cinnamon on the glans penis was generally well tolerated, but may cause sporadic erectile dysfunction, excessively delayed ejaculation, mild pain, and local irritation and burning (Choi et al. 2000).
- A patient with orofacial granulomatosis was found to improve after a cinnamon- and benzoate-free diet (White et al. 2006).
- Asthma has been reported as a common condition in workers at cinnamon plantations (Uragoda 1984).

Safety pertaining to pregnancy and lactation

There were no reports in the scientific literature of common or cassia cinnamon being safe or harmful during pregnancy and lactation. Since common and cassia cinnamon are GRAS when used in amounts commonly found in food (level 4), it is presumed that food amounts consumed during pregnancy and lactation would also be safe (USFDA 2006). There is no clinical, animal, or in vitro evidence, however, to support this evaluation that common and cassia cinnamon are safe in food amounts during pregnancy and lactation.

With respect to therapeutic doses, the safety of cassia cinnamon in pregnancy and lactation is unknown (level 5). Common cinnamon is reported as unsafe for therapeutic use during pregnancy and lactation in 2 textbooks and “unknown safety” when used during lactation (Newall et al. 1996; McGuffin et al. 1997). It is unclear whether the listing as unsafe is an expert opinion based on the absence of reli-

able scientific evidence that perhaps would be better interpreted and cited as “unknown.”

Drug interactions

Although theoretical, the antidiabetic effect of common and cassia cinnamon may have an additive effect with anti-diabetic medication and insulin. Patients taking antidiabetic medication or insulin should be monitored by their health care provider when taking common or cassia cinnamon.

Pharmacology

Both bark and flower can be used medicinally; however, the bark is used more commonly. Levels of the active constituents vary depending on the method used in the extraction process. Extensive gas chromatography analysis of cinnamon leaf, stem bark, and root bark oils indicated a total of 72 compounds in varying proportions (Senanayake et al. 1978). Common and cassia cinnamon (*C. verum* and *C. aromaticum*) contain volatile oils (1%–4%) such as cinnamaldehyde (60%–80%, 1400–30 000 ppm), eugenol (up to 10%), and *trans*-cinnamic acid (5%–10%); phenolic compounds (4%–10%) such as condensed tannins, catechins, and proanthocyanidins; monoterpenes and sesquiterpenes (pinene); calcium-monoterpenes oxalate; gum; mucilage; resin; starch; sugars; and traces of coumarin (Duke 1992; Bruneton 1995; Leung and Foster 1996; Anderson et al. 2004).

Antioxidant

The polyphenolic polymers found in *C. verum* and *C. aromaticum* have antioxidant activity and have been shown to reduce oxidative stress in a dose-dependant manner through inhibition of 5-lipoxygenase enzyme (Anderson et al. 2004; Blomhoff 2004; Ranjbar et al. 2006).

Antidiabetic

Methylhydroxychalcone polymer (MHCP) in common and cassia cinnamon was found to be an effective mimetic of insulin (Jarvill-Taylor et al. 2001). MHCP demonstrated in vitro activation of glycogen synthase and inhibition of glycogen synthase kinase-3 β as well as insulin receptor phosphorylation homologous to the effects of insulin in 3T3-LI adipocytes (Jarvill-Taylor et al. 2001). In vivo studies show an increase in insulin-stimulated IR- β and the IRS-1 tyrosine phosphorylation treated with cassia cinnamon (Qin et al. 2003). Cinnamon acts as a synergetic agonist

Table 3. Cassia and common cinnamon evidence table.

Condition	Study design	Reference	n	Results	Statistically significant	Type of cinnamon	Dosage (daily)	Evidence grade	Comments
Type 2 diabetes	Randomized controlled trial	Mang et al. 2006	79	Reduced fasting glucose by 10.3%. No effect on HbA1c and lipid profile	Yes	Cassia	3 g	B1	Strong scientific evidence. Moderate effect on fasting glucose
Type 2 diabetes	Randomized controlled trial	Khan et al. 2003	60	Reduced fasting serum glucose by 18%–29%, reduced triglyceride by 23%–30%, reduced LDL cholesterol by 7%–27%, and reduced total cholesterol by 12%–26%	Yes	Cassia	1, 3, or 6 g	B1	Strong scientific evidence. Strong effect of fasting glucose and lipid profile markers (TG, LDL-C, and total-C)
Type 2 diabetes	Randomized controlled trial	Vanschoonbeek et al. 2006	25	No change in fasting glucose, insulin, HbA1c, oral glucose tolerance, or lipid profile	No	Cassia	1.5 g	B2	Good scientific evidence. No effect. Small sample size
<i>Helicobacter pylori</i> infection	Randomized controlled trial	Nir et al. 2000	23	Not effective at eradicating <i>H. pylori</i>	No	Cassia or cinnamon— not specified	80 mg	B2	Good scientific evidence. No effect. Small sample size. Study does not specify whether cassia or cinnamon was the intervention
Activation of olfactory cortex of the brain	Observational study	Gonzalez et al. 2006	23	Reading the word “cinnamon” elicited activation in the primary olfactory cortex	No	“Cinnamon” as a word	N/A	C	Fair scientific evidence. Observational study using the word “cinnamon”
Oral candidiasis in HIV	Case series	Quale et al. 1996	5	Improvement in oral candidiasis	No	Common	N/A	D	Weak scientific evidence. No placebo. Small sample size. Quantity of dosage not described
Chronic salmonellosis	Case report	Rosti and Gastaldi 2005	1	Eradication of chronic <i>S. enteritidis</i> infection	No	Common	Unknown	E	Very weak evidence. Very small sample size. No placebo

Note: HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; TG, triglycerides; total-C, total cholesterol; N/A, not available.

with insulin in vivo to decrease blood glucose levels after a glucose tolerance test (Verspohl et al. 2005) and in chronically high fructose diets (Qin et al. 2004).

Neurological

A natural medicine compendium reported that cinnamaldehyde is a central nervous system (CNS) stimulant in high doses, a CNS sedative in low doses, increases peripheral blood flow, slows heart rate, reduces blood pressure, and has antipyretic and hypothermic effects (Jellin 2006a, 2006b). Common cinnamon bark reduces the amplitude of penile somatosensory-evoked potentials in a mechanism that is not clearly understood, but may be useful in the treatment of premature ejaculation (Choi et al. 2000; Anderson et al. 2004).

Antimicrobial

The essential oil has demonstrated strong antibacterial and antifungal activities in vitro. Antifungal, antiviral, bactericidal, and larvicidal actions have been reported for the volatile oil. Its constituents eugenol, eugenol acetate, and methyl eugenol have been reported to enhance trypsin activity in vitro (Bruneton 1995). Cinnamaldehyde has broad spectrum gram-positive and gram-negative antibacterial activity in which it was shown to inhibit the growth of *Clostridium perfringens*, *Bacteroides fragilis*, *Bifidobacterium bifidum* (Lee and Ahn 1998), *Staphylococcus aureus*, *Listeria monocytogenes*, *Escherichia coli*, *Enterobacter aerogenes*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, *V. parahaemolyticus*, and *Salmonella typhimurium* (OAI et al. 2006) as well as broad-spectrum vaginal microflora (Arnal-Schnebel et al. 2004). One mechanism that has been explored for this antibacterial activity is that cinnamaldehyde destroys the cytoplasmic membrane of both gram-positive and gram-negative bacteria and induces depletion of the intracellular ATP concentration (Oussalah et al. 2006).

Cinnamaldehyde has also been shown to inhibit growth of fungi, including yeasts (4 species of *Candida*: *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. krusei*), filamentous molds (3 *Aspergillus* spp. and 1 *Fusarium* sp.), and dermatophytes (*Microsporum gypseum*, *Trichophyton rubrum*, and *T. mentagrophytes*) (OAI et al. 2006), as well as the eggs and adult females of human head louse *Pediculus humanus capitis* (Yang et al. 2005). Aqueous and alcohol extracts of cinnamon have demonstrated antibacterial effects against *H. pylori* (Tabak et al. 1999; O'Mahony et al. 2005).

Immunomodulatory and antineoplastic

Cinnamaldehyde was shown to inhibit lymphocyte proliferation and modulate T-cell differentiation (Koh et al. 1998). Cinnamaldehyde has an antitumour activity in which it was shown in vitro to be cytotoxic to human solid tumour cells (Kwon et al. 1998), cancer cell lines (Park et al. 2004), and a modulator of the phosphorylation signal pathways that block cellular proliferation at the G2/M phase of the cell cycle (Schoene et al. 2005).

Gastrointestinal

Cinnamon bark contains tannins, which, owing to their astringent properties, likely account for the antidiarrheal effect of common and cassia cinnamon (Newall et al. 1996).

Nonmutagenic

An in vitro study using *rec* assays with *Bacillus subtilis* strains demonstrated that the ethanol extract of common cinnamon (*C. zeylanicum*) was nonmutagenic (Ungsurungsie et al. 1984). The petroleum ether and chloroform extracts, however, were shown to be mutagenic, thereby suggesting that the mutagenic substances in cinnamon can be extracted by a nonpolar solvent (petroleum ether) or a semipolar solvent (chloroform) (Ungsurungsie et al. 1984).

Discussion

According to the World Health Organization (WHO), approximately 150 million people have type 2 diabetes worldwide, and this number may well double by the year 2025 (WHO 2002). Because diabetes is a growing health concern, there is a need for effective control and management of this disease. Another growing health concern is metabolic syndrome, which is a cluster of conditions (abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance and (or) glucose intolerance, prothrombotic state, and proinflammatory state) that increase the risk for heart disease, stroke, and diabetes. According to a cross-sectional survey, the incidence of metabolic syndrome in the United States is 21.8% (Ford et al. 2002).

Common and cassia cinnamon have been investigated in animal studies for their antidiabetic properties. Cassia cinnamon, however, has been the subject of 3 clinical trials, whereas common cinnamon remains unstudied in humans. The 3 trials on cassia cinnamon ranged from "strong" to "good" with respect to their grade of evidence. The Khan et al. (2003) trial reported the largest benefit of cassia cinnamon in lowering fasting glucose and lipid profile markers. Though the Mang et al. (2006) trial also observed a significant decrease in fasting glucose, the magnitude of the effect was far less dramatic; no significant change was observed in lipid profile markers nor in HbA1c after cassia cinnamon intake. The third trial, by Vanschoonbeek et al. (2006), did not observe a significant change in blood sugar or lipid profile markers, but this may have been due to the small sample size involved.

The principal criticism of the Khan et al. (2003) study was that baseline fasting glucose values were quite high (11.4–16.7 mmol/L) in comparison with those of the other 2 trials. This could be indicative of cassia cinnamon being more effective in reducing fasting glucose levels in patients with uncontrolled diabetes versus those with controlled diabetes. Mang et al. (2006) reported that the decrease in fasting plasma glucose correlated significantly with baseline concentrations, thereby supporting the hypothesis that subjects with poorly controlled diabetes would benefit more from cassia cinnamon intake. Another possible explanation is that the elevated baseline fasting glucose values in the Khan et al. (2003) trial could reflect differences in diabetic treatment (medications, diet, and exercise recommendations), and thus variations in blood sugar control, among the 3 studies. Fasting glucose levels as high as those observed in the Khan et al. study are unusual in Western patients with diabetes, due perhaps to disparities in treatment protocols. Lastly, Vanschoonbeek et al. (2006) suggested that their results differ owing to the inclusion of only women in their

study. Given that the other 2 trials contained women, it is unclear whether this would have had any bearing on the results.

The dosing is likely not an explanation of the observed difference between the 3 trials, as the Khan et al. (2003) trial reported a measurable effect with cassia cinnamon administered between 1 and 6 g daily, whereas the 2 other trials were well within that dosing range (i.e., 1.5 and 3 g). The quality of cassia cinnamon could also be a consideration, as the products used may have contained different amounts of MHCP, which is considered to be the active insulin-mimetic ingredient in common and cassia cinnamon (Jarvill-Taylor et al. 2001). Mang et al. (2006) reported that each cassia cinnamon capsule contained 112 mg of the aqueous cassia cinnamon extract TC112 (corresponding to 1 g of cinnamon), as prepared by Finzelberg (Andernach, Germany) and obtained from Truw Arzneimittel Vertriebs GmbH (Diabetruw, Gütersloh, Germany). Khan et al. (2003) described their cassia cinnamon product as "*Cinnamomum cassia*" as certified by the Office of the Director, Research and Development/Non-Timber Forest Products, NWFP Forest Department, Peshawar, Pakistan, and manufactured by Mehran Traders Pharmaceutical Suppliers, Peshawar, Pakistan. Vanschoonbeek et al. (2006), however, provided a far less detailed description of their cassia cinnamon product, as they describe their product as "*Cinnamomum cassia* prepared by a local pharmacy." Despite relatively good to very poor quality assurance reporting, none of the trials provided detailed chemical analysis of the constituents in their cassia cinnamon intervention. It would be more useful if future studies use cassia cinnamon products that are well characterized chemically and provide, at a minimum, assurance of botanical identity, source of raw material, processing steps, existence of voucher specimens of raw materials, and saved specimens for future reference.

Although there is strong to good evidence on the efficacy of cassia cinnamon in lowering fasting blood glucose, none of the clinical trials have been able to demonstrate that cassia cinnamon reduces HbA1c. Since glucose stays attached to hemoglobin for the life of the red blood cell (normally about 120 days), the level of HbA1c reflects the average blood glucose levels over the past 3 months. The HbA1c data from the Vanschoonbeek et al. (2006) study are not clinically relevant, as the study was conducted over 6 weeks from baseline to endpoint. In the Mang et al. (2006) study, HbA1c was not significantly reduced after 4 months of treatment with cassia cinnamon, nor was there a decreasing trend in HbA1c data from baseline to post-treatment. Before cassia or common cinnamon can be recommended as a natural alternative to pharmacological agents in treating type 2 diabetes, effectiveness in lowering HbA1c needs to be demonstrated. When conducting future randomized controlled clinical trials, the study length should be extended to perhaps 6 months or even a year to truly evaluate a change, if any, in HbA1c.

Common and cassia cinnamon have been shown to have antioxidant activity in vitro, and studies in humans have demonstrated that common cinnamon appears to have antioxidant activity when consumed as a tea. Ranjbar et al. (2006) showed individuals consuming cinnamon tea had increased total antioxidant levels, increased thiols, and decreased lipid peroxidation when compared with controls and

individuals consuming regular tea. It has been suggested that the antioxidant properties of common and cassia cinnamon may contribute to its antidiabetic effects, as there are a small number of clinical studies in which antioxidants, such as vitamin E, buckwheat herb, Ruscus extract, and troxerutinaos, were shown to reduce or slow the progression of diabetic complications (Ceriello et al. 1991; Paolisso et al. 1993; Archimowicz-Cyrylowska et al. 1996; Anderson et al. 2004). This is perhaps an area of future clinical research for both common and cassia cinnamon.

Although cinnamon was shown to have antibacterial activity against *H. pylori* in vitro, a small pilot study demonstrated that an alcoholic cinnamon extract over 4 weeks did not eradicate *H. pylori*. Based on weak scientific evidence from a case series, common cinnamon was shown to be beneficial in treating oral candidiasis in HIV patients. One case of salmonellosis was reported in which a chronic carrier of *Salmonella enteritidis* was resolved after ingesting ground common cinnamon bark. At this time, however, the clinical data do not indicate that cassia, common, or any other species of cinnamon should be recommended as a natural alternative for treating *H. pylori* infections, oral candidiasis in HIV patients, or salmonellosis. Although these studies are promising, further clinical research on common and cassia cinnamon is needed to strengthen the evidence grade for these therapeutic indications.

With respect to safety, common and cassia cinnamon appear to be generally well tolerated. The most common adverse effects are related to contact irritation or allergic reaction. There is one case wherein squamous cell carcinoma was reported after long-term cinnamon-gum chewing. Although cinnamon has not been specifically implicated as a carcinogenic agent given that its ethanolic extract was shown to be nonmutagenic, caustic chemical irritants acting through cytotoxic mechanisms can have carcinogenic activity when excessive doses exceed threshold levels. Of some concern is the case in which first- and second-degree burns were convincingly linked to cinnamon oil exposure. A number of cases of cinnamon oil abuse were reported in adolescent males (11–16 years), who complained of nausea or abdominal pain but showed no systemic effects. With respect to pregnancy and lactation, the safety of cassia and cinnamon at therapeutic levels remains unknown, but they are regarded as safe when taken in the amounts generally found in food. When designing future clinical studies, researchers should note the irritating effects of common and cassia cinnamon on mucus membranes and use products that are encapsulated versus liquid extracts.

Lastly, reading the word "cinnamon" appears to activate the olfactory cortex in the brain as determined by fMRI. Given that the inclusion criteria of our search strategy included all human studies, this study was presented in this systematic review. Although interesting, the results from this study were not discussed in detail as our systematic review is primarily concerned with the preclinical and clinical effects of common and cassia cinnamon.

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