Cinnamon and Cassia Nomenclature Confusion: A Challenge to the Applicability of Clinical Data

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Several *Cinnamomum* species' barks are generally labeled as cinnamon, although only *Cinnamomum verum* carries the common name of true cinnamon. Cassia, a common name for a related species, is rarely used on labels; instead, various cassia types may also be labeled "cinnamon." Confusion of true cinnamon and cassia spices in foods generally does not present a risk to health, except possibly at the highest intake levels. However, clinical studies with *Cinnamomum* investigational products have been published that inadequately describe or lack botanical identification information. The results of such studies are confounded by an inability to determine which species was responsible for the observed effects. Due to differences in the quality and composition of various *Cinnamomum* species, safety and efficacy data are not generalizable or transferable. Pharmacopeial monographs for characterizing the identity, composition, purity, quality, and strength of *Cinnamomum* investigational products should be applied to remove the ambiguity of cinnamon.

To most people, the name cinnamon refers to the spice obtained from the bark of plants of the genus *Cinnamomum* (family Lauraceae). The genus *Cinnamomum* comprises ~300 species, at least four of which are sources of the spice cinnamon.[1]

The most economically important sources of cinnamon are Ceylon cinnamon, also known as Sri Lankan or true cinnamon (*Cinnamomum verum* J.Presl; syn. *C. zeylanicum* Blume; **Figure 1**d–f); Chinese type (*C. cassia* (L.) J.Presl; syn. *C. aromaticum* Nees; **Figure 1**a–c); Indonesian type, also known as Korintje, Java, or Padang cinnamon (*C. burmanni* (Nees & T. Nees) Blume; **Figure 2**a,b); and Vietnamese type, also known as Saigon cinnamon (*C. loureiroi* Nees; **Figure 2**c–e).[2] There is also Indian cinnamon (*C. tamala* (Buch.-Ham.) T.Nees & Eberm.). The *Cinnamomum* species called cassia should not be confused with the completely unrelated laxative medicinal plant senna (*Senna alexandrina* Mill.), formerly known as various species of *Cassia*, which is in the family Fabaceae.

Apart from its use as a spice, cinnamon bark, as well as the essential oils and extracts obtained from it, are also popularly used as ingredients in dietary supplements and in traditional herbal medicinal products and formulations. For use in the Asian systems of medicine, Chinese type cinnamon (*C. cassia*) is monographed in the pharmacopoeias of the People's Republic of China,[3] Japan,[4] South Korea,[5] and Taiwan (Republic of China).[6] Indonesian type cinnamon (*C. burmanni*) is monographed in the Indonesian Herbal Pharmacopoeia,[7] as well as "sintok" cinnamon bark (*C. sintoc* Blume).[8] Wild cinnamon (*C. iners* Reinw. ex Blume) appears in the Malaysian Herbal Monographs[9] and Vietnamese type cinnamon (*C. loureiroi*) in the Pharmacopoeia Vietnamica.[10] Both Ceylon cinnamon (*C. verum*) and Indian cinnamon (*C. tamala*) are included in the Ayurvedic Pharmacopoeia of India.[11]

In Ayurvedic medicine, for example, the dried inner bark of the coppiced shoots of Ceylon cinnamon (*C. verum*) stem is used in formulations for the treatment of hemorrhoids, helminthic infestations, morbid thirst, dryness of mouth, throat and mouth diseases, and respiratory ailments (chronic rhinitis/sinusitis).[11]

In Traditional Chinese medicine (TCM), the dried stem bark of Chinese cinnamon (*C. cassia*) is used in formulations to treat

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Received 15 March 2018; accepted 7 June 2018; advance online publication 4 August 2018. doi:10.1002/cpt.1162

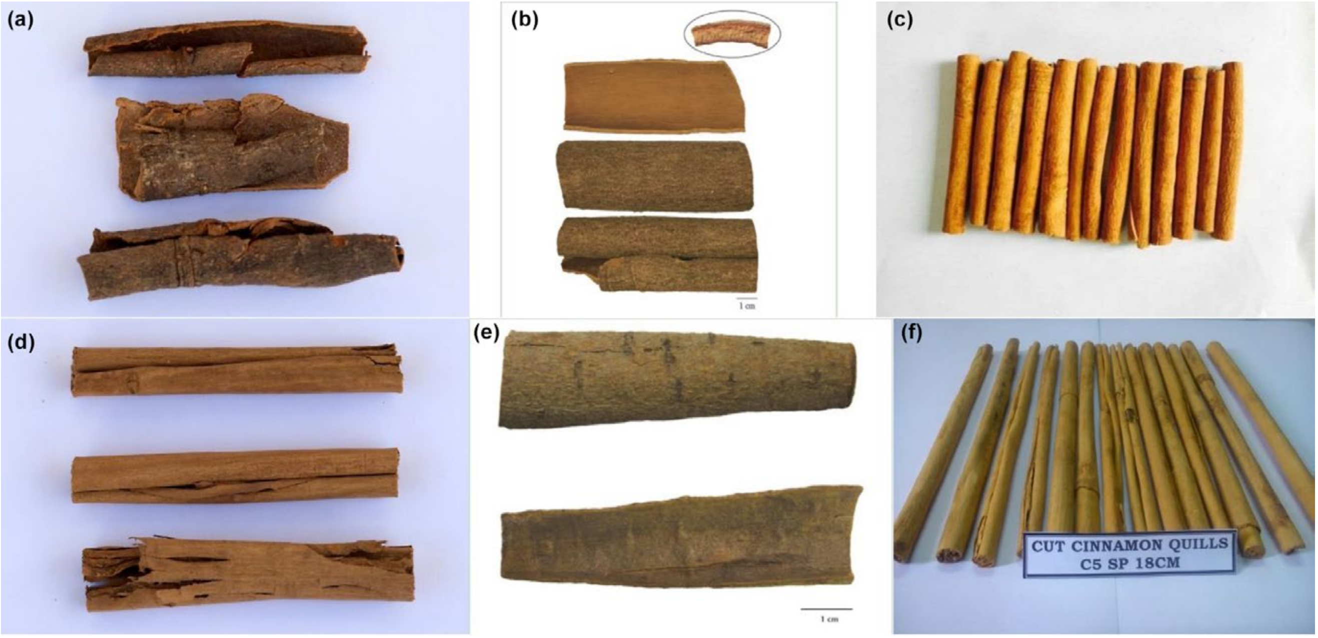

Figure 1 Commercial samples of cinnamon bark (Chinese type and Sri Lankan type). (**a**) Chinese-type cinnamon branch bark, broken. (**b**) Chinese type cinnamon, inner surface and outer surface. (**c**) Chinese-type cinnamon, sticks, scraped. (**d**) Sri Lankan-type cinnamon bark, quills. (**e**) Sri Lankan-type cinnamon bark, broken quills, outer (top) and inner (bottom) surfaces. (**f**) Sri Lankan-type cinnamon bark quills, grade CS SP (Continental 00000 Special). Photographs: **a**, **d** (Thomas Brendler; samples courtesy of Pure Ground Ingredients, Carson City, Nevada); **b**, **e** (courtesy of United States Pharmacopeia Dietary Supplements Compendium); c, f (courtesy of Martin Bauer GmbH & Co. KG, Vestenbergsgreuth, Germany).

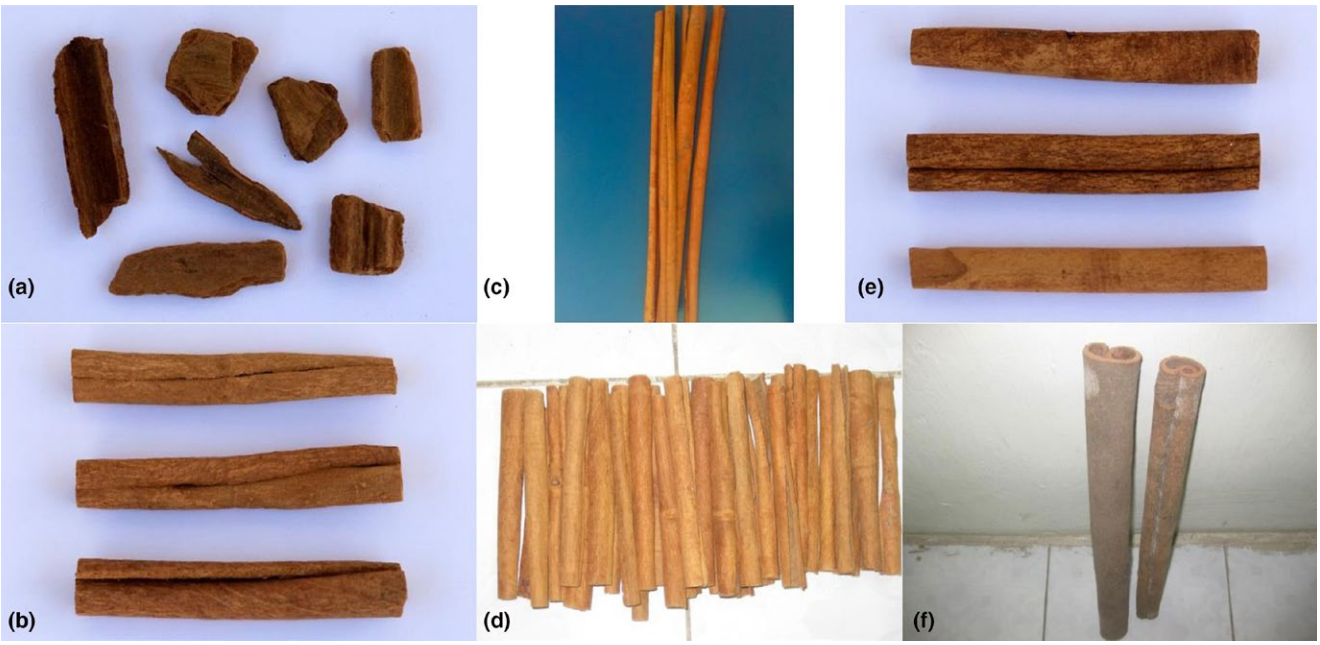

Figure 2 Commercial samples of cinnamon bark (Indonesian type and Vietnamese type). (**a**) Indonesian-type cinnamon bark, broken pieces. (**b**) Indonesian-type cinnamon, scraped, grade KA (Korintje A (prima)). (**c**) Indonesian-type cinnamon, quills, partially scraped. (**d**) Vietnamese-type cinnamon rolls. (**e**) Vietnamese-type "cigarette" cinnamon. (**f**) Vietnamese-type cinnamon tubes. Photographs: **a**, **c**, **d** (Thomas Brendler; samples courtesy of Pure Ground Ingredients, Carson City, Nevada); **b**, **e**, **f** (courtesy of Martin Bauer GmbH & Co. KG, Vestenbergsgreuth, Germany).

impotence, uterine coldness, abdominal pain, vomiting, and diarrhea, as well as to restore normal menstruation (for both amenorrhea and dysmenorrhea). Not only the tree bark but other plant parts are also used in TCM. For example, the dried young branch (twigs) of *C. cassia* are also used in TCM formulations for common cold conditions, epigastric pain with cold feeling, amenorrhea, arthralgia, and gastrointestinal neurosis, among other ailments.[3,12] In fact, almost all parts of *Cinnamomum* species trees (including the bark, leaves, flowers, fruits, and roots) are used for medicinal or culinary purposes.

Because of the many purported medicinal benefits[13,14] related to blood glucose control, anti-inflammatory properties, antimicrobial activity, prevention of cardiovascular disease, and enhancement of cognitive function, among other properties, many studies (clinical, animal, and *in vitro*) have been carried out to elucidate and evaluate the claimed actions. In this review, to illustrate the problem of inadequate identification of *Cinnamomum* species, we focus on studies of one aspect of the purported antidiabetic effects of cinnamon (blood glucose control), which has been demonstrated in both *in vitro* and *in vivo* studies.[15,16] Here, we show that a lack of proper identification of the study materials in clinical studies may contribute to the equivocal outcome in most meta-analyses of these studies.

Many patients with diabetes seek complementary or alternative treatments for diabetes mellitus (DM), including the use of dietary supplements that contain cinnamon to control their blood sugar.[17] An important question is whether such products (e.g., herbal medicines or dietary supplements) made with cinnamon and used as complementary or alternative therapy for DM or to control blood sugar have been correctly identified.

The lack of clarity regarding species used in studies is paralleled by the lack of clarity regarding the identity of materials sold in the market. In most products on the market, the ingredient is referred to by the common name "cinnamon" but the reality is that these ingredients may be sourced from different quality grades, types, or varieties of cinnamon, or even different *Cinnamomum* species, which may have different compositions and potencies.

ECONOMIC FACTORS IN CINNAMON AND CASSIA CONFUSION

There are five main *Cinnamomum* bark producing countries, accounting for over 99% of global production: Indonesia, China, Vietnam, Sri Lanka, and Madagascar. Over the last 10 years, Indonesia was the world's leading producer of *Cinnamomum* bark in terms of both volume (91,400 tonnes in 2014) and reported value ($127,237,055 in 2014) (see **Figure S1**). Indonesia produces and exports not only its own native species (*C. burmanni*), obtained from both wild collection and some cultivation, but Indonesia also cultivates and exports barks of introduced *Cinnamomum* species, such as Ceylon cinnamon (*C. verum*) and Chinese cinnamon (*C. cassia*). The Food and Agriculture Organization of the United Nations (FAO) data for production of all species of *Cinnamomum* is combined under the group term canella, FAOSTAT Commodity List Item 0693, which is defined as "the inner bark of young branches of certain trees of the Laurus family." Canella also includes cinnamon flowers, cinnamon fruit, and cinnamon waste (chips), whether whole, crushed, or ground.[18]

Curiously absent from the FAO data is India, which is indeed exporting cinnamon as shown in other United Nation (UN) trade databases. The increase in exports of Indian cinnamon may be due to the increasing commercialization of barks of wild-growing Indian cassia (*C. tamala*) trees, possibly substituted for other cinnamons. Additionally, *C. verum* is native to both Sri Lanka and India, where there is some cultivation in the state of Kerala.[19]

For determining export trade volume, the United Nations Commodity Trade Statistics (UN COMTRADE) provide three six-digit harmonized system (HS) tariff codes. Tariff code HS 090611 is assigned solely to Ceylon cinnamon (*C. verum*, syn. *C. zeylanicum*), whole or ground; HS 090619 designates whole barks (neither crushed nor ground) of all other *Cinnamomum* species, including Chinese type cassia (*C. cassia* syn. *C. aromaticum*; **Figure 2a–c**), Indonesian type cassia (*C. burmanni*; **Figure 2a–c**), and/or Vietnamese type cassia (*C. loureiroi*; **Figure 2d–f**); and HS 090620 designates the crushed or ground (powdered) barks of *Cinnamomum* species (other than Ceylon cinnamon).[20]

It is worth noting that the trade data indicates that Vietnam exports not only its native species (*C. loureiroi*), which is obtained from both wild collection and cultivation, but also, questionably, Ceylon cinnamon (*C. verum*). As Vietnam is known mainly as a producer and exporter of both Chinese-type and Vietnamese-type barks, it is more likely that certain exporters may be incorrectly assigning the HS Code for Ceylon cinnamon in their export documentation.

Thus, agricultural production and trade classifications of *Cinnamomum* species as crops and commodities lump together different species, giving wholesalers and retailers little evidence or incentive to identify accurately the species of cinnamon or cassia they are selling.

CINNAMOMUM NOMENCLATURE IN US REGULATIONS

The regulatory environment in the United States has contributed to the confusion about the names used for this ingredient in the market. Articles of botanical origin may potentially be used as components of cosmetic, food, dietary supplement, and/or drug products. The naming convention for the article may differ depending on the regulatory framework governing the product. For example, when the inner bark of *C. cassia* (syn. *C. aromaticum*) is used as an ingredient of a dietary supplement product, Title 21 of the Code of Federal Regulations (CFR) §101.4(h)[21] requires that its common or usual name shall be consistent with the names standardized in the American Herbal Products Association's (AHPA) *Herbs of Commerce*,[22] which is incorporated by reference in accordance with 5 United States Code (5 USC) §552(a) and 1 CFR Part 51. Furthermore, 21 CFR §101.4(h)(2) states that if a standardized common name (SCN) is not available in *Herbs of Commerce*, the Latin binomial name of the plant should be provided in parentheses following the common or usual name listed on the label, or the Latin binomial name may be listed before the part of the plant on the label. However, if the very same inner bark of *C. cassia* is used as a spice or flavoring component of a food product, 21 CFR §101.22[23] becomes relevant and refers to Generally Recognized as Safe (GRAS) spices listed in 21 CFR §182.10.[24] In this example, as per §101.4(h), the SCN of *C. cassia* for labeling of a dietary supplement product will be cassia, whereas the common name for labeling as a spice component of a food product can be either Chinese cassia or Chinese cinnamon as per as per §182.10.[24]

Similarly, the common names provided in 21 CFR §182.10 are Saigon cassia and Saigon cinnamon for *C. loureiroi*, and Batavia

Table 1 English common names of *Cinnamomum* species in US regulations

Species	21 CFR §101.4(h)	21 CFR §182.10 and §182.20	40 CFR §180.41
C. aromaticum (accepted *C. cassia*)	Cassia	Chinese cassia or Chinese cinnamon	Cassia
C. burmannii	Not listed	Batavia cassia or Padang cassia	Not listed
C. loureirii	Saigon cinnamon	Saigon cassia or Saigon cinnamon	Not listed
C. tamala	Indian cassia	Not listed	Not listed
C. verum (syn. *C. zeylanicum*)	Cinnamon	Ceylon cinnamon	Cinnamon

CFR, Code of Federal Regulations.

Table 2 English common names of *Cinnamomum* species in Canadian regulations

Species	Food and Drug Regulations, Part B, Division 7: Spices, Dressings, and Seasonings B.07.011. [S] B.07.012. [S]	Food and Drug Regulations, Part B, Division 10: Flavoring Preparations B.10.012. [S] B.10.013. [S]	Natural Health Products Ingredients Database
C. cassia (syn. *C. aromaticum*)	Cinnamon or Cassia	Cassia or Cassia cinnamon	Cassia or Cassia cinnamon or Chinese cinnamon or Cinnamon
C. burmanni (syn. *C. burmannii*)	Cinnamon or Cassia	Not listed	Batavia cinnamon
C. loureirii (accepted *C. loureiroi*)	Cinnamon or Cassia	Not listed	Saigon cinnamon
C. tamala	Not listed	Not listed	Indian bark
C. zeylanicum (accepted *C. verum*)	Ceylon cinnamon	Ceylon cinnamon	Cinnamon or Ceylon cinnamon

cassia and Padang cassia for *C. burmanni*, whereas *C. zeylanicum* is given the common name Ceylon cinnamon. The AHPA *Herbs of Commerce* names the latter cinnamon without the regional qualifier of Ceylon and uses the Latin binomial *Cinnamomum verum*. Thus, the accepted, common, or usual names for various species of *Cinnamomum* are inconsistently applied within the US Food and Drug Administration (FDA) regulations.

Table 1 shows the English common names of *Cinnamomum* species as listed in various US regulations, wherein *C. cassia* is assigned the common name of cassia in the FDA regulations (21 CFR) concerning the labeling of dietary supplement products. **Table 1** also shows the names used in the US Environmental Protection Agency (EPA) regulations (40 CFR §180.41),[25] which concern pesticide tolerances established for cassia and cinnamon as food crops.

CINNAMOMUM NOMENCLATURE INTERNATIONALLY

In addition to the reporting of agricultural and trade statistics, a review of regulatory text, international specifications, and official compendia of other countries helps to explain, in part, *Cinnamomum* species nomenclatural confusion in the literature and labeling. **Table 2** shows the English common names of *Cinnamomum* species as specified in Canadian regulations,[26] wherein several *Cinnamomum* species may be represented interchangeably as cassia or as cinnamon when used in food products. However, when used as medicinal ingredients of licensed Natural Health Products (NHPs), specific qualifiers are used, such as Batavia cassia or Batavia cinnamon (*C. burmanni*), Indian bark (*C. tamala*), and Saigon cinnamon (*C. loureiroi*).[27]

There are inconsistencies in the cinnamon and cassia monograph naming policies of other authoritative compendia, such as the pharmacopeias of China,[3] Japan,[4] and Korea,[5] as well as in the specifications of the International Organization for Standardization (ISO).[28,29] For example, whereas the Ayurvedic Pharmacopoeia of India (API) refers to *C. verum* as cinnamon, the pharmacopoeias of Japan and Korea instead refer to *C. cassia* as cinnamon, whereas the ISO specifications define *C. cassia* as Chinese-type cassia.[28] **Table 3** shows the English common names of *Cinnamomum* species used in monograph titles of other compendia.

CINNAMOMUM CONFUSION IN PEER-REVIEWED CLINICAL JOURNALS

Most systematic reviews and meta-analyses that examined the potential benefit of cinnamon as adjunct treatment for type 2 diabetes mellitus (T2DM) concluded that the available evidence is insufficient to support the use of cinnamon for type 1 or type 2 DM.[30] A recent narrative review by Costello *et al.*,[31] which examined the same studies as Leach and Kumar[30] plus two other studies, found evidence to indicate that cinnamon supplements *when added to standard hypoglycemic medications and other lifestyle therapies* [emphasis added] had a modest effect on fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c). However, they concluded that the evidence to date does not suggest that supplementation with cinnamon could achieve hypoglycemic treatment goals or cause a reliable and clinically significant drop in FPG or HbA1c in patient patients with T2DM.[31]

Table 3 English common names of Cinnamomum species in other compendia

Species	API	ISO (ISO 6538 and ISO 6539)	Japanese Pharmacopoeia	Korean Pharmacopoeia	European Pharmacopoeia
C. aromaticum (accepted: *C. cassia*)	No monograph	Chinese type cassia	Cinnamon	Cinnamon	Not listed
C. burmannii	No monograph	Indonesian type cassia	No monograph	No monograph	Not listed
C. loureirii	No monograph	Vietnamese type cassia	No monograph	No monograph	Not listed
C. tamala	Indian cinnamon	No specification	No monograph	No monograph	Not listed
C. verum (syn. *C. zeylanicum*)	Cinnamon	Cinnamon (Sri Lankan type; Seychelles type; and Madagascan type)	No monograph	No monograph	Cinnamon

API, Ayurvedic Pharmacopoeia of India; ISO, International Organization for Standardization.

Unfortunately, in all of these reviews, the criteria for including studies in the review allowed the aggregation of studies that used cinnamon as test material without taking into consideration the different species of cinnamon that may be involved.

The systematic review by Leach and Kumar[30] evaluated the effects of orally administered cinnamon mono-preparations as an adjunct therapy in patients with type 1 or type 2 DM. The selection criteria for including studies in the review were randomized controlled trials that orally administered mono-preparations of cinnamon (which would include different *Cinnamomum* species) and compared the effects to that of placebo, active medication, or no treatment in persons with either type 1 or type 2 DM. Ten studies qualified for inclusion into the review, resulting in a total of 577 study participants[32–41] (see **Table S1**). A closer examination of each individual study included in the review was conducted to determine the identity of the test material used. We found that a majority did not confirm the identity of the plant material used to prepare the test material. This observation calls into question the identity of the materials used in the studies and possibly the outcome of the systematic review. Phytochemical studies have shown significant differences in the chemical profiles of the different *Cinnamomum* species.[42]

As a first step to identify key articles for this review, a search was made using the PubMed database with the search term "cinnamon" and a limit for review article types covering the period from inception of the database to December 2017. This search retrieved 159 articles on all aspects of cinnamon research. Of the 159 articles, 28 were review articles (systematic reviews as well as narrative reviews) on the effects of cinnamon on some aspect of diabetes or metabolic syndrome. The articles evaluated below in detail were those primary literature articles cited in the selected reviews that described clinical trials examining the antidiabetic effects of cinnamon.

A total of 10 studies[32–41] that were cited in more than one of the 28 reviews have been examined to illustrate the confusion in the identity of test materials used. Most of the titles of the primary articles and descriptions of the test materials in the "Materials and Methods" sections used the common name cinnamon regardless of the *Cinnamomum* species that was investigated. For example, recent articles have used the term cinnamon to describe test materials composed of *C. burmanni*,[43] *C. loureiroi*,[44] *C. osmophloeum*,[45] and *C. verum*.[46]

Leach and Kumar[30] reviewed 10 clinical studies and concluded that the available evidence was insufficient to support the use of cinnamon for the treatment of type 1 or type 2 DM. Of the 10 studies included in the review by Leach and Kumar, six stated that the powder or extract test material used in the study was made with *Cinnamomum cassia*.[32,34–36,38,41] However, only one of these studies reported the verified identity of the study material to be *C. cassia*.[36] This study was done in Pakistan and reported that the test material used was certified as *C. cassia* by the Office of the Director, Research, and Development/Non-Timber Forest Products, NWFP Forest Department, Peshawar, Pakistan. All of the four remaining studies relied on the manufacturers' label information as confirmation of the identity of the material tested. In the article by Vanschoonbeek *et al.*,[41] the authors indicated that the material used was *C. cassia* sourced from a particular company in the United Kingdom. However, the authors indicated in the discussion that the whole bark of the Indonesian cinnamon tree was used. Although there is some commercial cultivation of Chinese cinnamon (*C. cassia*) in Indonesia, Indonesian cinnamon is typically *C. burmanni* and not *C. cassia*. This calls into question the true identity of the plant material used to prepare the test material studied. We inquired about the identity of the plant from which the company obtains material for the cinnamon powder. The UK company's unofficial response was that they use both *C. cassia* (mainly for powdered cinnamon) and *C. verum* for the whole cinnamon material. We have been unable to obtain official confirmation.

Assuming that the information from the vendor companies cited in the primary articles was correct, we can consider that six studies in the Leach and Kumar review used *C. cassia* bark, and all of these studies observed positive effects on the lowering of blood glucose, blood pressure, and HbA1c.

On the other hand, the study by Rosado[39] used an aqueous extract of *C. burmanni* bark and did not observe a reduction in fasting blood glucose or HbA1c levels.

The remaining four studies in the review did not specify the species of material used to prepare the test material and did not provide information on the origin of the study material. In describing the investigational products for their prospective, double-blind, placebo-controlled study, Altschuler *et al.*[33] merely indicated that "All pills were prepared in advance by the University of California San Francisco Investigational Pharmacy. Pills contained either 1 g cinnamon or an equivalent amount of lactose." The authors did not provide information on the source of the plant material used to prepare the pills (later in the article it was clarified to be capsules), and no information was provided regarding the composition, botanical identification, quality, purity, or strength of the cinnamon pills. Khan *et al.*[37] reported that their study material was purchased from the local market, finely ground, and filled into capsules so that each capsule contained 0.5 g of cinnamon powder or wheat flour (for the placebo). No further information was provided regarding the identity or quality of the cinnamon used. When powder is used in a clinical trial, it is important to control the powdering process. The quality of *Cinnamomum* bark degrades after comminution at varying rates depending on the particle size, storage containers, and conditions and duration of storage after powdering, up until the production of the final dosage form. Last, Suppapitiporn *et al.*[40] indicated in their article title that the study involved *C. cassia*. However, the text primarily refers to the test material as simply cinnamon and no information is provided in the Materials and Methods section to indicate the identity or source of the study material.

An update of a systematic review and meta-analysis by Allen *et al.*[47] included data from 10 clinical studies, including eight of the studies in the Leach and Kumar review[32,34,36–38,40,41] and two additional studies.[48,49] The Allen *et al.*[47] review concluded that the intake of cinnamon increased high-density lipoprotein cholesterol (HDL-C) levels and decreased FPG, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, but had no significant effect on HbA1c levels. Lu *et al.*[48] described the tablets used in their study as containing cinnamon extract prepared from the bark of Chinese *Cinnamomum aromaticum*. No additional information was provided regarding the identity, composition, or quality of raw material. However, the authors indicate that the tablets used were approved for human use by the State Food and Drug Administration of China with the approval number G20110080. The second new article, by Wainstein *et al.*,[49] indicated that the test material was provided as herbal gelatin capsules manufactured by a company in Israel. The treatment capsules contained freshly ground cinnamon of broken cassia (*C. cassia*) with zinc gluconate (21 mg) and tricalcium phosphate, whereas the placebo capsules contained 400 mg of microcrystalline cellulose. Evidently, the researchers relied on the manufacturer-provided information for identity of their test material.

As discussed above, the studies cited analyzed in the systematic reviews examined here have used test materials from different species of *Cinnamomum*. Key questions are whether these species are chemically similar or different, and, if different, what might be the pharmacological consequences.

WHY NOMENCLATURE MATTERS: PHYTOCHEMICAL DIFFERENCES BETWEEN *C. VERUM* AND *C. CASSIA*

Significant phytochemical differences have been reported between various species of *Cinnamomum*.[13,50,51] Furthermore, different plant parts of cinnamon are also on the market. For example, the twig has a different chemical composition than the bark and is a separate article of commerce.[52] Thus, when ascertaining identity of the material to species level it is also important to ascertain the specific part of the plant being used. These chemical composition differences suggest that their biological effects are also likely to differ. Consequently, analyses that combine results from different species of *Cinnamomum* may result in erroneous conclusions.

The main constituents of oils extracted from *C. verum* stem bark are *trans*-cinnamaldehyde (49.9–62.8%), eugenol, cinnamyl acetate, linalool, and benzyl benzoate.[1,53] Oils extracted from the root bark contain camphor (up to 60%), 1,8-cineole, eugenol, terpinol, and cinnamaldehyde. The leaf oil contains eugenol (60–90%), cinnamaldehyde, linalool, and cinnamyl acetate.[1,53] The fruit oil contains cadinene (30–40%), cadinol, and β-caryophyllene. The *C. verum* contains only traces (0.004%) or no detectable levels of coumarin.[51]

In contrast, *C. cassia* usually is used to produce only one main type of oil, from the stem bark. Almost 95% of this oil consists of cinnamaldehyde; there are slight variations in composition between the different parts of the plant.[54] Other constituents of *C. cassia* include methoxycinnamaldehyde, benzaldehyde, coumarin, limonene, eugenol, and cinnamyl acetate.[55] Methods of distinguishing *C. verum* oils from *C. cassia* oil are based mainly on the presence of a higher content of benzaldehyde, methoxycinnamaldehyde, and coumarin in *C. cassia* oil.[55]

The *Cinnamomum cassia* bark content of coumarin varies considerably with subspecies or climatic conditions under which it is grown. The German Federal Institute for Risk Assessment (BfR) cited literature values for coumarin in cassia bark ranging from as low as 700 mg/kg up to a maximum of 12,200 mg/kg, with an estimated average of 3,000 mg/kg (0.3%) based on analysis of more than 170 samples.[56] The twigs of *C. cassia* typically contain between 0.02% and 0.15% coumarin.[52] The essential oil obtained by steam distillation of the leaves and young branches of *C. cassia* contains from 1.25–4.0% coumarin.[55,57]

Wang *et al.*[42] analyzed samples of cinnamon in the US market and reported variations in the constituents of *C. verum*, *C. burmanni*, *C. loureiroi*, and *C. cassia*. Although cinnamaldehyde was the dominant volatile compound in all four species studied, the concentration differed significantly between the species, showing the following concentrations: 16.8 g/kg (*C. verum*), 46.3 g/kg (*C. burmanni*), 55.8 g/kg (*C. loureiroi*), and 18.7 g/kg (*C. cassia*). Similarly, the coumarin concentration was also significantly different among these species, with concentrations recorded as 0.017 g/kg (*C. verum*), 2.15 g/kg (*C. burmanni*), 6.97 g/kg (*C. loureiroi*), and 0.31 g/kg (*C. cassia*), for the four species studied. Other compounds, such as cinnamyl alcohol, cinnamaldehyde, cinnamic acid,

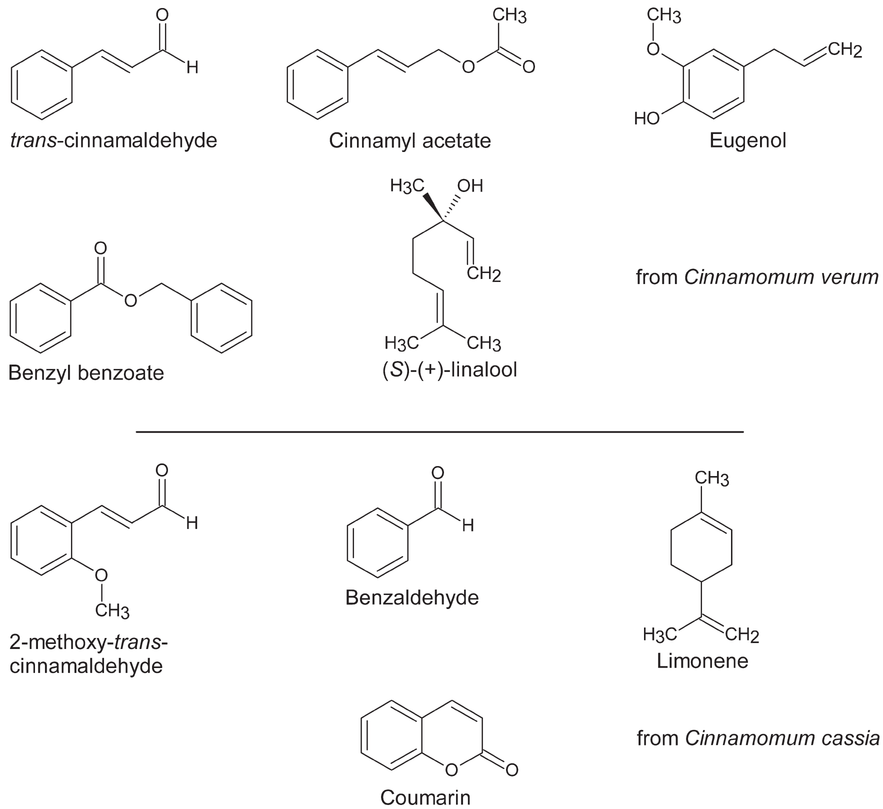

Figure 3 Selected cinnamon constituents.

and cinnamyl acetate, were detected in all four species. Eugenol was detected in *C. verum* and *C. loureiroi* but was absent from *C. burmanni* and *C. cassia*. Based on this study, two distinct profiles of cinnamon emerge: one profile is attributable to *Cinnamomum* species rich in cinnamaldehyde and coumarins (*C. burmanni* and *C. loureiroi*), whereas the other two species have low concentrations of these compounds.[42] In other studies, oils from authenticated samples of *C. verum* were found to contain high concentrations of *E*-cinnamaldehyde (77.1%), *E*-carophyllene (6%), terpinol (4.4%), and *E*-eugenol 3%. This finding indicates that there is a wide range in the concentrations of individual components.[42]

Cinnamomum osmophloeum is another species known to contain high levels of cinnamaldehyde and often substituted for *C. cassia* in commerce.[58]

Among the aforementioned constituents, cinnamaldehyde, coumarins, and polyphenols have been studied for hypoglycemic effects.[59–62] Particular attention will be devoted to coumarin in the discussion that follows because of its pharmacological and toxicological properties, presenting a potential safety concern at high levels of intake, in addition to the distinctive flavor and aroma it imparts to products made from species of *Cinnamomum* other than *C. verum*. **Figure 3** shows the chemical structures of selected cinnamon constituents.

WHY NOMENCLATURE MATTERS: *CINNAMOMUM* PHARMACOLOGY

In traditional Asian systems of medicine, the whole bark extract (rather than individual components of the bark) is believed to be responsible for its biological activity. This belief system is lent some credence by recent research using omic techniques in systems biology approaches to the scientific evaluation of traditional medicines, which have allowed correlation of the multiple components of complex phytochemical mixtures with their biological effects.[63] Two compounds that have been of great interest in cinnamon and cassia are coumarin and cinnamaldehyde.

Coumarin is one of the constituents of cassia that has been studied for its hypoglycemic effects. In one study, it was shown that the oral administration of coumarin to diabetic rats modified glucose metabolism causing a significant reduction in the levels of plasma glucose levels and HbA1c as well as an increase in insulin and hemoglobin levels.[64,65] Further evidence for a possible role of coumarin in the hypoglycemic effects of cinnamon was demonstrated in a study that administered hydroalcoholic extracts of Ceylon cinnamon. This study demonstrated a significant hypoglycemic effect of the hydroalcoholic extracts compared to aqueous extracts that contained less coumarin.[66] Wickenberg *et al.*[67] hypothesized that the intake of *C. zeylanicum* (accepted name *C. verum*) would lower the postprandial glucose and insulin response in subjects with impaired glucose tolerance (IGT). However, the administration of 6 g *C. zeylanicum* to individuals with IGT had no significant effect on glucose level, insulin response, HbA1c, or body mass index (BMI). The authors concluded that the ingestion of *C. zeylanicum* did not affect postprandial plasma glucose or insulin levels in human subjects. It is unclear whether the lack of hypoglycemic effects in the aqueous extract was due to the absence of coumarin in *C. verum*, as the samples tested were not analyzed for coumarin content.

However, considering that coumarins are less polar and would be better extracted with alcohol, one could infer that the aqueous extract contained a lower quantity of coumarins compared to the hydroalcoholic extract. In other studies that support the possible hypoglycemic effects of coumarin, several benzopyrone analogues containing the same benzopyrone pharmacophore have shown antidiabetic activity in diabetic rats that is equivalent to or superior to that of one of the standard antidiabetic drugs, glibenclamide.[68] However, these studies in rodents ignore the well-established differences in coumarin metabolism in primates compared to rodents, another possible reason for a lack of a similar effect in humans.[69]

Cinnamaldehyde, another major compound in cinnamon, has also been shown to possess antidiabetic activity. In streptozotocin-induced hypoglycemic mice (a commonly used animal model of diabetes), the administration of cinnamaldehyde dose-dependently reduced the plasma glucose concentration and decreased HbA1c, serum total cholesterol, and triglyceride levels. Concurrently, there was a marked increase in plasma insulin, hepatic glycogen, and HDL-C levels.[59] Anderson *et al.*[70] isolated a water-soluble polyphenol polymer from *C. burmanni* that increased insulin-dependent *in vitro* glucose metabolism by roughly 20-fold. Subsequently, a cinnamon bark extract (species not specified) that was standardized to this polyphenol demonstrated significant hypoglycemic effects, reducing fasting blood glucose and systolic blood pressure.[71] Similar oligomeric procyanidins have been reported in aqueous fractions from *C. cassia*.[72]

From the foregoing discussion, *C. cassia* seems to possess most of the compounds that have been shown to lower blood glucose levels; cinnamaldehyde, coumarin, and polyphenol polymer. It would be interesting to study the correlation between the hypoglycemic effects of different *Cinnamomum* species and the concentration of the various components of cinnamon that have already been shown to possess hypoglycemic activity.

CINNAMON SAFETY WITH REGARD TO COUMARIN LEVELS

Although the major focus of this article is on the identity of cinnamon materials used in clinical research on antidiabetic activity of cinnamon, reproducible evidence for efficacy is not the only concern. There is also a potential risk to health associated with excessive intake of coumarin, for example, from *C. cassia*, *C. burmanni*, and *C. loureiroi*.

Coumarin is a benzopyrone compound that is widespread in plants, including vegetables, spices, fruits, and medicinal plants. Coumarin has been used as a flavoring agent in food and tobacco. However, the FDA banned the use of coumarin as a flavoring agent[73] after studies showed hepatotoxic effects in animal models.[74] Later work clarified that the metabolism of coumarin in rats is different than that in humans, and that the hepatotoxicity of coumarin observed in humans was an idiosyncratic effect, as it only occurred in some human populations.[74]

In 2004, after reviewing all the available data, the European Food Safety Authority (ESFA), established a tolerable daily intake (TDI) for coumarin of 0.1 mg/kg body weight based on a no observed-adverse effect level (NOAEL) in animals.[75] In 2007, the BfR also reviewed the human data and confirmed the TDI of 0.1 mg/kg of coumarin.[65,76]

After further evaluation of the evidence for coumarin toxicity, in 2012, the BfR[56] concluded that there was sufficient bioavailability of coumarin from foods containing cassia-type cinnamon to pose a potential risk to health. They put this concern in the context that even where these maximum levels are reached, exceeding the TDI of 0.1 mg of coumarin per kg of body weight is possible only if very large quantities of cinnamon-containing foods are consumed on a daily basis (e.g., high coumarin levels of up to 100 mg/kg were discovered in typical German Christmas cookies with high cinnamon content).[77] For small children with a body weight of 15 kg, the TDI would be reached if they ate 30 g of cinnamon stars (i.e., about 6 small cinnamon stars) or 100 g of gingerbread per day. Because exceeding the TDI by a small degree for 1–2 weeks can be considered safe, risk to health would only occur for consumers who eat large quantities of cassia-type cinnamon with high coumarin content over a relatively long period of time. For an adult with a body weight of 60 kg, the TDI would be reached if 2 g of cassia-type cinnamon with average coumarin content is consumed per day. For an infant with a body weight of 15 kg, this would the case if 0.5 g of cassia-type cinnamon with average coumarin content were consumed per day. The BfR's recommendation that cassia-type cinnamon with high coumarin content should only be consumed in moderation remained unchanged. The BfR also recommended that consumers who frequently eat large quantities of cinnamon as a spice should, therefore, opt for the low-coumarin-containing Ceylon cinnamon. Of course, this is predicated on adequate labeling so that consumers know which type of cinnamon they are buying.

Because clinical research with encapsulated cinnamon powders or extracts may entail significantly higher intakes (e.g., as much as 12 mg of coumarin per capsule of cinnamon bark powder)[77] than would be likely with foods, the presence of a high content of coumarin in some species of *Cinnamomum* represents a potential risk to the health of the clinical trial participants.

CONCLUSION AND PROPOSED SOLUTIONS

In order to ensure reproducible and safe outcomes in clinical trials, we propose that clinical researchers adhere to the methods for interventions as outlined in the Consolidated Standards of Reporting Trials (CONSORT) Statement for the reporting of randomized, controlled trials of herbal interventions. The CONSORT recommends the inclusion of precise descriptions (e.g., the Latin binomial name together with the botanical authority and family name for each herbal ingredient, common names, and product manufacturer names) as well as characteristics of the herbal product (e.g., plant part(s), type of product, preparation method, chemical analysis, dosage including herbal constituents, and method of authentication, lot number, and information on where a voucher specimen was deposited with the reference number).[78,79]

To address the cinnamon/cassia issue for clinical research and avoid the ambiguity of the common name cinnamon, the United States Pharmacopeia (USP) has developed monographs that are titled by their Latin binomials, for example, "*Cinnamomum cassia* Bark USP,"[80] "*Cinnamomum cassia* Twig USP,"[52] and "*Cinnamomum verum* Bark USP."[81] These monographs set out quality standards and testing methods. If clinical researchers specify USP-quality *Cinnamomum* bark products and follow the CONSORT Statement recommendations, the research would likely result in more consistent, reproducible outcomes.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1: Ten years' production of cinnamon top 5 countries world.
Table S1: Selected *Cinnamomum* species clinical trials.

ACKNOWLEDGMENTS

The authors wish to thank colleagues at USP: Dr. Jaap Venema, Dr. Nandakumara Sarma, Alissa Jijon JD, and Dr. Andrzej Wilk, for critically reviewing the manuscript and Dr. Alison Roland for copyediting the manuscript. We thank Mr. Thomas Brendler of PlantaPhile and also Martin Bauer GmbH & Co. KG for providing photographs of various types of *Cinnamomum*.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

FUNDING INFORMATION

Funding to support this research was provided by the United States Pharmacopeial Convention (USP).

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