

An Evidence-Based Systematic Review of Cinnamon (*Cinnamomum* spp.) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review of cinnamon (*Cinnamomum* spp.), including written and statistical analysis of scientific literature, expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing, by the Natural Standard Research Collaboration is discussed in this monograph.

KEYWORDS. Adverse effects, dosing, evidence-based, cinnamon (*Cinnamomum* spp.), interactions, pharmacodynamics, pharmacology, pharmacokinetics, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOP, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from the inception of the study to October 2009. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases) and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in

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the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, or human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts, and consulted experts when applicable. Authors of the studies were contacted when clarification was required (Natural Standard Systematic Review [www.naturalstandard.com] © 2011).

Synonyms/Common Names/Related Substances

- Cassia bark, cassia-bark tree, cassia cinnamon, cinnamal, cinnamaldehyde, cinnamate, cinnamic acid, cinnamic aldehyde, cinnamom-dhal chini, Cinnamomi cassiae, Cinnamomi cassiae cortex, Cinnamomi ceylanici cortex, Cinnamomi cortex, Cinnamomi flos, Cinnamomi osmophloeum, Cinnamomi ramulus, Cinnamomom, *Cinnamomum aromaticum*, *Cinnamomum aromaticum* Nees, *Cinnamomum burmannii*, *Cinnamomum cassia*, *Cinnamomum cassia* Blume, *Cinnamomum cassia* J. Presl, *Cinnamomum cinnamon*, *Cinnamomum loureiroi*, *Cinnamomum mairei* Levl., *Cinnamomum migao*, *Cinnamomum obtusifolium*, *Cinnamomum osmophloeum* clones (A and B), *Cinnamomum osmophloeum* Kaneh., *Cinnamomum sieboldii*, *Cinnamomum sieboldii* Meissn., *Cinnamomum tamala*, *Cinnamomum tejpata*, *Cinnamomum verum*, *Cinnamomum verum* J. Presl, *Cinnamomum zeylanicum*, *Cinnamomum zeylanicum* bark, *Cinnamomum zeylanicum* Blume, *Cinnamomum zeylanicum* Nees, cinnamon, cinnamon bark, cinnamon bark essential oil, cinnamon bark oil, cinnamon cortex, cinnamon leaf, cinnamon leaf essential oil, coca (Sanskrit), cocam (Sanskrit), Ceylon cinnamon, taj (Sanskrit).
- **Note:** This monograph focuses on cinnamon varieties that are edible and does not include *Cinnamomum camphora*, or the camphor tree, which may be lethal to humans in large doses, or *C. kotoense*, which is an ornamental species.

TABLE 1. Scientific evidence

Allergic rhinitis	C
Angina	C
Antioxidant	C
Bacterial infection	C
Candidiasis	C
Diabetes	C
Eye disorders	C
<i>Helicobacter pylori</i> infection	C
Insect repellent	C
Lung cancer	C
Metabolic syndrome (coronary heart disease)	C

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Cinnamon has been used as a spice for centuries by countless cultural groups around the world. Individuals have also used cinnamon for its purported healing properties. It was traditionally used mainly as a stomachic and carminative medicine for gastrointestinal complaints and is still used for these conditions today [488]. The bark of *C. zeylanicum* and *C. cassia* is used as a spice (cinnamon bark). These two species are the only approved medicinal herbs of the genus *Cinnamomum*.
- At this time, high-quality human trials supporting the efficacy of cinnamon for any human indication are lacking. However, recent in-vitro and in-vivo research has discovered new potential properties of several cinnamon species.
- The treatment of diabetes (type 2) seems to be the most promising field of research for cinnamon [15, 39, 69, 101, 412]. Although there are conflicting results from two randomized studies, the results from in-vitro and animal studies indicate significant hypoglycemic effects. Cinnamon was shown to be highly effective in improving glucose and insulin metabolism. Researchers have recommended more studies for comparing the effectiveness of cinnamon in lowering A1C [131].
- Furthermore, due to the various potential effects of cinnamon and its constituents, including anti-inflammatory, antibacterial, antifungal, and antioxidant properties, it may prove effective in the supportive treatment of conditions such as cancer or severe viral infections (Table 1).

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment, and are reflected in a separate section of each review (“Expert Opinion and Historic/Folkloric Precedent”).
- Evidence of harm is considered separately; the grades presented in Table 2 apply only to evidence of benefit.

TABLE 2. Evidence-based grading and criteria

Level of evidence grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly conducted randomized controlled trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case–control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT without adequate size, power, statistical significance, or quality of design by objective criteria, ^a OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case–control/non-randomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case–control/non-randomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria. ^a
Lack of evidence ^b	Unable to evaluate efficacy due to lack of adequate available human data.

^aObjective criteria are derived from validated instruments for evaluating study quality, including the five-point scale developed by Jadad et al. [205], in which a score below 4 is considered to indicate lesser quality methodologically.

^bListed separately in the “Historical or Theoretical Uses That Lack Sufficient Evidence” section.

Historical or Theoretical Uses That Lack Sufficient Evidence

- Abdominal pain, abortifacient, abscess, acaricidal, acne, Alzheimer’s disease [232, 323], analgesic [557], anesthetic, anthelmintic [290, 394], anticoagulant [543], antidepressant [198], anti-inflammatory [117, 132, 183, 195, 402, 452], antimutagenic [8, 102, 178, 207, 217, 218, 447, 447], antiparasitic [549], antiplatelet [206], antipyretic [256], antiseptic [99], antispasmodic, antiviral, arrhythmia [466, 471], arthritis, asthma [199], benign prostatic hyperplasia [327], bloating, blood purification, bronchitis, chronic bronchitis [559], chronic diarrhea, cognitive function [349], cold/flu, colic, cough, cystitis, dental caries [138, 414], deodorant [475], dermatitis, diarrhea [557], digestive aid [483], digestive disorders [51], diuretic [553], dyspepsia, eczema, emmenagogue, flavoring, food poisoning [441], food preservation [507, 544], food uses, gastric ulcer [483, 557], gastritis, gout [248, 552], gum disease [369], gynecologic disorders, HIV/AIDS [385], hypercholesterolemia [420], hypertension [517], hyperthyroid [134], immunostimulation [221,

244, 444], inflammatory conditions [277, 526], kidney disorders [24], lice [511], liver disease, long-term debility, loss of appetite, memory loss [251], movement disorders [117], muscle aches, nausea, neuralgia, neuroprotective [452], premature ejaculation, respiratory tract infection [202], rheumatoid arthritis [76], sciatica, sinusitis, skin conditions, snake repellent [89], sore throat, spermicide [44], toothache, tumors [171, 216, 257, 269, 355, 438], urethritis, urinary disorders [24], viral infections, weight gain, and wound healing [219].

Expert Opinion and Historic/Folkloric Precedent

- Cinnamon is a spice derived from the bark of the cinnamon tree. In western cuisine, cinnamon is often used with nutmeg, clove, and anise in baked goods, such as gingerbread. In Middle Eastern cuisine, it is often used in savory dishes. It has also been used in aromatherapy for supposed mood-enhancing effects [198]. Cinnamon is also a reported folk remedy in Pakistan [388]. *C. zeylanicum* has also been used in combination with other botanical species in order to treat kidney and urinary disorders in the tribal communities of the Ladakh region in India [24]. Guizhi (*C. zeylanicum*) decoctions have also been used in traditional Chinese medicine (TCM) [550], including the combination Shi-Quan-Da-Bu-Tang (Ten Significant Tonic Decoction) or SQT (Juzentaihoto, TJ-48) [548].
- Cinnamon may be used for various medical conditions [26, 277]. In a survey of parents in Germany determining the use of CAM in children with type 1 diabetes in four pediatric diabetes centers (located in Leipzig, Berlin, Stuttgart, and Bonn), 5.6% reported using cinnamon for this indication [98]. Cinnamon has been touted as having a positive effect on postprandial glucose metabolism [362]. Its ability to lower blood sugar in individuals with diabetes has been discussed [7]. Naturally occurring compounds found in cinnamon (*C. cassia*), including chromium and polyphenols, may improve insulin sensitivity [17]. Human data suggest that cinnamon exhibits “sweet” properties and may be used in strategies for reduction in sugar intake [32].
- As the sense of smell may be affected in individuals with Parkinson’s disease (PD), cinnamon has been used in selective olfactory deficit tests to help diagnose PD-related hyposmia [114]. A cinnamon and citronellyl oil mixture has been used for the detection of allergy to perfumes [413].
- Cinnamaldehyde has been used as a filtering agent and a rubber-reinforcing agent. It is also used as a brightener in electroplating processes, as an animal repellent, an insect attractant, and an antifungal agent [5]. *Trans*-cinnamaldehyde is used as a flavor and fragrance ingredient.
- Cinnamon has been granted Generally Recognized as Safe (GRAS) status as a food additive by the US Food and Drug Administration (FDA). GRAS substances are considered safe and are not restricted, as is the case with other food additives. The FDA has sought fully up-to-date toxicology information on cinnamon (*Cinnamomum* species), including cinnamon bark oil, cinnamon oil, cinnamon leaf oil, and cinnamon oleoresin. The German Commission E and the European Scientific Cooperative on Phytotherapy (ESCO) approved two medicinal herbs of the genus *Cinnamomum*: *C. zeylanicum* [35, 129] and *C. cassia* [35]. The bark is the only part of these plants that is used as a spice or for medical purposes (Cinnamomi cortex) [35].

Brief Safety Summary

- **Likely Safe:** When used orally and for short term (up to 6 weeks) in dosages up to 6 g daily [229].
- **Possibly Unsafe:** When used in patients taking drugs metabolized by cytochrome P450 (1A2 and 2E1, specifically), as cinnamon may alter agents metabolized by these enzymes based on in-vitro studies [87, 419, 527]. When used in patients using anticoagulant or antiplatelet agents, as cinnamon may decrease platelet counts and increase the risk of bleeding, based on animal study [206, 367]. When used in patients with diabetes or taking antidiabetic medications as, based on in-vitro and animal evidence, cinnamon has demonstrated lowering of blood glucose levels and acted as an insulin mimetic [6, 18, 29, 41, 56, 95, 121, 185, 200, 208, 223, 225, 228, 229, 252, 271, 309, 344, 367, 390–392, 405, 460, 461, 474, 481, 558]. Human data, however, have demonstrated conflicting results [13, 22, 33, 121, 242, 378, 476, 510]. When used in patients with autoimmune diseases or those who use immunosuppressants, as cinnamon has been found to have immunomodulatory effects in animal and in-vitro studies [244, 342, 343, 444]. When used in patients with liver damage or who are using hepatotoxic drugs, as in animal study of the essential oil of *C. cassia* stem bark, coumarin was isolated [87]. Coumarin may cause hepatotoxicity. When used in patients using antiarrhythmic agents, as cinnamon has demonstrated antiarrhythmic properties in animal studies [77, 466, 471, 473, 543, 553]. The effects of cinnamon with antiarrhythmic agents are not well understood. When used in patients using antilipemics, as based on animal evidence, cinnamon decreased serum total cholesterol and triglyceride concentrations and markedly increased HDL (high-density lipoprotein) cholesterol levels [273, 467]. In animals, cinnamate produced higher HDL cholesterol levels and lower atherogenic index compared with lovastatin, and inhibited hepatic 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase activity [273]. In in-vivo evidence in hamsters, a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels and inhibited cluster of differentiation 36 (CD36) and microsomal triglyceride transfer protein (MTTP) [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats [420].
- **Likely Unsafe:** When used in patients with a known allergy/hypersensitivity to cinnamon, its constituents, members of the Lauraceae family, or Balsam of Peru [3, 12, 37, 53, 91, 100, 116, 126, 127, 133, 150, 151, 156, 172, 173, 222, 240, 266, 298, 303, 325, 328, 329, 341, 358, 359, 373, 422, 433, 434, 493, 519, 525]. When used in large amounts (*C. aromaticum* (cassia)) (more than those found in foods), due to the potential for high levels of coumarin [299] and due to possible abortifacient effects (secondary sources).

DOSING/TOXICOLOGY

General

- Listed doses are based on those most commonly used in available trials, on historical practice or on manufacturer recommendations. However, with natural

products, it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active components of a product are, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- Information about standardization of cinnamon products is lacking, but several studies have focused on processing and storage procedures for cinnamon. Gamma irradiation of cinnamon did not bring about any distinct qualitative or quantitative chemical changes based on spectrophotometric analysis [214]. However, another study demonstrated significant losses of total ascorbate in cinnamon as well as a significant decrease in carotenoid content 3 months after gamma irradiation [52]. Factors influencing the variation in constituents of cinnamon volatile oils, specifically in terms of their effect on aroma, have been investigated. In one study, compared with packaging material and storage duration, storage temperature has been suggested as the most important factor in altering cinnamon volatile oil aroma [245]. After disinfection by ethylene oxide and storage by ethylene oxide, a fast loss of residual ethylene oxide and ethylene glycol in cinnamon has been observed [63].
- Cinnamon bark has been confused with “yin xiang” [555]. “Yin xiang,” according to secondary sources, may correspond with *C. burmannii* (Nees & T. Nees) Blume. A botany study was conducted that found that the pattern of morphology and distribution of calcium oxalate crystals may be an index for the identification of the crude drug of *Cinnamomi cortex* [535]. A *Compliance Policy Guide* has been published on the FDA’s current Good Manufacturing Practices (cGMP) website regarding the levels that constitute legal action of insect infestation, mold, mammalian excreta, and rodent filth for whole cassia or ground cinnamon.

Dosing

Adult (age ≥ 18)

Oral.

- **Antioxidant:** Capsules containing 250 mg of an aqueous extract of cinnamon (Cinnulin PF[®]) twice daily for 12 weeks have been used with some evidence of benefit on the antioxidant status in overweight or obese individuals with impaired fasting glucose [411].
- **Candidiasis:** In a pilot study, eight lozenges of a commercially available cinnamon candy (not further specified) were taken daily for 1 week and were shown to be effective in three out of five HIV patients [393]. For oral candidiasis, a solution was made by cooking 250 g of cinnamon in 2,000 ml of water on medium heat until there was 500 ml of solution left (solution defined as 50% cinnamon solution) [55]. The treatment group gargled the solution 4–6 times a day, and each time with 20–30 ml of the solution.

- **Diabetes:** In a clinical trial, 1–6 g of cinnamon daily was used for 40 days [13, 33, 229]. In other such trials, cinnamon was administered in different ways: daily oral cinnamon (one capsule containing 333 mg of cinnamon extract three times daily) for 8 weeks [514], aqueous cinnamon extract corresponding to 3 g of cinnamon powder per day (duration unspecified) [309], 1.5 g of cinnamon cassia powder daily for 12 weeks [474], or cinnamon capsules 1 g daily for 90 days [95].
- ***Helicobacter pylori* infection:** In a clinical trial, 80 mg of cinnamon extract daily was used for 4 weeks [354].
- **Metabolic syndrome:** Two capsules (250 mg) of a water-soluble cinnamon extract, Cinnulin PF[®], twice daily [558]. According to the manufacturer, 500 mg of Cinnulin PF[®] is equivalent to around 10 g of cinnamon powder (20:1 extract). It contains approximately 1% double-linked polyphenol type-A polymers, which are considered to be the bioactive component of cinnamon.

Topical.

- **Insect repellent:** Single applications of: (1) cream containing 5% (w/w) cassia oil formulated with 5 g of cassia oil evaluated for up to 120 min, (2) 0.006–0.102 mg/cm² of *C. cassia* bark-derived extract (patch bioassay), (3) 0.013–0.153 mg/cm² of *trans*-cinnamaldehyde or cinnamyl alcohol (patch bioassay), (4) 0.006–0.102 mg/cm² of *C. cassia* bark-derived methanol extract (skin bioassay), or (5) 0.003–0.051 mg/cm² of *trans*-cinnamaldehyde or cinnamyl alcohol (skin bioassay) for up to 40 min [65].

Children (age < 18)

- Insufficient available evidence.

Toxicology

- Based on human study (two randomized trials, one controlled trial, and one pilot study) of the effects of cinnamon on type-2 diabetes, *H. pylori* infection, and candidiasis, no toxic effects were observed [229, 354, 393, 510].
- Ethanolic extracts of *C. zeylanicum* bark demonstrated no acute or chronic oral toxicity in mice [439]. However, *C. zeylanicum* treatment caused reduction in liver weight of the treated animals compared with the control. Hematological studies revealed a fall in hemoglobin level. The extract also induced an increase in reproductive organ weight, sperm motility, and sperm count, and it failed to illicit any spermatotoxic effect. The volatile oils of cinnamon and eugenol have also revealed a potent spermicidal action, whereas the fixed oils were devoid of action on spermatozoa [44].
- Cinnamon has been shown to affect xanthine dehydrogenase, aldehyde oxidase, and pyridoxal oxidase activity during development in *Drosophila melanogaster* [43]. High doses of cinnamon oil caused a depressive effect in rats, probably due to toxicity; the authors note that at the lowest dose, it caused weak or “doubtful” effects [148]. The ethanol extract of cinnamon has shown no in-vitro mutagenic activity [498]. *Trans*-cinnamaldehyde was found to induce lethal mutations

in *Drosophila melanogaster* (“fruit flies”) [531]. Ceylon cinnamon (the bark of *C. zeylanicum*) has also displayed mutagenic activity [499]. Cinnamaldehyde, cinnamyl alcohol, methyl eugenol, eugenol, isoeugenol, as well as cinnamon bark oil, were positive in the *Bacillus subtilis* DNA-repair test (rec assay) without S9. All samples tested were negative in the *Escherichia coli* WP2 uvrA reversion test. The essential oil was positive in the DNA-repair test [435]. *C. mairei* extract was positive in the chromosomal aberration and micronucleus assays in mice [539]. *C. zeylanicum* bark showed low mutagenic activity in *B. subtilis* strains H17 (rec+) and M45 (rec-) [498]. *Trans*-cinnamaldehyde caused increased rates of structural and numerical chromosome abnormalities and increases in frequencies of cells containing $3n$ and $4n$ chromosomes [226].

- After two years of study, rats and mice given diets of 1,000, 2,100, or 4,100 ppm of *trans*-cinnamaldehyde showed no evidence of carcinogenic activity [5]. Exposure to *trans*-cinnamaldehyde resulted in olfactory epithelial pigmentation in male and female mice [5].
- Squamous cell papillomas and carcinomas of the forestomach were observed in male and female mice. In the 3-month studies, rats and mice were given diets containing 4,100, 8,200, 16,500, or 33,000 ppm of *trans*-cinnamaldehyde. The incidence of squamous epithelial hyperplasia of the forestomach was significantly increased in rats exposed to 8,200 ppm or greater and female mice exposed to 33,000 ppm. In rats, feed consumption was reduced in all exposed groups. In mice, feed consumption was reduced in the highest-dose groups. Body weights of all treated males were less than those of controls. Body weights were reduced in female rats exposed to 16,500 or 33,000 ppm and female mice exposed to 8,200 ppm or greater. All rats survived to the end of the study, but some male mice in the highest dose groups died due to inanition from unpalatability of the dosed feed. In mice, the incidence of olfactory epithelial degeneration of the nasal cavity was significantly increased in males and females exposed to 16,500 ppm and those to 33,000 ppm [5].
- Raw cinnamon (*C. zeylanicum*) has been shown to be tumorigenic in high doses [23]. A case report mentions a 24-year-old woman who developed a squamous cell carcinoma of the tongue following persistent and prolonged exposure to cinnamon-flavored gum [525].
- Cinnamon oil ingestion led to toxic manifestations in a child, according to a case report [379].
- Molecules similar to cinnamic acid, such as styrene and the related aldehyde, alcohol, and esters, are all considered more toxic than cinnamic acid [189]. Screening tests are performed to test food additives such as cinnamic aldehyde for mutagenicity and carcinogenicity [203].
- Cinnamon oil has been used recreationally by children and adolescents to “get high.” Nausea or abdominal pain, but no systemic effects, have been reported [375, 432].
- In animal study of the essential oil of *C. cassia* stem bark, coumarin was isolated [87]. Coumarin may cause hepatotoxicity. Due to the potential for high levels of coumarin, European health agencies have recently warned against the consumption of large amounts of *C. aromaticum* (cassia) [299].

- Cinnamaldehyde and N,N-dimethylcinnamylamine, chemical analogs of the neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), lacked dopaminergic nigrostriatal neurotoxic effects in animal study [376].

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

- Known allergy/hypersensitivity to cinnamon, its constituents, members of the Lauraceae family, or Balsam of Peru [1, 46, 50, 100, 103, 108, 113, 116, 128, 135, 151, 156, 190, 222, 227, 230, 240, 279, 304–307, 315, 319, 325, 348, 352, 353, 358, 415, 417, 426, 429, 465, 487, 508, 521]. However, scratch-chamber testing often leads to false-positive irritant reactions. A positive test to Balsam of Peru may indicate a spice allergy, but the absence of such reaction does not rule it out [113].
- Concomitant reactions to cinnamyl alcohol may be due to cross-sensitization in patients with contact allergy to ketoprofen [141, 155].
- One case of allergic contact dermatitis has been reported as a result of airborne exposure to cinnamon [9].
- Cinnamon is one of the 10 major food allergens [463]. Cinnamaldehyde seems to be considered the “true” allergen, while cinnamyl alcohol and cinnamic acid are transformed in the skin to cinnamaldehyde before contact allergic reactions may occur [194, 524]. Studies confirmed the sensitivity of patients to cinnamic aldehyde in a toothpaste [241, 407, 490]. Based on review, cinnamon constituents found in cosmetics, including cinnamic alcohol, eugenol, and coumarin, may be more likely to cause hypersensitivity and sensitization reactions than other compounds, such as cinnamic aldehyde [97, 307]. However, results from other studies are not consistent with these findings. Cinnamic aldehyde has been found to be a potent sensitizer and a strong cross-sensitizer [437].
- Immunologic reactions to spices such as cinnamon may be related to acute symptoms and lung function changes, but not to chronic changes [560]. Concerning allergic reactions to cinnamon dust, it may be the cellulose content that is responsible for the histological reactions [485]. Cinnamon powder has shown low cross-reactivity in patients with positive skin tests to birch or mugwort pollens and celery [464]. Alcohol as a vehicle was shown to have a higher sensitization potential than petrolatum when cinnamon bark oil was used in predictive tests [316].
- Allergic contact stomatitis to cinnamon in chewing gum was mistaken as facial angioedema [238].
- Cinnamon has produced nonimmunologic contact urticaria (NICU), which may occur without previous immunologic sensitization in exposed individuals [157, 162, 260–264]. Acetylsalicylic acid (aspirin) has been shown to inhibit this effect through prostaglandin bioformation [264]. Indomethacin and dexamethasone may also inhibit these reactions, based on animal study; however, the mechanism is not well understood [263]. In laboratory study, eugenol and d-limonene may quench (inhibit) the sensitization potential of cinnamaldehyde through competitive inhibition at the receptor level [162].

- An ingredient in perfume that is a sensitizer may become hypoallergenic during the aging process of the perfume. Patients may tolerate an aged perfume that contains cinnamic aldehyde without acquiring allergic reactions [140].

Adverse Effects

- **General:** No adverse effects were observed in a pilot trial with five HIV patients [393]. In two randomized trials on the effects of cinnamon on type 2 diabetes, no adverse effects were observed [229, 510]. One controlled trial reported minor adverse effects in five out of 15 patients [354].
- As with any spice or drug, cinnamon may be contaminated by microorganisms during storage. The microbiological quality of cinnamon was evaluated in several studies. Cinnamon showed mainly satisfactory microbiological quality [404, 431]. However, contamination by aflatoxin-producing fungi may constitute health hazards in humans, as the aflatoxin level is not reduced by domestic cooking [27, 125, 302]. Furthermore, cinnamon may contain detectable ethylene oxide [142].
- **Dermatologic:** Allergic hypersensitivity and contact allergic reactions may occur in sensitive individuals [46, 50, 100, 103, 108, 113, 116, 151, 156, 190, 222, 230, 240, 267, 304, 305, 315, 325, 352, 353, 358, 415, 417, 426, 429, 465, 487, 508, 521]. Dermatitis, photodermatitis, stomatitis, glossitis, gingivitis, perioral dermatitis, perioral leukoderma (simulating vitiligo), oral lesions, cheilitis, eczema, lip edema, irritation, and depigmentation have been noted in case reports after external application of cinnamon (e.g., cinnamon oils in fragrances or cinnamic aldehyde in deodorant) as well as after the use of flavored chewing gums, mints, or toothpastes [3, 12, 20, 27, 31, 40, 47, 50, 51, 52, 59, 91, 98, 100, 107, 110, 112, 135, 136, 137, 142, 156, 157, 158, 159, 163, 164, 167, 170, 178, 187, 188, 206, 237, 242, 243, 246, 247, 269, 285, 286, 297, 317, 323, 330, 339, 340, 346, 349, 350, 362, 369, 370, 380, 381, 403, 409, 429, 432, 447, 440, 451, 452, 456, 459, 460, 461, 484, 493, 503, 515, 519, 522, 539, 549, 551]. One case of allergic contact dermatitis has been reported as a result of airborne exposure to cinnamon [9]. Cinnamaldehyde may provoke orofacial granulomatosis, urticaria, dermatitis, and stomatitis [116, 240, 266, 373, 397]. Squamous cell carcinoma of the tongue and “speckled” lesions have been reported following exposure to cinnamon-flavored gum [84, 525]. A case report of a burn from cinnamon oil has been reported [462]. A case of a 68-year-old Caucasian female with type 2 diabetes mellitus who experienced an acute exacerbation of her rosacea 2 weeks after self-initiating cinnamon oil pills to lower her blood sugar levels has been reported [54]. In a clinical trial using 1 g of cinnamon in capsule form daily, one adverse event (rash) was reported by an individual who withdrew from the study [95].
- Cinnamal may be added to soaps and douches as a fragrance and may cause anogenital dermatitis [521]. Based on retrospective report, the incidence of allergic reactions to cinnamic aldehyde has decreased over time [351].
- **Gastrointestinal:** Nausea and abdominal pain have been reported with cinnamon use [375, 432].
- **Hematologic:** Cinnamon bark caused a significant decrease in platelet counts in normal rats after long-term use [367].

- **Hepatic:** In animal study of the essential oil of *C. cassia* stem bark, coumarin was isolated [87]. Coumarin may cause hepatotoxicity. Due to the potential for high levels of coumarin, European health agencies have recently warned against the consumption of large amounts of *C. aromaticum* (cassia) [299].
- **Neurologic:** Based on secondary sources, cinnamon oil has been used recreationally by children and adolescents to induce an altered state of consciousness.
- **Pulmonary/respiratory:** Asthma and other chronic respiratory symptoms were seen in spice-factory workers [500, 501, 560].
- **Renal:** Based on secondary information, supplementation with cinnamon may increase risk of hyperoxaluria; however, this was not found to be the case based on human evidence [484].

Precautions/Warnings/Contraindications

- Avoid in patients with a known allergy/hypersensitivity to cinnamon, its constituents, members of the Lauraceae family, or Balsam of Peru [3, 12, 37, 53, 91, 100, 116, 126, 127, 133, 150, 151, 156, 172, 173, 222, 240, 266, 298, 303, 325, 328, 329, 341, 358, 359, 373, 422, 433, 434, 493, 519, 525].
- Avoid large amounts of cinnamon (more than those found in foods) due to possible abortifacient effects, based on secondary sources.
- Avoid large amounts of *C. aromaticum* (cassia) (more than those found in foods) due to the potential for high levels of coumarin [299].
- Use cautiously in patients taking drugs metabolized by cytochrome P450 (1A2 and 2E1, specifically), as cinnamon may alter agents metabolized by these enzymes based on in-vitro studies [87, 419, 527].
- Use cautiously in patients using anticoagulant or antiplatelet agents, as cinnamon may decrease platelet counts and increase the risk of bleeding, based on animal study [206, 367].
- Use cautiously in patients with diabetes or those taking antidiabetic medications, as based on in-vitro and animal evidence, cinnamon has demonstrated lowering of blood glucose levels and acted as an insulin mimetic [6, 18, 29, 41, 56, 95, 121, 185, 200, 208, 223, 225, 228, 229, 252, 271, 309, 344, 367, 390–392, 405, 460, 461, 474, 481, 558]. Human data, however, have demonstrated conflicting results [13, 22, 33, 121, 242, 378, 476, 510]. Theoretically, concurrent use of cinnamon with blood sugar-lowering agents may have additive effects and may increase the risk of hypoglycemia.
- Use cautiously in patients with autoimmune diseases or who use immunosuppressants, as cinnamon has been found to have immunomodulatory effects in animal and in-vitro studies [244, 342, 343, 444].
- Use cautiously in patients with liver damage or who are using hepatotoxic drugs, as in animal study of the essential oil of *C. cassia* stem bark, coumarin was isolated [87]. Coumarin may cause hepatotoxicity.
- Use cautiously in patients using antiarrhythmic agents. as cinnamon has demonstrated antiarrhythmic properties in animal studies [77, 466, 471, 473, 543, 553]. The effects of cinnamon with antiarrhythmic agents are not well understood.
- Use cautiously in patients using antilipemics, as based on animal evidence, cinnamon decreased serum total cholesterol and triglyceride concentrations and

markedly increased HDL cholesterol levels [273, 467]. In animals, cinnamate produced higher HDL cholesterol levels and lower atherogenic index compared with lovastatin, and inhibited HMG-CoA reductase activity [273]. In in-vivo evidence in hamsters, a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels and inhibited CD36 and MTP [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats [420].

Pregnancy and Lactation

- Not suggested due to lack of sufficient data.
- Based on secondary sources, consumption of large amounts of cinnamon (more than those found in foods) may have abortifacient effects.
- The effect of cinnamon and eugenol on human spermatozoa motility in vitro has been studied [46]. The volatile oils studied revealed a potent spermicidal action, whereas the fixed oils were devoid of action on spermatozoa.
- Fish exposed to ethanol and cinnamaldehyde had greater adverse effects on fetal development when combined, compared with their individual effects [173].
- There is a lack of information for cinnamon in the National Library of Medicine's Drugs and Lactation Database (LACT-MED).

INTERACTIONS

Cinnamon–Drug Interactions

- **Alcohol:** Fish exposed to ethanol and cinnamaldehyde had greater adverse effects on fetal development when combined, compared with their individual effects [167].
- **Alzheimer's agents:** In laboratory study, chloroform extracts of *C. cassia* showed a marginal neuronal cell protection from direct betaA(1-42) insult [232]. Theoretically, concurrent use of cinnamon with Alzheimer's agents may have beneficial, additive effects.
- **Analgesics:** Based on animal evidence, an ethanolic extract of *C. zeylanicum* was shown to possess an antinociceptive effect [21]. Theoretically, concurrent use of cinnamon with analgesic agents may have additive effects.
- **Antiarrhythmics:** Cinnamon has demonstrated antiarrhythmic properties in animal studies [77, 466, 471, 473, 543, 553]. The effects of cinnamon with antiarrhythmic agents are not well understood.
- **Antibiotics:** In vitro, cinnamon has demonstrated antibacterial properties [109, 145, 201, 202, 369, 441, 459, 544]. A synergistic antimicrobial effect was noted when chlorhexidine was used in combination with essential oils of cinnamon, tea tree (*Melaleuca alternifolia*), manuka (*Leptospermum scoparium*), *L. morisonii*, arnica, eucalyptus, and grapefruit against biofilm and planktonic cultures of *Streptococcus mutans* and *Lactobacillus plantarum* [138]. Theoretically, concurrent use of cinnamon with antibiotic agents may have additive effects. Based on secondary sources, concomitant use of cinnamon with tetracyclines may slow

the absorption and reduce blood levels of tetracycline antibiotics. This effect may be due to adsorption of tetracycline by cinnamon.

- **Anticoagulants and antiplatelets:** Based on animal evidence, cinnamon bark, cinnamaldehyde, and two other *Cinnamomum* species (*C. altissimum* and *C. pubescens*) caused a decrease in platelet counts after long-term use [193, 206, 320, 367]. Cinnamic aldehyde inhibited arachidonic acid (AA) release and thromboxane B₂ formation, which may contribute to reduced platelet aggregation [480]. Theoretically, concurrent use of cinnamon with anticoagulants or antiplatelets may increase the risk of bleeding.
- **Antidiabetics:** Based on in-vitro and animal evidence, cinnamon has demonstrated lowering of blood glucose levels and acted as an insulin mimetic [6, 18, 29, 41, 56, 95, 121, 185, 200, 208, 223, 225, 228, 229, 252, 271, 309, 344, 367, 390–392, 405, 460, 461, 474, 481, 558]. Human data, however, have demonstrated conflicting results [13, 22, 33, 121, 242, 378, 476, 510]. Theoretically, concurrent use of cinnamon with blood sugar-lowering agents may have additive effects and increase the risk of hypoglycemia.
- **Antifungals:** Cinnamon has demonstrated antifungal effects in vitro [79, 174, 285, 317, 393, 457] and inhibited oral candidiasis in humans [55]. Based on laboratory study, *C. cassia* in combination with amphotericin B displayed additive antifungal effects and was less toxic compared with amphotericin B alone [154]. Theoretically, concurrent use of cinnamon with antifungal agents may have additive effects.
- **Antihypertensives:** *C. migao* oil reduced systolic and diastolic arterial blood pressure in animal study [473]. Based on animal study, whole cinnamon and aqueous extracts have been found to reduce systolic blood pressure (SBP) elevations as well as a genetic component of elevated blood pressure [386]. Human study also demonstrated a reduction in SBP upon treatment with Cinnulin PF[®] [558]. Theoretically, concurrent use of cinnamon with antihypertensive agents may have additive effects and increase the risk of hypotension.
- **Anti-inflammatories:** Based on in-vitro evidence, cinnamon bark may exert anti-inflammatory properties [256, 402]. Theoretically, concurrent use of cinnamon with anti-inflammatory agents may have additive effects.
- **Antilipemics:** Based on animal evidence, *C. zeylanicum* significantly decreased serum total cholesterol and triglyceride concentrations and markedly increased HDL cholesterol levels [273, 467]. In animal study, cinnamate, a phenolic compound in cinnamon bark, produced higher HDL cholesterol levels and lower atherogenic index compared with lovastatin [273]. Cinnamate inhibited HMG-CoA reductase activity [273]. In in-vivo evidence in hamsters, a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels and inhibited CD36 and MTP [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats when included in the diet at about fivefold the normal human intake level [420]. Theoretically, concurrent use of cinnamon with antilipemic agents may have additive effects.
- **Antineoplastics:** Based on in-vitro and animal evidence, cinnamon has exerted antitumor and antigenotoxic effects [8, 171, 216, 355]. Theoretically,

concurrent use of cinnamon with antineoplastic agents may have additive effects.

- **Antiobesity agents:** In a clinical trial studying the effects of Cinnulin PF[®], compared with placebo, the treatment group noted increases in lean mass (+1.1%: from 53.7 ± 11.8 kg [pre] to 54.3 ± 11.8 kg [post], $p < .002$) [558].
- **Antiretrovirals:** Based on clinical study, *C. cassia* bark extract inhibited virus-induced cytopathogenicity in MT-4 cells infected with HIV [385]. Theoretically, concurrent use of cinnamon with antiretroviral agents may have additive effects.
- **Antispasmodics:** Based on secondary sources, cinnamon may have antispasmodic effects. Theoretically, concurrent use of cinnamon with antispasmodic agents may have additive effects.
- **Aspirin:** Aspirin (acetylsalicylic acid) has been shown to reduce contact urticaria reactions caused by cinnamic aldehyde and cinnamic acid due to inhibitory effects of aspirin on prostaglandin bioformation [271].
- **Cytochrome P450-metabolized agents:** Based on in-vitro evidence, cinnamon or its constituents may interact with hepatic microsomal cytochrome P450 [87, 419, 469, 527]. Cinnamon bark was found to inhibit aminopyrine N-demethylation in rat liver microsomes. The component inhibiting drug oxidations catalyzed by CYP1A2 and CYP2E1 was isolated from Cinnamomi cortex and was identified as o-methoxycinnamaldehyde (OMCA) [176]. *C. burmannii* bark inhibited CYP3A4 and 2D6 via erythromycin N-demethylation and dextromethorphan O-demethylation activities in human liver microsomes [468]. Theoretically, cinnamon may alter the levels of drugs metabolized by cytochrome P450, specifically 1A2 and 2E1.
- **Dexamethasone:** Based on animal study, dexamethasone inhibited nonimmunologic contact urticaria reactions to cinnamic acid and cinnamic aldehyde [263].
- **Drugs that affect GABA:** In animal study, cinnamon may exert an anxiolytic effect via regulation of the serotonergic and GABAergic systems [542]. Theoretically, concurrent use with other drugs that affect GABA (gamma-amino butyric acid) may have additive effects.
- **Estrogens:** Cinnamomi cortex as a component of the unkei-to combination product stimulated estradiol secretion in laboratory study [472]. Theoretically, concurrent use of cinnamon with estrogens may have additive effects.
- **Hepatotoxics:** In animal study of the essential oil of *C. cassia* stem bark, coumarin was isolated [87]. Coumarin may cause hepatotoxicity. Due to the potential for high levels of coumarin, European health agencies have recently warned against the consumption of large amounts of *C. aromaticum* (cassia) [299]. Theoretically, concurrent use of cinnamon with hepatotoxic agents may increase the risk of liver damage.
- **Immunosuppressants:** Based on in-vitro and animal evidence, cinnamon demonstrated immunomodulatory effects [244, 342, 343, 444]. Theoretically, cinnamon may alter the effects of immunosuppressants.
- **Indomethacin:** Based on animal study, indomethacin inhibited nonimmunologic contact urticaria reactions to cinnamic acid and cinnamic aldehyde [263].
- **Sympathomimetics:** In animal study, TRPA1 agonists, such as cinnamaldehyde, have been shown to activate the sensory nerves and induce adrenaline secretion

via the central nervous system [204]. Theoretically, concurrent use with sympathomimetics may have additive effects.

- **Terfenadine:** Based on human study, terfenadine did not inhibit contact urticaria reactions caused by cinnamic aldehyde [260].
- **Tetracyclines:** Based on secondary sources, concomitant use of cinnamon with tetracyclines may slow the absorption and reduce blood levels of tetracycline antibiotics. This effect may be due to adsorption of tetracycline by cinnamon.

Cinnamon–Herb–Supplement Interactions

- **Alzheimer’s herbs:** In laboratory study, chloroform extracts of *C. cassia* showed a marginal neuronal cell protection from direct betaA(1–42) insult [232]. Theoretically, concurrent use of cinnamon with Alzheimer’s herbs may have beneficial, additive effects.
- **Analgesics:** Based on animal evidence, an ethanolic extract of *C. zeylanicum* was shown to possess an antinociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation in mice [21]. Theoretically, concurrent use of cinnamon with analgesic agents may have additive effects.
- **Antiarrhythmics:** Cinnamon has demonstrated antiarrhythmic properties in animal studies [77, 466, 471, 473, 543, 553]. The effects of cinnamon with antiarrhythmic agents are not well understood.
- **Antibacterials:** In vitro, cinnamon has demonstrated antibacterial properties [145, 201, 202, 369, 441, 459, 544]. Theoretically, concurrent use of cinnamon with other antibacterial agents may have additive effects. Based on secondary sources, concomitant use of cinnamon with tetracyclines may slow the absorption and reduce blood levels of tetracycline antibiotics. This effect may be due to adsorption of tetracycline by cinnamon.
- **Anticoagulants and antiplatelets:** Based on animal evidence, cinnamon bark, cinnamaldehyde, and two other *Cinnamomum* species (*C. altissimum* and *C. pubescens*) caused a decrease in platelet counts after long-term use [193, 206, 320, 367]. Cinnamic aldehyde inhibited AA release and thromboxane B2 formation, which may contribute to reduced platelet aggregation [480]. Theoretically, concurrent use of cinnamon with anticoagulants/antiplatelets may increase the risk of bleeding.
- **Antifungals:** Cinnamon has demonstrated antifungal properties in vitro [79, 174, 285, 317, 393, 457] and inhibited oral candidiasis in humans [55]. Based on laboratory study, *C. cassia* in combination with amphotericin B displayed additive antifungal effects and was less toxic compared with amphotericin B alone [154]. Theoretically, concurrent use of cinnamon with antifungal agents may have additive effects.
- **Anti-inflammatory herbs:** Based on in-vitro evidence, cinnamon bark exerted anti-inflammatory properties [256, 402]. Theoretically, concurrent use of cinnamon with anti-inflammatory agents may have additive effects.
- **Antilipemics:** Based on animal evidence, *C. zeylanicum* significantly decreased serum total cholesterol and triglyceride concentrations and markedly increased HDL cholesterol levels [273, 467]. In animal study, cinnamate, a phenolic compound in cinnamon bark, produced higher HDL cholesterol levels and lower

atherogenic index compared with lovastatin [273]. Cinnamate inhibited HMG-CoA reductase activity [273]. In in-vivo evidence in hamsters, a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels and inhibited CD36 and MTTP [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats when included in the diet at about fivefold the normal human intake level [420]. Theoretically, concurrent use of cinnamon with antilipemic agents may have additive effects.

- **Antineoplastics:** Based on in-vitro and animal evidence, cinnamon has exerted antitumor and antigenotoxic effects [8, 171, 216, 355]. Theoretically, concurrent use of cinnamon with antineoplastic agents may have additive effects.
- **Antiobesity herbs and supplements:** In a clinical trial studying the effects of Cinnulin PF[®], compared with the placebo, the treatment group noted increases in lean mass (+1.1%: from 53.7 ± 11.8 kg [pre] to 54.3 ± 11.8 kg [post], $p < .002$) [558].
- **Antioxidants:** Cinnamon bark has been shown to contain very high concentrations of antioxidants [115]. Several animal and in-vitro studies demonstrate the antioxidant effects of the essential oil obtained from the bark of *C. zeylanicum* and its main components [83, 175, 210, 236, 272, 278, 455, 491]. Etheric, methanolic, and aqueous cinnamon extracts have also inhibited oxidative processes in vitro [106, 187, 248, 275, 286, 308, 318, 451]. In human study, a dried aqueous extract of cinnamon (Cinnulin PF[®]), increased the antioxidant status [411]. Theoretically, concurrent use of cinnamon with antioxidants may have additive effects.
- **Antispasmodics:** Based on secondary sources, cinnamon may have antispasmodic effects. Theoretically, concurrent use of cinnamon with antispasmodic agents may have additive effects.
- **Antivirals:** Based on clinical study, *C. cassia* bark extract may be effective against HIV-1 and HIV-2 replication in terms of inhibition of virus-induced cytopathogenicity in MT-4 cells infected with HIV [385]. Theoretically, concurrent use of cinnamon with antiviral agents may have additive effects.
- **Artemisia:** In laboratory study, when *C. camphora* was mixed with *Artemisia princeps* Pamp. (1:1 mixture), a synergistic insecticidal effect was noted [291].
- **Cytochrome P450-metabolized herbs and supplements:** Based on in-vitro studies, cinnamon or its constituents may interact with hepatic microsomal cytochrome P450 [87, 419, 469, 527]. Cinnamon bark was found to inhibit aminopyrine N-demethylation in rat liver microsomes. The component inhibiting drug oxidations catalyzed by CYP1A2 and CYP2E1 was isolated from Cinnamomi cortex and was identified as OMCA [176]. *C. burmannii* bark inhibited CYP3A4 and 2D6 via erythromycin N-demethylation and dextromethorphan O-demethylation activities in human liver microsomes [468]. Theoretically, cinnamon may alter the levels of drugs metabolized by cytochrome P450, specifically 1A2 and 2E1.
- **Clove:** Based on a review, synergistic antibacterial effects have been observed between cinnamaldehyde and eugenol, a constituent of clove [47].

- **Ephedra:** Components of ephedra reportedly interact with cinnamon; however, details of this interaction are not well documented [416].
- **Hepatotoxic herbs:** In animal study of the essential oil of *C. cassia* stem bark, coumarin was isolated [87]. Coumarin may cause hepatotoxicity. Due to the potential for high levels of coumarin, European health agencies have recently warned against the consumption of large amounts of *C. aromaticum* (cassia) [299]. Theoretically, concurrent use of cinnamon with hepatotoxic herbs may increase the risk of liver damage.
- **Hypoglycemics:** Based on in-vitro and animal evidence, cinnamon has demonstrated lowering of blood glucose levels and acted as an insulin mimetic [6, 18, 29, 41, 56, 95, 121, 185, 200, 208, 223, 225, 228, 229, 252, 271, 309, 344, 367, 390–392, 405, 460, 461, 474, 481, 558]. Human data, however, have demonstrated conflicting results [13, 22, 33, 121, 242, 378, 476, 510]. Theoretically, concurrent use of cinnamon with blood sugar-lowering agents may have additive effects and increase the risk of hypoglycemia.
- **Hypotensives:** *C. migao* oil reduced systolic and diastolic arterial blood pressure in animal study [473]. Human study also demonstrated a reduction in SBP upon treatment with Cinnulin PF[®] [558]. Based on animal study, whole cinnamon and aqueous extracts have been found to reduce SBP elevations as well as a genetic component of elevated blood pressure [386]. Theoretically, concurrent use of cinnamon with antihypertensive agents may have additive effects and increase the risk of hypotension.
- **Immunosuppressants:** Based on in-vitro and animal evidence, cinnamon has demonstrated immunomodulatory effects [244, 342, 343, 444]. Theoretically, cinnamon may alter the effects of immunosuppressants.
- **Insect repellants:** In a clinical trial, (E)-cinnamaldehyde and cinnamyl alcohol appeared to be effective against *Aedes aegypti* (L.) female mosquitoes [65].
- **Neurologic herbs and supplements:** In animal study, cinnamon may exert an anxiolytic effect via regulation of the serotonergic and GABAergic systems [542]. Theoretically, concurrent use with other herbs or supplements that affect GABA may have additive effects.
- **Phytoestrogens:** Cinnamomi cortex as a component of the unkei-to combination product stimulated estradiol secretion in laboratory study [472]. Theoretically, concurrent use of cinnamon with estrogens may have additive effects.
- **Sympathomimetics:** In animal study, TRPA1 agonists, such as cinnamaldehyde, have been shown to activate the sensory nerves and induce adrenaline secretion via the central nervous system [204]. Theoretically, concurrent use with sympathomimetics may have additive effects.
- **Vitamin E:** In laboratory study, pretreatment with vitamin E markedly prevented cinnamaldehyde-mediated apoptosis [534].

Cinnamon–Food Interactions

- **Carrots:** In laboratory study, a low concentration of cinnamaldehyde enhanced the taste of carrot broth [506].
- **Foods containing clove:** Based on a review, synergistic antibacterial effects have been observed between cinnamaldehyde and eugenol, a constituent of clove [47].

- **Foods containing vitamin E:** In laboratory study, pretreatment with vitamin E markedly prevented cinnamaldehyde-mediated apoptosis [534].

Cinnamon–Laboratory Interactions

- **Blood glucose:** Based on in-vitro and animal evidence, cinnamon has demonstrated lowering of blood glucose levels and acted as an insulin mimetic [6, 18, 29, 41, 56, 95, 121, 185, 200, 208, 223, 225, 228, 229, 252, 271, 309, 344, 367, 390–392, 405, 460, 461, 474, 481, 558]. Human data, however, have demonstrated conflicting results [13, 22, 33, 121, 242, 378, 476, 510].
- **Blood pressure:** Based on animal study, *C. migao* oil reduced systolic and diastolic arterial blood pressure [473]. Based on animal study, whole cinnamon and aqueous extracts have been found to reduce SBP elevations as well as a genetic component of elevated blood pressure [386]. Human study also demonstrated a reduction in SBP upon treatment with cinnamon [558].
- **Carbon clearance test:** A polysaccharide isolated from the bark of *C. cassia* Blume was found to exert reticuloendothelial system-potentiating activity in a carbon clearance test [221].
- **Coagulation panel:** Based on animal evidence, cinnamon bark, cinnamaldehyde, and two other *Cinnamomum* species (*C. altissimum* and *C. pubescens*) caused a decrease in platelet counts after long-term use [193, 206, 320, 367]. Cinnamic aldehyde inhibited AA release and thromboxane B2 formation, which may contribute to reduced platelet aggregation [480].
- **Estrogens:** Cinnamomi cortex as a component of the unkei-to combination product stimulated estradiol secretion in laboratory study [472].
- **Heart rate:** In animal study, various cinnamon species [77, 466, 473, 543, 553], including *C. migao* [471], decreased the heart rate.
- **Lipid profile:** Based on animal evidence, *C. zeylanicum* significantly decreased serum total cholesterol and triglyceride concentrations and markedly increased HDL cholesterol levels [273, 467]. In animal study, cinnamate, a phenolic compound in cinnamon bark, produced higher HDL cholesterol levels and lower atherogenic index compared with lovastatin [273]. Cinnamate inhibited HMG-CoA reductase activity [273]. In in-vivo evidence in hamsters, a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels and inhibited CD36 and MTTP [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats when included in the diet at about fivefold the normal human intake level [420].
- **Urate levels:** Oral administration of *C. cassia* oil significantly reduced serum and hepatic urate levels in hyperuricemic mice [552]. In normal mice, urate levels in liver, but not in serum, were altered with dose-dependent decrease after *C. cassia* oil treatment.

Cinnamon–Nutrient Depletion

- **Glucose:** Based on in-vitro and animal evidence, cinnamon has demonstrated lowering of blood glucose levels and acted as an insulin mimetic [6, 18, 29, 41,

58, 95, 121, 185, 200, 208, 223, 225, 228, 229, 252, 271, 309, 344, 367, 390–392, 405, 460, 461, 474, 481, 558]. Human data, however, have demonstrated conflicting results [13, 22, 33, 121, 242, 378, 476, 510].

- **Lipids:** Based on animal evidence, *C. zeylanicum* significantly decreased serum total cholesterol and triglyceride concentrations and markedly increased HDL cholesterol levels [273, 467]. In animal study, cinnamate, a phenolic compound in cinnamon bark, produced higher HDL cholesterol levels and lower atherogenic index compared with lovastatin [273]. Cinnamate inhibited HMG-CoA reductase activity [273]. In in-vivo evidence in hamsters, a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels and inhibited CD36 and MTTP [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats when included in the diet at about fivefold the normal human intake level [420].

MECHANISM OF ACTION

Pharmacology

- **Constituents:** Cinnamon has been shown to contain allylbenzenes and their isomers, the propenylbenzenes [198]. Cinnamon also contains monomeric and oligomeric proanthocyanidins [161, 268], e.g., procyanidin B-2 and procyanidin B-3 [383, 482], and organic compounds *trans*-cinnamaldehyde, alpha-amyl cinnamaldehyde, and *trans*-cinnamic alcohol [124]. Quercetin, kaempferol, luteolin, and pelargonidin have been identified as the major flavonoids [211, 255, 345, 366]. Inorganic constituents of Cinnamomi cortex include potassium, calcium, iron, manganese, and strontium. A feature of the metals profile of Cinnamomi cortex is high manganese content [330].
- Cinnamon species contain volatile oils [4, 147, 282, 489]. At least 94 volatile components are present in cinnamon bark [158]. Fifty-four constituents were identified in the essential oil from cinnamon bark and twigs [450]. The main components of the essential oil obtained from the bark of *C. zeylanicum* are eugenol, cinnamaldehyde, and linalool [83, 146, 169, 196, 445, 457, 458, 502, 503]. Each cinnamon plant part has a different primary constituent: cinnamaldehyde (bark oil), eugenol (leaf oil), and camphor (root-bark oil) [293, 311, 332, 430, 443, 528]. *C. cassia* bark contains cinnamaldehyde, cinnamic acid, cinnamyl alcohol, coumarin, 5,7,3',4'-tetrahydroxyflavan-3,4-diol, OMCA, lignans, and phenylpropanoids [42, 45, 163, 188, 237, 296, 333, 335]. Other *Cinnamomum* species, *C. wilsonii*, *C. japonicum*, *C. mairei*, and *C. burmannii*, contain low contents of cinnamaldehyde (< 2.00 mg/g) [180].
- The leaves of *C. kotoense* contain isoobtusilactone A, cinnakotolactone, isolinderanolide B, kotomolide A, kotomolide B, isokotomolide A (IKA), secokotomolide A, and secobutanolide [70, 71, 74, 75, 293, 536].
- The leaves of *C. subavenium* contain subamolides A–E, secosubamolide A, as well as 21 known compounds [72, 254, 289].
- Constituents of *C. balansae* leaves include cinbalansan [6]; 1,2-dimethoxy-4-(1-E-propenyl)benzene; 1,2-dimethoxy-4-(1-Z propenyl)benzene; 1,2-

dimethoxy-4-(2-propenyl)benzene; 3,4 dimethoxybenzaldehyde; and E-(3,4-dimethoxyphenyl)-2-propenal [96].

- The stems of *C. tenuifolium* contain tenuifolide A, isotenuifolide A, tenuifolide B, secotenuifolide A, and tenuifolin [288].
- *C. insularimontanum* contains actinodaphnine [191].
- The fruit of *C. laubatii* contains EBC-23, 24, 25, 72, 73, 75, and 76 [111, 112].
- The volatile oil from *C. zeylanicum* fruit stalks contains hydrocarbons (44.7%) and oxygenated compounds (52.6%). Twenty-seven compounds constituting approximately 95.98% of the volatile oil have been characterized. (E)-Cinnamyl acetate (36.59%) and (E)-caryophyllene (22.36%) were found to be major compounds [210]. *C. zeylanicum* buds contain 34 compounds representing approximately 98% of the oil and consist of terpene hydrocarbons (78%) and oxygenated terpenoids (9%). Alpha-bergamotene (27.38%) and alpha-copaene (23.05%) were found to be the major compounds [212]. The steam-distilled oil of *C. zeylanicum* flowers consists of 23% hydrocarbons and 74% oxygenated compounds. A total of 26 compounds constituting approximately 97% of the oil have been characterized. (E)-Cinnamyl acetate (41.98%), *trans*-alpha-bergamotene (7.97%), and caryophyllene oxide (7.2%) were found to be major compounds [209]. The essential oil isolated from *C. osmophloeum* leaves contains six chemotypes: cinnamaldehyde type, cinnamaldehyde/cinnamyl acetate type, cinnamyl acetate type, linalool type, camphor type, and mixed type [79, 82, 132]. The major constituents of *C. osmophloeum* leaf essential oil are the monoterpenes, 1,8-cineole (17.0%) and santolina triene (14.2%), and the sesquiterpenes, spathulenol (15.7%) and caryophyllene oxide (11.2%) [67]. The lignan sesamin has been isolated from *C. kanehirae* [192].
- **Acaricidal effects:** Cinnamon displayed acaricidal activity against red mites (*Dermanyssus gallinae*) [235]; however, the mechanism of action is not well understood.
- **Adrenergic effects:** TRPA1 agonists, such as cinnamaldehyde, have been shown to activate the sensory nerves and induce adrenaline secretion via the central nervous system [204].
- **Alzheimer's effects:** Cinnamon extracts have been shown to inhibit tau aggregation and filament formation; a significant portion of the effect attributed to an A-linked proanthocyanidin trimer molecule [377].
- **Analgesic effects:** An ethanolic extract of *C. zeylanicum* was shown to possess an antinociceptive effect against both acetic acid-induced writhing and hot plate-induced thermal stimulation in mice [21]. However, cinnamaldehyde is a specific TRPA1 (mammalian transient receptor potential [TRP] ion channel) activator, and has been shown to excite a subset of sensory neurons highly enriched in cold-sensitive neurons and to elicit nociceptive behavior in mice [25, 324]. Secondary sources indicate that cinnamon may contain the following potentially bioactive constituents: ascorbic acid, borneol, caffeic acid, camphor, caryophyllene, coumarin, eugenol, linalool, mannitol, myrcene, P-cymene, phenol, thiamin, and zinc. These constituents have been proposed to have analgesic properties, although the exact mechanisms of action for each constituent are unclear.
- **Antibacterial effects:** Extracts of cinnamon, as well as the major components cinnamaldehyde and eugenol, have demonstrated activity against *Campylobacter*

jejuni, *E. coli*, *Listeria monocytogenes*, *B. subtilis*, *Salmonella* spp., *Morganella morganii*, *Clostridium perferingens*, *B. cereus*, and *Staphylococcus aureus* in vitro [59, 99, 143–145, 153, 182, 243, 259, 357, 436, 441, 459, 507, 518, 541, 544, 545]. Cinnamaldehyde exhibits bactericidal activity against *Listeria monocytogenes*. Inhibition of energy generation may be due to the inhibition of glucose uptake or utilization of glucose and effects on membrane permeability [153]. Cinnamaldehyde inhibited the swimming motility of *E. coli* in laboratory study. Cinnamaldehyde reduced biofilm formation by *E. coli* ATCC 33456 in part by interfering with its ability to reach the substratum [357]. Cinnamaldehyde has also demonstrated antimicrobial effects against BacPre-targeted ruminal bacteria [136]. Based on review, synergistic antibacterial effects have been observed between cinnamaldehyde and eugenol [47].

- Cinnamon bark oil, the alcoholic extract, and its major components showed antibacterial effects on the major respiratory and gastrointestinal tract pathogens *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, *Porphyromonas gingivalis*, *E. coli*, *B. cereus*, and *S. aureus* in vitro [143, 144, 201, 202, 369].
- Cinnamon oil was shown to have antibacterial activity against *B. cereus*, *E. coli*, and *S. aureus* in the following order: *B. cereus* (vegetative) \gg *S. aureus* approximately *E. coli* \gg *B. cereus* (spores) [143].
- *C. zeylanicum* tincture did not exhibit antibacterial properties in laboratory study [522].
- Cinnamon has antimicrobial properties that may improve energy or protein use in rumen and may therefore act as an alternative to ruminal modifiers. Cinnamon affected molar proportions of acetate, propionate, and butyrate between Day 2 and Day 6 of fermentation during the adaptation period. The accumulation of peptide nitrogen and the numerical decrease in amino acid nitrogen in cinnamon suggest that peptidolysis was inhibited [58, 310].
- Cinnamaldehyde has not been found to significantly inhibit multidrug resistance proteins MRP1 or MRP2 [532]. Extracts of cinnamon, as well as the major components cinnamaldehyde and eugenol, have demonstrated activity against *Campylobacter jejuni*, *E. coli*, *Listeria monocytogenes*, *B. subtilis* (ATCC 6633), and *Salmonella enterica* in vitro [59, 99, 145, 243, 436, 459, 544, 545]. Cinnamon bark oil and its major components showed antibacterial effects on the major respiratory and gastrointestinal tract pathogens *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *S. aureus* and *Porphyromonas gingivalis*, in vitro [201, 202, 369]. Furthermore, cinnamon exhibited significant inhibitory effects both in vitro and in vivo on *M. morganii* [441]. However, one study found no antibacterial activity in *C. zeylanicum* tincture using luminescent bacterial biosensors (*E. coli* strains) [522]. A case report studied an exclusively breastfed infant (4 months of age) with acute diarrhea and who became a chronic carrier of *S. enteritidis* [409]. The infant was administered ground cinnamon bark in homogenized fruit 3–4 times a day. One month later, stool samples of the infant tested negative for *S. enteritidis*; repeat tests, 2 and 4 months later, were also negative. In human trial using an alcoholic extract of cinnamon for *H. pylori* infection, the amount of *H. pylori* colonization measured by the ^{13}C urea breath test served as the outcome measure [354]. The mean urea breath test counts in

the study and control groups before and after therapy were 22.1 and 23.9 versus 24.4 and 25.9, respectively. The exact mechanism of action remains unclear.

- Cinnamon [300, 371, 380, 486], cinnamon extracts [61, 168, 246, 331, 442], cinnamon essential oils (alone and in combination with other plant oils) [28, 107, 118, 130, 149, 181, 296, 297, 321, 338, 339, 361, 370, 382, 400, 401, 406, 436, 458, 497, 520, 538], and constituents of cinnamon such as cinnamaldehyde (alone and in combination with other plant extracts) [20, 62, 64, 110, 137, 164, 215, 363, 398, 399, 408, 425, 456, 495, 505] and trans-cinnamaldehyde [14, 16, 68, 94, 423, 530] have all been reported to exhibit antimicrobial effects, although a tincture of *C. zeylanicum* was reported as ineffective against *E. coli* [522]. Cinnamaldehyde was found to induce multiple antibiotic resistance (MAR) in *Bacteroides fragilis* [387]. Cinnamaldehyde has also been reported to interfere with quorum sensing [38, 356] and cinnamon essential oil to interact synergistically with clindamycin [440].
- **Anticancer/antitumor effects:** Cinnamon and its constituents have displayed anticancer and chemopreventive properties in various studies [166, 171, 265, 355, 534]. The antitumor activity of *Cinnamomum* cortex is considered to be based on stimulation of the reticuloendothelial system (RES) and has been shown to be closely related to TNF (tumor necrosis factor) production [171]. A genotoxicity assay (micronucleus test) demonstrated dose-related antigenotoxic effects after urethane was coadministered orally with an aqueous extract of cinnamon to mice [8]. *C. cassia* induced the death of HL-60 cells, demonstrated by reduction in mitochondrial transmembrane potential and increase in caspase-3 activity [355]. Cinnamaldehyde derivative CB403 exerted cytostatic properties through the arrest of cell cycle progression in the G₂/M phase in laboratory study [213]. The bark of *C. cassia* displayed inhibitory effects against matrix metalloproteinase-2 and -9 (MMP-2 and -9) and invasion of SK-Hep1 hepatoma cells [166].
- Cinnamaldehyde is also a potent inducer of apoptosis. It has been shown to transduce the apoptotic signal via reactive oxygen species (ROS) generation, thereby inducing mitochondrial permeability transition (MPT) and cytochrome c release into the cytosol. Thus, the anticancer effects of cinnamaldehyde may result from the induction of ROS-mediated mitochondrial permeability transition and resultant cytochrome c release [216, 534]. Cinnamic aldehyde inhibited leukemia L1210 cells by blocking protein synthesis through trapping sulfhydryl-containing amino acids in the cell [334]. Cinnamaldehyde also upregulated the expression of pro-apoptotic protein (Bax) and downregulated the levels of antiapoptotic proteins such as Bcl-2, the inhibitor of apoptosis protein family (X-linked inhibitor of apoptosis protein [XIAP]), and the cellular inhibitor of apoptosis protein (cIAP-1 and cIAP-2) [534]. Of note, pretreatment with vitamin E markedly prevented cinnamaldehyde-mediated apoptosis, which was associated with the modulation of XIAP, cIAP-1, cIAP-2, Bcl-2, and Bax protein activity [534].
- A strong MMP-9 inhibition was found in the butanol fraction of *C. cassia* [438]. MMP-9 degrades type IV collagen, constituting the major structural component of the basement membrane and the extracellular membrane; the enzymatic activity is found to be elevated in tumor tissues. 2'-Hydroxy-cinnamaldehyde and 2'-benzoyloxycinnamaldehyde isolated from *C. cassia* strongly inhibited in-vitro growth of 29 kinds of human cancer cells and in-vivo growth of SW-620 human tumor xenograft in nude mice. HCA prevented adherence of SW-620 cells to the

culture surface but did not inhibit oncogenic K-Ras processing, implying its anti-tumor mechanisms at the cellular level [269]. HCT15 and SK-MEL-2 cells were very sensitive to the cinnamaldehyde analogs cinnamic acid, cinnamates, and cinnamyl alcohols [257]. Based on in-vitro evidence, polymeric polyphenols from cinnamon have been shown to block the G₂/M phase of the cell cycle by interacting with phosphorylation/dephosphorylation signaling activities in three myeloid cell lines (Jurkat, Wurzbug, and U937) and a leukemic cell line [427, 428].

- Cinnamon [30, 258], cinnamon extracts and essential oils [446], and constituents of cinnamon [112, 288], including a *Cinnamomum* monoterpene [289], cinnamaldehyde [120, 239, 448, 533], isobutylacetone A [71, 293], kotomolide A [253], subamolides A–C [72] and subamolides D and E [254], isokotomolide A [73], cinnamyl compounds related to 2'-hydroxycinnamaldehyde [454], 2'-hydroxycinnamaldehyde [188], and isobutylacetone A [74] have all been reported to exhibit anticancer, antitumor, antiproliferative, or antimutagenic effects.
- **Antidiabetic effects:** Based on human and animal study, cinnamon has been used to control blood sugar either alone or in combination with other essential oils such as fenugreek and oregano [6, 13, 33, 95, 121, 229, 309, 344, 378, 474, 481, 510, 558]. However, results have not been consistent, and various human trials have found that cinnamon did not significantly alter A1C, FBG, or lipid parameters in patients with type 1 or type 2 diabetes [22, 242]. Pharmacological studies have shown that cinnamon may play a possible role in improving glucose and insulin metabolism [367], but that these effects are short lived (i.e., up to 12 hr) once cinnamon feeding is stopped [460, 461].
- In animal and laboratory studies, cinnamon has been shown to potentiate the insulin effect through upregulation of the glucose uptake in cultured adipocytes and to potentiate insulin-regulated glucose utilization by enhancing the insulin-signaling pathway in skeletal muscle [18, 29, 41, 56, 200, 228, 390].
- Cinnamon was highly active in the insulin-dependent utilization of glucose using a rat epididymal adipocyte assay. In animal study, cinnamon prevented insulin resistance in rats fed a high-fructose diet in part by enhancing insulin signaling and possibly via the nitric oxide (NO) pathway in skeletal muscle [391]. A hydroxychalcone from cinnamon functioned as an insulin mimetic in 3T3-L1 adipocytes [208]. Furthermore, in-vitro evidence showed that adipocytes exposed to 0.2 mg/ml of cinnamon extract in the absence of insulin showed an approximate twofold increase in glucose uptake relative to controls [405]. Cinnamaldehyde exhibited strong inhibition against aldose reductase [271], an enzyme in carbohydrate metabolism that converts glucose to its sugar alcohol form, sorbitol, using NADPH as the reducing agent. Aqueous extracts of cinnamon significantly lowered the absorption of alanine, an important amino acid for gluconeogenesis, from the rat intestine [252]. Blood glucose-lowering effects within 2 weeks have been shown for *C. tamala* in alloxan diabetic albino rats [225]. However, another pharmacological study demonstrated that consumption of diets containing *C. tamala* did not alter diabetes parameters in streptozotocin diabetic mice [476].
- Kannappan et al. showed that cinnamon extract improved glucose metabolism in vivo in fructose-fed rats [223]. Qin et al. showed that cinnamon extract

improved insulin action via increasing glucose uptake in vivo possibly through enhancement of the nitric oxide pathway in skeletal muscle [390, 391]. Based on human evidence, ingestion of 3 g of cinnamon reduced postprandial serum insulin and increased glucagon-like peptide 1 (GLP-1) concentrations without significantly affecting blood glucose, glucose-dependent insulintropic polypeptide (GIP), ghrelin concentration, satiety, or gastric emptying rate (GER) [185]. Additional study has shown that addition of cinnamon to rice pudding significantly delayed gastric emptying and lowered the postprandial glucose response, with no effects on satiety in healthy subjects [184].

- **Antifungal effects:** Based on human and in-vitro study, cinnamon oil, cortex cinnamon solution, *trans*-cinnamaldehyde, cinnamaldehyde, and the essential oils have been found to have inhibitory effects against several fungi, including *Candida*, *Coriarius versicolor*, *Laetiporus sulphureus*, *Eurotium* spp., *Aspergillus* spp., and *Penicillium* [55, 79, 85, 165, 174, 285, 294, 317, 335, 374, 457, 504, 541]. High concentrations of cinnamon, however, have been shown to stimulate mycelial growth of *A. flavus* [301]. *C. zeylanicum* has shown potent in-vitro activity against fluconazole-resistant and -susceptible *Candida* isolates [393]. Cinnamaldehyde and *trans*-cinnamaldehyde have also displayed strong activity against various types of fungi [515]. Colonies formed by heat-stressed cells of *S. cerevisiae* showed a reduction in size, and heated *Rhodotorula rubra* cells demonstrated a slight increase in sensitivity to cinnamon oil [92].
- **Anthelmintic effects:** Ceylon cinnamon reportedly has anthelmintic effects; however, these properties are not well documented [60].
- **Anti-inflammatory effects:** Cinnamon bark showed anti-inflammatory properties in vitro [256, 402] and in vivo in the carbon clearance test [221]. Eugenol and cinnamaldehyde were found to inhibit cyclooxygenase-2 (COX-2) in vitro in a rapid semi-homogeneous COX-2 enzymatic assay [195]. Cinnamaldehyde has been shown to inhibit 5-lipoxygenase, a key enzyme involved in the biosynthesis of leukotrienes [384]. This effect was more potent than that of piperine, capsaicin, and allyl sulfide, but less potent than that of quercetin, eugenol, and curcumin. *C. massoiae* cortex extract inhibited IgE-dependent histamine release [199]. Extracts obtained from *C. osmophloeum* leaf essential oil and from the twigs of *C. osmophloeum* Kaneh. have shown in-vitro anti-inflammatory activity [67, 132, 496]. Cinnamaldehyde has been demonstrated to possess anti-inflammatory properties [66, 274]; to alleviate neuropathic and inflammatory pain via antagonism of TRPA1 [123]; to suppress TNF-induced signaling pathways [283], to activate nuclear factor (NF)-kappaB and interferon regulatory factor 3 (IRF3) induced by lipopolysaccharides (LPS), a toll-like receptor (TLR4) agonist, leading to the decreased expression of target genes such as COX-2 and interferon (IFN)beta [540]; to reduce expression of inflammatory cytokines (in combination with other plant extract) [281]; and to inhibit age-related activated NF-kappaB upregulation of NF-kappaB targeting genes, inflammatory inducible nitric oxide (iNOS), and COX-2 via three signal transduction pathways (NIK/IKK, ERK, and p38 MAPK) [231]. Cinnamon essential oils [287] and extracts [396] have also been documented as having anti-inflammatory action.
- Components of *Cinnamomi ramulus* have demonstrated an anti-inflammatory effect via inhibition of the expression of iNOS and COX-2 and by suppressing

nitric oxide (NO) production in both the peripheral and the central nervous systems [197]. Cinnamon bark extract has been suggested as possibly protecting the liver from acute alcohol-induced steatosis through the inhibition of MyD88 expression [224]. Research has also suggested that cinnamon polyphenol extract may affect immune responses by regulating inflammatory dynamics and glucose transporter (GLUT) gene expression [57].

- Secondary sources indicate that cinnamon may contain the following potentially bioactive constituents: (–)-epicatechin, 1,8-cineole, alpha-pinene, alpha-terpineol, ascorbic acid, beta-pinene, beta-sitosterol, borneol, caffeic acid, caryophyllene, caryophyllene oxide, cinnamaldehyde, cinnamic acid, copper, coumarin, delta-3-carene, eugenol, eugenyl acetate, isoeugenol, limonene, linalool, mannitol, oleic acid, oligomeric proanthocyanidins (OPCs), salicylates, and stigmaterol. These constituents have been proposed to have anti-inflammatory properties, although the exact mechanisms of action for each constituent are unclear.
- **Antilipemic effects:** Based on animal evidence, *C. zeylanicum* significantly decreased serum total cholesterol and triglyceride concentrations and markedly increased HDL cholesterol levels [273, 467]. In animal study, cinnamate, a phenolic compound in cinnamon bark, produced higher HDL cholesterol levels and lower atherogenic index compared with lovastatin. Cinnamate inhibited HMG-CoA reductase activity [273]. In-vivo evidence in hamsters has shown that a water extract of cinnamon (Cinnulin PF[®]) inhibited the postprandial overproduction of apoB48-containing lipoproteins and serum triglyceride levels [389]. However, these results were in contrast to another study that did not show any cholesterol-lowering effect in serum and liver cholesterol levels of rats [420]. Further in-vitro evidence from this study showed that cinnamon extract treatment inhibited CD36 and MTP [389].
- Research has suggested that postprandial hypertriglycerides and overproduction of apoB48 may be acutely inhibited by cinnamon extract via improved insulin sensitivity of intestinal enterocytes and regulation of MTP and SREBP1c levels [392]. Cinnamaldehyde has been observed to reduce serum total cholesterol and triglyceride levels in rats [467].
- **Antimutagenic effects:** The antimutagenic activity of cinnamon and its constituents have been reported in various laboratory studies [8, 102, 178, 207, 217, 218, 447]. *C. cassia* exerted significant antimutagenic effects against benzo[a]pyrene (B[a]P) and cyclophosphamide in mice pretreated with the plant extract, as was observed in the Ames test, bone marrow chromosomal aberration assays, and micronucleus tests [447]. In one laboratory study, *trans*-cinnamaldehyde showed antimutagenic activity against select *Salmonella typhimurium* tester strains TA1535 (hisG46 uvrB rfa) and TA100 (TA1535/pKM101) [102]; however, other evidence revealed no mutagenic effects [284]. *C. cassia* pretreatment decreased liver cytochrome P450 content but increased glutathione content and the activity of glutathione-dependent antioxidant enzymes glutathione S-transferase, glutathione reductase, and glutathione peroxidase. These findings might demonstrate that the antimutagenic potential of *C. cassia* may be attributed to its modulatory effect on xenobiotic bioactivation and detoxification processes. α,β -unsaturated carbonyl compounds in

(E)-2-cinnamaldehyde were found to induce oxidative purine modifications (formamidopyrimidine DNA glycosylase [FPG]-sensitive sites) in mammalian cells, in addition to direct DNA breakage [207, 364]. Cinnamyl anthranilate enhanced SA7 transformation; cinnamaldehyde produced some evidence of enhanced activity [178].

- The antimutagenic effects of cinnamaldehyde have been evaluated in various studies [364, 365]. Cinnamaldehyde suppressed the umuC-dependent mutagenesis induced by 4-nitroquinoline 1-oxide (4-NQO), furylfuramide, or captan, but was less effective against the umuC-independent mutagenesis by alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine and ethylmethanesulfonate [364]. Cinnamaldehyde did not affect prophage induction or tif-mediated filamentous growth, suggesting it does not prevent the induction of the SOS functions [364]. An increase was observed in the survival of 4-NQO-treated WP2s cells after exposure to cinnamaldehyde, suggesting the promotion of some DNA repair system by cinnamaldehyde [364]. An enhancement in survival was also observed in uvr B, polA, recF, or umuC mutants and less in lexA or recBC mutants; it was not observed in recA mutants [364]. Cinnamaldehyde may enhance an error-free recombinational repair system by acting on recA-enzyme activity [364]. Cinnamaldehyde displayed antimutagenic effects against mutations induced by UV-mimic mutagens but not those induced by -methyl-N'-nitro-N-nitrosoguanidine or ethyl methanesulfonate, and may therefore act by interfering with an inducible error-prone DNA repair pathway [365].
- **Antioxidant effects:** Cinnamon and cinnamon bark have been shown to contain very high concentrations of antioxidants [34, 115, 300]. Several animal in-vitro studies have demonstrated the antioxidant effects of the essential oil obtained from the bark of *C. zeylanicum* and its main components [18, 83, 175, 210, 236, 272, 278, 455, 491]. In animal study, cinnamate suppressed lipid peroxidation by enhancing hepatic antioxidant enzyme activities [273]. It elevated catalase and glutathione peroxidase activity and reduced thiobarbituric acid-reactive substances [273]. Cinnamon extracts [88, 119, 336], essential oils [418, 458, 513, 523], bark [383], and cinnamaldehyde [66, 159] have all been identified as possessing antioxidant properties. Cinnamon has also been found to synergistically increase the antioxidant capacity of some teas [48], protect against peroxynitrite damage [186], and scavenge NO (nitric oxide) [494]. In addition, constituents of cinnamon, such as cinnamic aldehyde and methyl-1-cinnamoyl-5-oxo-2-pyrrolidine-carboxylate, have been identified as potent nuclear factor-erythroid 2 (Nrf2)-activators (involved in cellular antioxidant response) [529]. Furthermore, cinnamon extracts have been observed to significantly increase levels of reduced glutathione and the activities of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase, and superoxide dismutase in the liver of rats [233]. In other research, cooking and storage has been found to reduce the antioxidant capacity of cinnamon extract [86].
- In one study, cinnamon showed higher antioxidant activity and was a better superoxide radical scavenger than anise, ginger, licorice, mint, nutmeg, and vanilla [340].
- In various studies, etheric, methanolic, and aqueous cinnamon extracts also inhibited oxidative processes in vitro [106, 187, 248, 275, 286, 308, 318, 451].

- A randomized controlled trial (RCT) examined the effects of a dried aqueous extract of cinnamon (Cinnulin PF[®]) on the antioxidant status of overweight or obese individuals with impaired fasting glucose [411]. Plasma antioxidant status and plasma thiol (SH) increased, while plasma malondialdehyde levels decreased in subjects receiving the cinnamon extract. A positive correlation was also observed between malondialdehyde and plasma glucose ($r = 0.74, p = .014$).
- Ethanol extracts of dry bark of *C. cassia* (96.30%) exhibited a greater inhibition of FeCl₂-ascorbic acid-induced lipid peroxidation of rat liver homogenate in vitro than that by alpha-tocopherol (93.74%) [286]. A highly positive linear relationship was obtained between total equivalent antioxidant capacity (TEAC) values and total phenolic content; the authors conclude that phenolic compounds in *C. zeylanicum* and *C. cassia* bark may contribute significantly to their antioxidant capacity [443].
- Suganthi et al. showed that a spice mixture containing 1.0 g/100 g of cinnamon bark increased levels of peroxidation indices such as thiobarbituric acid-reactive substances (TBARS) and concentration of lipid hydroperoxides in tissues [470].
- Secondary sources indicate that cinnamon may contain the following potentially bioactive constituents: (-)-epicatechin, acetyl eugenol, ascorbic acid, beta carotene, caffeic acid, campesterol, camphene, eugenol, gamma terpinene, isoeugenol, lauric acid, linalyl acetate, manganese, mannitol, methyl eugenol, myrcene, myristic acid, OPCs, P-coumaric acid, palmitic acid, phenol, proanthocyanidins, riboflavin, stigmasterol, terpinen-4-ol, terpinolene, and vanillin. These constituents have been proposed to have antioxidant properties, although the exact mechanisms of action for each constituent are unclear.
- **Antipyretic effects:** The active compounds of guizhi tang, cinnamaldehyde, and cinnamic acid have been found to have antipyretic action by inducing EP3 prostaglandin receptors [280].
- **Antiseptic effects:** Cinnamaldehyde has been shown to be an effective periodontal disinfectant, significantly reducing levels of oral endotoxin in rats [292]. Secondary sources indicate that cinnamon may contain the following potentially bioactive constituents: 1,8-cineole, alpha-pinene, alpha-terpineol, ascorbic acid, benzaldehyde, benzyl alcohol, beta-pinene, caffeic acid, camphor, chlorine, citronella, eugenol, furfural, geraniol, hexanol, iodine, limonene, linalool, methyl eugenol, nerol, OMCA, oxalic acid, P-coumaric acid, phenol, proanthocyanidins, sabinene, safrole, sulfur, terpinen-4-ol, and zinc. These constituents have been proposed to have antiseptic properties, although the exact mechanisms of action for each constituent are unclear.
- **Antispasmodic effects:** Secondary sources indicate that cinnamon may contain the following potentially bioactive constituents: 1,8-cineole, alpha-pinene, alpha-terpinene, ascorbic acid, benzaldehyde, benzyl benzoate, beta-pinene, borneol, bornyl acetate, caffeic acid, camphor, caryophyllene, cinnamaldehyde, cinnamic acid, eugenol, eugenyl acetate, farnesol, geraniol, limonene, linalool, linalyl acetate, mannitol, myrcene, niacin, P-coumaric acid, potassium, and terpinen-4-ol. These constituents have been proposed to have antispasmodic properties, although the exact mechanisms of action for each constituent are unclear.
- **Antiviral effects:** *C. cassia* bark extract has been highly effective against HIV-1 and HIV-2 replication in terms of inhibition of virus induced cytopathogenicity

in MT-4 cells infected with HIV [385]. Cinnamaldehyde derived from cinnamon bark has shown an inhibitory effect on the growth of influenza A/PR/8 virus in vitro and in vivo [179]. Cinnamon extract have been shown to prevent HIV-1 infection in vitro, an effect attributed to the extract's flavonoid content [139]. Cinnzeylanine, a constituent of cinnamon, has also been shown to inhibit herpes simplex virus proliferation in vitro [368]. Another constituent, *trans*-cinnamaldehyde, has been shown to have a similar inhibitory effect on influenza A/PR/8 viral growth [179]. Secondary sources indicate that cinnamon may contain the following potentially bioactive constituents: (–)-epicatechin, alpha-pinene, ascorbic acid, beta-sitosterol, bornyl acetate, caffeic acid, chlorine, cinnamaldehyde, eugenol, geranial, iodine, lauric acid, limonene, linalool, OPCs, P-cymene, phenol, proanthocyanidins, stigmasterol, and vanillin. These constituents have been proposed to have antiviral properties, although the exact mechanisms of action for each constituent are unclear.

- **Anxiolytic effects:** As indicated by research in mice, cinnamon may exert an anxiolytic effect via regulation of the serotonergic and GABAergic systems [542].
- **Cardiovascular effects:** *C. cassia* bark has been shown to affect the blood and cardiovascular system [77]. It has been shown to reduce blood pressure in animal studies either alone or in combination with other essential oils such as fenugreek and oregano [386, 481]. *C. cassia* increased the level of atrial natriuretic factor (ANF) in the plasma of mice [553]; ANF acts to reduce the water, sodium, and adipose loads on the circulatory system, thereby reducing blood pressure. Another human trial also demonstrated lowered SBP upon treatment with a water-soluble cinnamon extract (–3.8%: from 133 ± 14 mmHg [pre] to 128 ± 18 mmHg [post], $p < .001$) [558]. In experimental arrhythmia, *C. migao* reduced the incidence of ventricular fibrillation caused by chloroform in mice and the ventricular tachycardia induced by adrenalin in rabbits, delayed the onset time of this arrhythmia, increased the arrhythmic doses of strophantin-K in guinea pigs, reduced the incidence of some arrhythmias caused by barium chloride in rats, and slowed down their heart rate [471]. *C. migao* oil reduced systolic and diastolic arterial blood pressure, slowed down the heart rate, decreased carbon monoxide levels, and reduced left ventricular pressure in anesthetized open-chest cats after i.d. application [473]. Cinnamophilin, a thromboxane A(2) antagonist isolated from *C. philippinense*, inhibited sodium inward current, calcium inward current, and transient outward current in rat cardiac tissue and converted episodes of ischemia-reperfusion arrhythmia to normal sinus rhythm [466]. Cinnamophilin dose-dependently inhibited human platelet-rich plasma (PRP) aggregation induced by AA, collagen, and U-46619 [543].
- **Cell cycle effects:** Cinnamaldehyde has been shown to promote more cells in G₀/G₁ phase into S phase [551].
- **Coagulation effects:** Based on animal evidence, cinnamon bark, cinnamaldehyde, and two other *Cinnamomum* species (*C. altissimum* and *C. pubescens*) caused a decrease in platelet counts after long-term use [193, 206, 320, 367]. Cinnamic aldehyde inhibited AA release and thromboxane B2 formation, which may contribute to reduced platelet aggregation [480].

- **Cytochrome P450 effects:** 5'-hydroxy-5-hydroxymethyl-4'',5''-methylenedioxy-1,2,3,4-dibenzo-1,3,5-cycloheptatriene, a constituent of cinnamon extract, has been shown to inhibit CYP3A4 in vitro [469].
- **Enzymatic effects:** ATPases are a class of enzymes that catalyze the decomposition of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and a free phosphate ion. Water extracts of cinnamon inhibited the activity of rat liver Na⁺/K⁺ ATPase and Cu²⁺ ATPase but, as did cinnamaldehyde and eugenol, stimulated rat mitochondrial F₀F₁ ATPase, reduced mitochondrial membrane potential, inhibited NADH oxidase or Complex I of the respiratory chain, and had no effect on succinate dehydrogenase activity [502, 503]. These effects resulted in a decrease in ATP level; defects in proton and ion transports, leading to electrolyte imbalance; and derangements in mitochondrial function. Furthermore, cinnamon water extract most potently inhibited the in-vitro activity of the rat jejunal Na⁺-/K⁺-ATPase, the in-vitro Na⁺-/K⁺-ATPase activity in a crude kidney homogenate, and the activity of an isolated dog kidney Na⁺-/K⁺-ATPase. The alcoholic extract of cinnamon, compared with the aqueous extract, had a stronger inhibitory action on the jejunal enzyme, as did cinnamaldehyde. Eugenol is the major inhibitory component in both alcoholic and aqueous extracts [252].
- Cinnamon extracts [350], essential oils [313], and constituents, including *trans*-cinnamaldehyde thiosemicarbazone [556], and cinnamic acid [249] have all been identified as inhibiting tyrosinase. Cinnamon essential oils have also been identified as inhibiting xanthine oxidase [516]. In addition, cinnamon extracts have been found to inhibit PKA [337] and elastase [276].
- **Gastrointestinal effects:** Chinese cinnamon (the stem bark of *C. cassia*) prevented serotonin-induced ulcerogenesis and inhibited gastric ulcers in rats after oral administration [483]. In a pharmacological study, Chinese cinnamon inhibited the secretion of gastric acid to a small extent but promoted gastric blood flow [10].
- Cinnamon reportedly contains lipase, a digestive enzyme [177]. In poorly documented research, however, *Cassia nomame* extracts appear to have lipase-inhibiting activity [322].
- In animal study, cinnamic aldehyde, eugenol, and eugenol acetate exhibited relaxant effects on tracheal and ileal smooth muscles [403].
- TRPA1, of which cinnamaldehyde is an agonist, has been shown to act as a sensor molecule for enterochromaffin cells and may regulate gastrointestinal function [360]. Cinnamaldehyde has been shown to induce intestinal HCO₃(-) secretion, likely via direct activation of nicotinic receptors on epithelial cells [36]. In other gastrointestinal research, cinnamon extract has been shown to have antidiarrheal effects [395].
- **Hormonal effects:** Cinnamomi cortex as a component of the unkei-to combination product was found to stimulate estradiol secretion in laboratory study [472].
- **Hypouricemic effects:** Oral administration of *C. cassia* oil significantly reduced serum and hepatic urate levels in hyperuricemic mice [552]. In normal mice, urate levels in liver, but not in serum, were altered with a dose-dependent decrease after *C. cassia* oil treatment.
- **Immunomodulatory effects:** In vitro, an extract of *C. cassia* markedly stimulated human lymphocytes to proliferate [444]. Cinnamaldehyde derivatives inhibited the lymphoproliferation and induced a T-cell differentiation through the

blockade of early steps in signaling pathways leading to cell growth [244]. *C. cassia* has shown anticomplement action and inhibited the complement-dependent allergic reaction [342]. In rat nephrotoxic serum (NTS) nephritis, *C. cassia* clearly inhibited the excretion of protein into the urine and the increase in peripheral leukocyte counts [343]. Cinnamomi cortex as a component of the unkei-to combination product was found to stimulate the secretion of cytokines (interleukin [IL]-1, IL-6, and IL-8) and the hypothalamus–pituitary axis in laboratory study [472].

- Research has suggested that cinnamon polyphenol extract may affect immune responses by regulating inflammatory response and GLUT gene expression [57]. In another work, sodium benzoate in combination with a cinnamon metabolite ameliorated disease processes associated with experimental allergic encephalomyelitis, an animal model for multiple sclerosis [40].
- **Insecticidal effects:** Cinnamon essential oils have been shown to serve as effective larvicides against mosquitoes [80] and various harmful flies [449]. Larvicidal tests demonstrated that the leaf essential oils of cinnamaldehyde type, cinnamaldehyde/cinnamyl acetate type, and cinnamyl alcohol had an excellent inhibitory effect against the fourth-instar larvae of *Aedes aegypti* (yellow fever mosquito) [65, 82]. The alcohol extract of *C. camphora* demonstrated effects on *Aphidius gifuensis* and *Diaeretiella rapae* [554]. Results of the 24-hr mosquito larvicidal assays also showed that the effective constituents in leaf essential oils were cinnamaldehyde, eugenol, anethole, and cinnamyl acetate. Cinnamaldehyde exhibited the strongest mosquito larvicidal activity.
- Cinnamon oils and cinnamaldehyde have both been shown to have insecticidal action against *Sitophilus oryzae* [270]. In addition, cinnamon essential oils displayed insecticidal action against *Solenopsis invicta* [81] and repellent action against *Resseliella oculiperda* [509].
- **Metabolic effects:** Cinnamon (*C. zeylanicum*) extracts stimulated 3T3-L1 preadipocytes [479]. Induction of adipocyte formation by cinnamtannin B1 extract gave similar effects related to insulin activity in adipogenesis [479].
- In clinical study, cinnamon increased lean mass [558]. The exact mechanism of action, however, is not well understood.
- **Nematicidal effects:** Cinnamon essential oils have been observed as having nematicidal effects [247].
- **Neurologic effects:** Cinnamon and various constituents displayed neuroprotective effects in animal and laboratory study [232, 372, 452, 453]. A water extract from the bark of *C. cassia* significantly protected against glutamate-induced cell death and also inhibited glutamate-induced $^{45}\text{Ca}^{2+}$ influx using cultured rat cerebellar granule cells [452]. The authors suggest that *C. cassia* bark may have a protective effect on glutamate-induced neuronal death through the inhibition of Ca^{2+} influx. In a model of cytotoxic brain edema in ischemic injury, cinnamon polyphenol extract reduced oxygen–glucose deprivation-induced cell swelling and caused a decline in inner mitochondrial membrane potential in vitro; researchers suggested that cinnamon polyphenol extract may exert its protective effects through mitochondrial permeability transition inhibition [372]. Keishibukuryo-gan, a herbal combination product that contains cinnamon, displayed neuroprotective effects against NO donor-induced neuronal death in cultured

cerebellar granule cells [453]. In laboratory study, chloroform extracts of *C. cassia* showed a marginal neuronal cell protection from direct betaA(1-42) insult, a major cause of Alzheimer's disease pathology [232].

- In animal study, cinnamaldehyde reduced the amplitude of nerve action potential in sciatic nerves [312]; this effect was almost completely reversible.
- Cinnamaldehyde is a known agonist of TRPA1, a receptor implicated in nociception (as well as other functions), and has been used as such in various experiments [11, 19, 49, 122, 123, 160, 250, 326, 346, 347, 360, 546, 547]. As indicated by research in mice, cinnamon may exert an anxiolytic effect via regulation of the serotonergic and GABAergic systems [542]. Cinnamon extracts have been shown to inhibit tau aggregation and filament formation; a significant portion of the effect is attributed to an A-linked proanthocyanidin trimer molecule [377].
- **Phototoxic effects:** Alpha-amyl cinnamic aldehyde, cinnamic alcohol, cinnamic aldehyde, and alpha-amyl cinnamic aldehyde have all been identified as increasing phototoxicity [381].
- **Pigmentation effects:** Cinnamic acid has been shown to reduce melanin production, likely via inhibition of tyrosinase [249, 313].
- **Psychiatric effects:** Cinnamon has been found to contain allylbenzenes and their isomers, the propenylbenzenes, which have been speculated to be potential metabolic precursors of amphetamines, which may be responsible, in part, for potential mood-enhancing effects [198]. Humans may be exposed to these precursors during baking and cooking; however, the authors note that the biotransformation, pharmacodynamics, and pharmacokinetics of these aromatic allylbenzene compounds are not well understood in human clinical or laboratory studies.
- **Reproductive effects:** Cinnamomi cortex as a component of the unkei-to combination product stimulated the ovulatory process [472].
- **Wound-healing effects:** In animal study, *C. zeylanicum* bark extract enhanced the wound breaking strength in the case of incision wound, the rate of wound contraction, and the period of epithelization in the case of excision wound. The granulation tissue weight, its breaking strength, and its hydroxyproline content (a nonessential amino acid) were also increased by the extract in the dead space wound [219].

Pharmacodynamics/Kinetics

- **Absorption:** A pharmacokinetic study was performed for measuring the absorption of orally administered procyanidin B-2 and procyanidin B-3 isolated from Cinnamomi cortex (the bark of *C. cassia*) in rat plasma [482]. Intestinal absorption of cinnamaldehyde in anesthetized dogs administered intradermally occurred very early and was long lasting [170].
- A broad range (in terms of molecular mass) of protein-cinnamaldehyde adducts was detected (as formed in a time- and concentration-dependent manner) in skin treated with cinnamaldehyde and cinnamic alcohol but not with alpha-amyl cinnamaldehyde [124].
- The pharmacokinetics of cinnamic acid was compared following oral administration of a decoction of ramulus Cinnamomi (7.4 g/kg; containing cinnamyl alcohol 7.62×10^{-5} mol/kg and cinnamaldehyde 1.77×10^{-5} mol/kg) and pure

cinnamic acid (7.62×10^{-5} mol/kg) in rats [78]. Results showed that the areas under the plasma concentration AUC(0–*t*) and AUC(0–infinity) of cinnamic acid were higher in the decoction group than those in the pure group, and that the bioavailability of cinnamic acid from the decoction was higher than that from pure cinnamic acid.

- **Bioavailability:** A study of the pharmacokinetics and relative bioavailability of a combination of radix *Angelicae sinensis* and cortex *Cinnamomi* revealed that the combination significantly improved the relative bioavailability of ferulic acid to 226.75% [537].
- **Excretion:** In animal study, constituents of cinnamon, cinnamyl alcohol, and cinnamic aldehyde (the compound which gives cinnamon its odor and flavor) were found to be excreted in the urine [105]. Rats given cinnamic aldehyde excreted two mercapturic acids in the urine, N-acetyl-S-(1-phenyl-3-hydroxypropyl)cysteine (major) and N-acetyl-S-(1-phenyl-2-carboxyethyl)cysteine (minor) [105]. Cinnamic aldehyde may be an intermediate in mercapturic acid formation of cinnamyl alcohol [104, 105].
- **Metabolism:** The metabolism of OMCA (intragastrically) was studied in rats [421]. The major metabolic pathway (approx. two thirds of the dose) was oxidation to the corresponding cinnamic and phenylpropionic acids (C6–C3 acids), which were largely excreted as glycine conjugates. Intermediate amounts (approx. 10% of the dose) of the O-demethylated C6–C3 acids were excreted. Urinary excretion of metabolites was rapid (91% in 24 hr and 98% in 48 hr) [421].
- Based on in-vitro studies, cinnamon or its constituents may inhibit hepatic microsomal cytochrome P450 [87, 419, 527]. Cinnamon bark was found to inhibit aminopyrine N-demethylation in rat liver microsomes. The component inhibiting drug oxidations catalyzed by CYP1A2 and CYP2E1 was isolated from *Cinnamomi* cortex and was identified as OMCA [176].
- **Minimum inhibitory concentrations (MIC):** The MIC of cinnamaldehyde against *C. versicolor* and *L. sulphureus* was 50 and 75 ppm, respectively [515]. OMCA displayed a strong inhibitory effect on the growth of dermatophytoses species, including *Microsporum canis* (MIC 3.12–6.25 mcg/ml); no effect was observed at concentrations as high as 50 mcg/ml [335].

HISTORY

- Cinnamon has been mentioned in historical documents as a well-known spice in the New World and Europe [152]. According to Herodotus (5th century BC): “Arabia is the only country which produces frankincense, myrrh, cassia, and cinnamon,” [492]. According to secondary sources, Zakariya al-Qazwini first made mention around the year 1270 that cinnamon grew in Sri Lanka in “Athar al-bilad wa-akhbar al-‘ibad” (“Monument of Places and History of God’s Bondsmen”). Indonesian traders would sail loads of cinnamon from a group of islands in eastern Indonesia, called the Moluccas, to East Africa. There, traders would transport the cinnamon to markets in Rome. Arab traders would also import the spice overland to Egypt, where Venetian traders would then procure the spice for trade in Europe. Upon the rise of the Ottoman Empire, European traders were obliged to seek out alternate trade routes.

- According to secondary sources, in the early 1500s, the Portuguese established their own monopoly on the cinnamon trade by establishing a stronghold in Sri Lanka. The Salagamas caste of Sri Lankans was traditionally associated with the highly skilled occupation of peeling cinnamon. The Portuguese used the Salagamas in the cinnamon trade. The Salagamas were also to provide cinnamon as a tax. The Dutch managed to dislodge the Portuguese monopoly by forming an alliance with the Kingdom of Maha Nuvara (Senkadagalapura) (i.e., Kandy) in central Sri Lanka. By the mid-1600s, the Portuguese were ousted, and the Dutch East India Company took control of the cinnamon trade. In the late 1700s, however, the British took control of the island and its spice trade. Sri Lanka gained independence from Britain in the late 1940s.
- Beyond Sri Lanka, cinnamon is commonly cultivated in tropical and subtropical regions such as India, Java, Sumatra, the West Indies, Brazil, Vietnam, and Madagascar. Cinnamon is a major product of the Seychelles, an archipelago located east of mainland Africa [2]. Secondary sources cite that in 2006, 90% of the world's cinnamon was produced in Sri Lanka, followed by China, India, and Vietnam.

Explanation of Columns Heads in Table 3

1	2	3	4	5	6	7	8	9	10
Condition	Study design	First author, year	N	Statistically significant?	Quality of study 0-2 = poor 3-4 = good 5 = excellent	Magnitude of benefit	Absolute risk reduction	Number needed to treat	Comments

Condition

- Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include:

- Randomized controlled trial (RCT): An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- Equivalence trial: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- Before and after comparison: A study that reports only the change in outcome in each group of a study and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.

TABLE 3. Evidence table

Condition treated (primary or secondary outcome)	Evidence/study type	First author, year	N (participants)	Statistically significant results?	Quality of study: 0-2 = poor 3-4 = good 5 = excellent	Magnitude of benefit (how strong is the effect?)	Absolute risk reduction	Number of patients needed to treat for one outcome	Comments
Antioxidant	RCT	Roussel, 2009	22	Yes	2	Medium	NA	NA	Study was conducted in overweight or obese individuals with impaired fasting glucose. No apparent between-groups analysis.
Bacterial infection	Systematic review	Dugoua, 2007	1 trial	NA	NA	Small	NA	NA	One study was a case report (one patient). Chronic salmonellosis.
Candidiasis	Systematic review	Dugoua, 2007	1 trial	NA	NA	Small	NA	NA	One study was a pilot study.
Candidiasis	Pilot study	Quale, 1996	5	No	NA	NA	NA	NA	Pilot study, unblinded, small sample size.
Candidiasis	RCT	Cao, 1993	61	Yes	1	Large	NA	NA	Statistically significant ($p < .05$), but study design and methods poorly described.
Diabetes	Meta-analysis	Baker, 2008	5 trials; 282 participants	No	NA	NA	NA	NA	Patients with type 1 or type 2 diabetes.
Diabetes	Systematic review	Dugoua, 2007	3 trials	NA	NA	Mixed results	NA	NA	Patients with type 2 diabetes.
Diabetes	Systematic review	Kleefstra, 2007	5 human trials	NA	NA	NA	NA	NA	Authors conclude that cinnamon is not effective for improvements in glycemic control.
Diabetes	Systematic review	Pham, 2007	3 trials	NA	NA	NA	NA	NA	Authors conclude that cinnamon may have modest effects in lowering plasma glucose levels.

Diabetes	Systematic review	Nahas, 2009	5 trials	NA	NA	NA	NA	NA	One trial not randomized, one trial investigated adolescents with type 1 diabetes. Other three were RCTs. FBG level reduction in two of three trials.
Diabetes (insulin potentiation)	RCT	Wang, 2007	15	Yes	Medium	NA	NA	NA	Women with polycystic ovary syndrome.
Diabetes	RCT	Altschuler, 2007	72	No	NA	NA	NA	NA	Adolescents with type 1 diabetes.
Diabetes	RCT	Blevins, 2007	77	No	NA	NA	NA	NA	Patients with type 2 diabetes.
Diabetes	RCT	Mang, 2006	79	Yes	Small	NA	NA	NA	Patients with diabetes type 2. Reduced fasting plasma glucose concentration.
Diabetes	RCT	Vanschoonbeek, 2006	25	No	NA	NA	NA	NA	Small sample size, limited collective, inadequate description of blinding, 1500 mg of cinnamon daily.
Diabetes	RCT	Suppattiporn, 2006	60	No	NA	NA	NA	NA	Patients with type 2 diabetes single blind.
Diabetes	RCT	Khan, 2003	60	Yes	Small	NA	NA	NA	Unblinded, no information on standardization of dosing, 1, 3, or 6 g of cinnamon daily.
Diabetes	RCT	Crawford, 2009	109	Yes	Small	NA	NA	NA	Unblinded, 1 g daily cinnamon capsules for 90 days.

(Continued on next page)

TABLE 3. Evidence table (Continued)

Condition treated (primary or secondary outcome)	Evidence/study type	First author, year	N (participants)	Statistically significant results?	Quality of study: 0-2 = poor 3-4 = good 5 = excellent	Magnitude of benefit (how strong is the effect?)	Absolute risk reduction	Number of patients needed to treat for one outcome	Comments
Diabetes	RCT	Solomon, 2007	7	Yes	1	Small	NA	NA	5 g vegi-capsulated micronized cinnamon spice (obtained from the <i>C. cassia</i> plant; Everythingcinnamon.com, Essex, UK). No blinding, randomization method unclear.
<i>H. pylori</i> infection	Systematic review	Dugoua, 2007	1 trial	NA	NA	None	NA	NA	Included one unblinded pilot study (Nir et al., 2000).
<i>H. pylori</i> infection	Systematic review	Martin, 2003	1 trial	NA	NA	NA	NA	NA	Included controlled trial (Nir et al., 2000).
<i>H. pylori</i> infection	Controlled trial	Nir, 2000	23	No	NA	NA	NA	NA	Pilot study, unblinded; 40 mg cinnamon extract daily.
Insect repellent	Controlled clinical trial	Chang, 2006	4	Mixed	NA	Mixed	NA	NA	Repellency of trans-cinnamaldehyde, cinnamyl alcohol, and cinnamon oil cream against female <i>Aedes aegypti</i> tested using different bioassays.
Metabolic syndrome (coronary heart disease)	RCT	Ziegenfuss, 2006	22	Yes	3	Small	NA	NA	Cinnulin PF [®] , 250 mg twice daily.

- Case series: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- Case-control study: A study in which patients with a certain outcome are selected and compared with similar patients (without the outcome) to see whether certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the CAM literature.
- Cohort study: A study which assembles a group of patients with certain baseline characteristics (e.g., use of a drug) and follows them forward in time for outcomes. This study design is not common in the CAM literature.
- Meta-analysis: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone, but in aggregate, can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- Review: An author's description of his or her opinion based on personal, nonsystematic review of the evidence.
- Systematic review: A review conducted according to prespecified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

First Author, Year

- Identifies the study being described in a row of the table.

N

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. *N* includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts who are not included in the analysis are considered to be weaker evidence of efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

Statistically Significant?

- Results are noted as being statistically significant if a study's authors report statistical significance or if quantitative evidence of significance is present (such as *p* values). P = pending verification.

Quality of Study

- A numerical score between 0 and 5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is

TABLE 4. Jadad score calculation.

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double-blind?	0/1
Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.).	0/−1
Deduct one point if the study was described as double-blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double-dummy).	0/−1

based on a well-established, validated scale developed by Jadad et al. [206]. This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the “Evidence Discussion” section).

- A Jadad score is calculated using the seven items presented in Table 4. The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant, “NA” for “not applicable” is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:
 - large if >1 SD,
 - medium if 0.5–0.9 SD,
 - small if 0.2–0.4 SD
- In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the SD of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled SD (Effect size = $[\text{Mean treatment} - \text{Mean placebo}]/\text{SD}_p$).

Absolute Risk Reduction

- This describes the difference between the percentage of people in the control/placebo group experiencing a specific outcome (control event rate) and the percentage of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, absolute risk

reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ($[\text{Control event rate} - \text{Experimental event rate}]/\text{Control event rate}$). Many studies do not include adequate data to calculate the ARR, in which cases “NA” is entered into this column. P = pending verification.

Number Needed to Treat

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the AAR into 1 (1/ARR). P = pending verification.

Comments

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, no intention to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc.). More detailed description of studies is found in the “Evidence Discussion” section.

EVIDENCE DISCUSSION

Allergic Rhinitis

- **Summary:** Cinnamon has demonstrated antiallergic properties in in-vitro study [342]. Based on one randomized, double-blind, placebo-controlled trial, a combination product including *C. zeylanicum*, *Malpighia glabra*, and *Bidens pilosa* has demonstrated reduced allergic nasal symptoms in patients with allergic rhinitis [93]. More well-designed trials are needed before a firm conclusion can be made.
- **Evidence (combination study not included in Table 3):** Corren et al. conducted a randomized controlled crossover trial to examine the effects of a combination product including *C. zeylanicum*, *Malpighia glabra*, and *Bidens pilosa* for the reduction in nasal symptoms in patients with seasonal allergic rhinitis [93]. Twenty subjects were randomized to receive the combination botanical product (CBP) including *C. zeylanicum*, *Malpighia glabra*, and *Bidens pilosa* (two tablets three times per day), 10 mg of loratadine once a day in the morning, or a placebo. The outcome was a nasal symptom score (NSS). The researchers assessed nasal lavage fluid for tryptase, prostaglandin D2, leukotriene E4 concentrations, and inflammatory cells. The CBP reduced NSS compared with placebo ($p = .034$). CBP prevented the increase in prostaglandin D2 release; the placebo and loratadine did not have this effect. Tryptase or leukotriene E4 release or inflammatory cell infiltration was not affected by the treatments. No adverse or toxic effects were reported. One of the major limitations of the study is that it employs a combination product. It is therefore difficult to deduce the effects of cinnamon on allergic nasal symptoms alone. It is also unclear as to who sponsored the study.

Angina

- **Summary:** The use of cinnamon for bacterial angina has been reviewed [512]. However, well-designed trials are needed before a firm conclusion can be made.
- **Meta-analysis (meta-analysis of combination studies, not included in Table 3):** Wang et al. conducted a meta-analysis to evaluate the safety and efficacy of compound salvia pellet (CSP; consisting of *Salvia miltiorrhiza*, *Panax notoginseng*, and *C. camphora*) compared with nitrates for the treatment of chronic stable angina [512]. A search was performed of MEDLINE, EMBASE, BA, Chinese Biomedical Database (CBM), and Chinese Cochrane Centre Controlled Trials Register (1994–2004). Regardless of language and publication status, 27 RCTs ($n = 3,722$) were isolated. The quality of the methodology of the trials, assessed by the Jadad scale, was determined to be suboptimal. One trial, however, reached a score of three points (quality = good). Pooled results indicated that, compared with nitrates, CSP treatment improved angina symptoms (RR = 1.13, 95% confidence interval [CI]: 1.07–1.20) and improved electrocardiogram (ECG) results (RR = 1.39, 95% CI: 1.28–1.50). Compared with nitrates, patients treated with CSP evinced a decreased percentage of adverse events (2.4% vs. 29.7%). The authors conclude that CSP has a significant, positive effect on angina symptoms and ECG results and has few adverse events. A limitation of the meta-analysis is that it analyzes results from trials studying a combination product; thus, the positive effect of cinnamon alone in the treatment of angina is unclear. The quality of the methodology of the various studies was suboptimal. The authors assert that outcome measures should be expanded to include other endpoints, including mortality and quality of life.

Antioxidant

- **Summary:** Cinnamon has been suggested as an antioxidant in various studies and reviews [106, 115, 175, 187, 236, 272, 275, 286, 308, 318, 366, 455, 491] due to the high antioxidant content of cinnamon bark [115]. Based on one randomized, double-blind, placebo-controlled trial, a dried aqueous extract of cinnamon (Cinnulin PF[®]) has been shown to improve the antioxidant status of overweight or obese individuals with impaired fasting glucose [411]. More well-designed trials are needed before a firm conclusion can be made.
- **Evidence:** Roussel et al. conducted an RCT to examine the effects of a dried aqueous extract of cinnamon (Cinnulin PF[®]) on the antioxidant status of overweight or obese individuals with impaired fasting glucose [411]. Twenty-two subjects with body mass index (BMI) ranging from 25 to 45 with impaired fasting blood glucose (FBG) received capsules containing 250 mg of an aqueous extract of cinnamon (Cinnulin PF[®]) or placebo two times per day for 12 weeks. Primary outcome measures included plasma malondialdehyde (MDA) concentrations, plasma antioxidant status (ferric reducing antioxidant power [FRAP] assay), erythrocyte Cu–Zn superoxide (Cu–Zn SOD) activity, and erythrocyte glutathione peroxidase (GPx) activity. Plasma antioxidant status and plasma SH increased, while plasma MDA levels decreased in subjects receiving the cinnamon extract. A positive correlation was also observed between MDA and plasma glucose ($r = 0.74$, $p = .014$). A lack of discussion regarding randomization or

blinding methods limits the usefulness of this study. Furthermore, there is a lack of apparent between-groups analyses and a lack of detailed information about study withdrawals. Integrity Nutraceuticals International (Spring Hill, TN, USA) also partially funded the study and supplied the placebo and cinnamon extract capsules used in the study.

Bacterial Infection

- **Summary:** Preliminary study suggests that cinnamon may treat bacterial infections, including chronic salmonellosis. The use of cinnamon for bacterial enteric infections has been reviewed [410]. However, well-designed trials are needed before a firm conclusion can be made.
- **Systematic reviews:** Dugoua et al. conducted a systematic review to examine the usefulness of common (*C. verum*, *C. zeylanicum*) and cassia (*C. aromaticum*) cinnamon in various medical conditions [121]. The authors searched nine electronic databases. One pharmacological study on antioxidant activity and seven clinical studies, including chronic salmonellosis (one case study), were found [409]. The authors conclude that common cinnamon showed weak-to-very weak evidence of efficacy in treating chronic salmonellosis.
- **Studies of lesser design quality (not included in the Table 3):** Rosti et al. report on an exclusively breastfed infant (4 months of age) with acute diarrhea [409]. After consuming raw seafood, the mother developed emesis and diarrhea. *S. enteritidis* was identified in the stool of both the mother and the infant; symptoms resolved after a few days. Stool samples from the mother tested negative for *Salmonella* spp. The infant became a chronic carrier of *S. enteritidis*. Upon the recommendation of a natural remedy expert, the mother fed the infant ground cinnamon bark in homogenized fruit 3–4 times a day. One month later, stool samples of the infant tested negative for *S. enteritidis*; repeat tests 2 and 3 months later were also negative.

Candidiasis

- **Summary:** Cinnamon has been found to have activity against fluconazole-resistant and -susceptible *Candida* isolates in in-vitro studies [393]. Preliminary human studies have yielded mixed results [55, 393]. Further clinical trials may be necessary to determine the usefulness of cinnamon for the treatment of mucosal candidiasis.
- **Systematic reviews:** Dugoua et al. conducted a systematic review to examine the usefulness of common (*C. verum*, *C. zeylanicum*) and cassia (*C. aromaticum*) cinnamon in various medical conditions [121]. The authors searched nine electronic databases. One pharmacological study on antioxidant activity and seven clinical studies, including one study on oral candidiasis in HIV, were found [393]. The authors conclude that common cinnamon showed weak-to-very weak evidence of efficacy in treating oral candidiasis in HIV patients.
- **Evidence:** Quale et al. conducted a pilot study in five patients with HIV infection and oral candidiasis to investigate the activity of cinnamon (*C. zeylanicum*) against fluconazole-resistant and -susceptible *Candida* isolates [393]. All included patients had pseudomembranous candida infection confirmed by culture.

Patients were given eight lozenges of cinnamon candy no. 1 daily. The commercially available extract was administered for 1 week. No adverse effects were reported. No toxic effects were reported. There were no dropouts. No interactions were reported. Improvement in oral candidiasis served as the outcome measure. Three of the five patients showed improvement in their oral candidiasis (no further details given). Limitations of this study include that it was neither randomized nor blinded and the sample size was very small.

- Cao et al. conducted an RCT to examine the effectiveness of a cortex cinnamon solution in the prevention and treatment of oral candidiasis in hospitalized patients who were likely to receive prolonged and aggressive treatment with antibiotics due to single- or multiple-organ failure [55]. Subjects were randomized to two groups: treatment ($N = 34$) or placebo ($N = 27$). The results (no outbreaks vs. 21 outbreaks in placebo group) were statistically significant ($p < .05$). In-vitro laboratory tests suggested that the cinnamon solution was efficacious in suppressing cell growth. In the discussion, however, the authors indicated that cinnamon solution was used to treat oral candidiasis infection in subjects in the placebo group. It was unclear with regard to whether the use of cinnamon solution was implemented during or after the study, which would have important implications in the validity of the study and interpretation of the results. Although the results were statistically significant, the study design and statistical methods were poorly and insufficiently described and information pertaining to the duration of the study was lacking.

Diabetes

- **Summary:** Based on human and animal study, cinnamon has been used to control blood sugar [6, 13, 33, 69, 121, 229, 309, 378, 474, 510]. However, results have not been consistent, and various human trial have found that cinnamon did not significantly alter A1C, FBG, or lipid parameters in patients with type 1 or type 2 diabetes [22, 242]. More research on the proposed health benefits of cinnamon supplementation is warranted.
- **Preclinical studies:** The insulin-sensitizing effect of cinnamon was established in in-vitro cell line studies with adipocytes as well as in in-vivo animal studies [29, 41, 200, 208, 228, 252, 271, 367]. The first published in-vivo study on cinnamon supplementation in humans reported a substantial reduction in fasting serum glucose concentration and improvement in blood lipid profile in patients suffering from type 2 diabetes [229].
- **Meta-analysis:** Baker et al. conducted a meta-analysis of RCTs of cinnamon to better characterize its impact on glucose and plasma lipids [22]. A literature search (through July 2007) was conducted; studies examining the effects of on A1C, FBG, or lipid parameters were included. Five prospective RCTs ($N = 282$) were identified [13, 33, 229, 309, 510]. Upon meta-analysis, the authors conclude that the use of cinnamon did not significantly alter A1C, FBG, or lipid parameters in patients with type 1 or type 2 diabetes.
- **Systematic reviews:** Dugoua et al. conducted a systematic review to examine the usefulness of common (*C. verum*, *C. zeylanicum*) and cassia cinnamon (*C. aromaticum*) in various medical conditions [121]. The authors searched

- nine electronic databases. One pharmacological study on antioxidant activity and seven clinical studies, including three randomized clinical trials on type 2 diabetes, were found [229, 309, 510]. The authors conclude that two of the three randomized clinical trials on type 2 diabetes provided strong scientific evidence that cassia cinnamon demonstrates a therapeutic effect in reducing FBG by 10.3%–29%; the third clinical trial did not observe this effect. Cassia cinnamon, however, did not have any effect in lowering glycosylated hemoglobin (HbA1c).
- Kleefstra et al. conducted a systematic review to identify published studies evaluating the effects of cinnamon on glycemic control [242]. The authors searched the MEDLINE database using the search terms (alone and in combination): cinnamon, diabetes mellitus, HbA1c, and glucose. Several animal studies and five randomized placebo-controlled trials in humans were found. Beneficial effects of cinnamon on fasting plasma glucose were observed in patients with type 2 diabetes in one placebo-controlled trial. No effects were observed on HbA1c in any of the studies. Cinnamon was not found to have any effect in patients with type 1 diabetes. The authors conclude that based on available evidence, cinnamon does not appear to have any beneficial effects on glycemic control.
 - Pham et al. conducted a systematic review to identify published studies evaluating the effectiveness of cinnamon in patients with type 2 diabetes [378]. The authors conducted a literature search, limited to English-language human studies, using MEDLINE (1966–August 2006), EMBASE (1980–August 2006), International Pharmaceutical Abstracts (1970–August 2006), and the Iowa Drug Information Service (1966–August 2006). References from articles and clinical trials were reviewed for additional sources; no abstracts were reviewed. Two prospective, randomized, double-blind, placebo-controlled, peer-reviewed clinical trials and one prospective, placebo-controlled, peer-reviewed clinical trial that evaluated the efficacy of cinnamon supplementation in patients with type 2 diabetes were identified; a total of 164 patients were involved in these trials [229, 309, 510]. In two of the studies, cinnamon was reported to lower blood glucose levels in small patient samples, while one trial showed no significant difference. The authors conclude that cinnamon may have a modest effect in lowering plasma glucose levels in patients with poorly controlled type 2 diabetes.
 - Nahas et al. conducted a review of the clinical evidence from human clinical trials that supports the use of integrative medicine interventions for the improvement in glycemic control in individuals with type 2 diabetes mellitus [344]. MEDLINE (January 1966–August 2008) and EMBASE (January 1966–August 2008) were searched using the search term “type 2 diabetes” in combination with each of the following terms for specific therapies: cinnamon, fenugreek, gymnema, green tea, fibre, momordica, chromium, and vanadium. Cinnamon improved FBG. Its effects on HbA(1c), however, were unknown. The authors conclude that further research on cinnamon is warranted.
 - **Evidence:** Wang et al. conducted a randomized, double-blind, placebo-controlled trial to examine the ability of cinnamon extract to reduce insulin resistance in women with polycystic ovary syndrome (PCOS) [514]. Fifteen women with PCOS were randomized to daily oral cinnamon (one capsule containing 333 mg of cinnamon extract, three times daily) or placebo for 8 weeks. Patients with diabetes, hyperprolactinemia, thyroid disorders, and hypertension were

excluded. Comparisons of post-treatment to baseline insulin sensitivity indices using fasting and 2-hr oral glucose tolerance tests showed significant reductions in insulin resistance in the cinnamon group but not in the placebo group. This was a well-designed study complete with descriptions of randomization, blinding methods, and study withdrawals.

- Altschuler et al. conducted a randomized, double-blind, placebo-controlled trial to determine the effect of cinnamon on glycemic control in adolescents with type 1 diabetes [13]. Seventy-two adolescent type 1 diabetic subjects were treated in an outpatient setting with cinnamon (1 g daily) or an equivalent-appearing placebo for 90 days. No statistically significant differences in final A1C (8.8 vs. 8.7, $p = .88$), change in A1C (0.3 vs. 0.0, $p = .13$), total daily insulin intake, or number of hypoglycemic episodes were observed between the cinnamon and the placebo group. The authors conclude that cinnamon is not effective in improving glycemic control in adolescents with type 1 diabetes. This study was well designed, although randomization methods were not described.
- Blevins et al. conducted a randomized, double-blind, placebo-controlled trial to examine the effect of cinnamon on glucose and lipid levels in non-insulin-dependent type 2 diabetes [33]. Seventy-seven individuals with type 2 diabetes were enrolled; 17 were excluded. Therefore, 60 patients were randomized to receive 500 mg of cinnamon (*C. cassia*) or placebo (wheat flour) two times daily for 3 months. Fasting glucose, cholesterol (total, low-density lipoprotein [LDL], and HDL), triglyceride, and insulin levels were measured at each visit; no significant changes were observed for any measure at any time point (from baseline to 3 months or from baseline to 1 and 2 months). A lack of discussion regarding randomization or blinding methods limits the usefulness of this study.
- Mang et al. conducted a randomized, double-blind, placebo-controlled trial to determine whether an aqueous purified cinnamon extract improves glycosylated HbA1c, fasting plasma glucose, total cholesterol, LDL, HDL, and triglyceride concentrations in patients with type 2 diabetes [309]. Seventy-nine patients with type 2 diabetes, not on insulin therapy but treated with oral antidiabetics or diet, received a cinnamon extract (equivalent to 3 g of cinnamon powder per day) or a placebo capsule three times a day for 4 months. There was a greater reduction in the cinnamon group (10.3%) than in the placebo group (3.4%) when pre- and post-intervention fasting plasma glucose levels were compared. No significant effects were observed for HbA1c or lipid profiles. Observed decreases in plasma glucose correlated with baseline concentrations; therefore, individuals with higher initial plasma glucose levels may have received more benefit from cinnamon supplementation. No adverse effects were observed. The authors conclude that cinnamon extract may have a moderate effect in reducing fasting plasma glucose concentrations in diabetic patients with poor glycemic control. A lack of discussion regarding randomization or blinding methods limits the usefulness of this study.
- Vanschoonbeek et al. conducted a randomized, placebo-controlled trial of 25 postmenopausal patients to investigate the effects of cinnamon supplementation on insulin sensitivity or glucose tolerance and blood lipid profile in patients with type 2 diabetes [510]. Postmenopausal women diagnosed with type 2 diabetes were included. Exclusion criteria were impaired liver or renal function,

- cardiovascular disease, and exogenous insulin therapy. All subjects were using either oral blood glucose-lowering agents or diet only. The subjects received either 1,500 mg of cinnamon (*C. cassia*) or 1,500 mg of a placebo daily. The cinnamon was consumed for 6 weeks. One capsule (500 mg) was to be ingested at each meal. No information is given concerning standardization of the drug. No allergies or adverse effects were reported. No toxic effects were observed. No dropouts were mentioned. No interactions were observed. Outcome measures were whole-body insulin sensitivity or oral glucose tolerance after 2 and 6 weeks of supplementation. In addition, glycosylated HbA1c and blood lipid profiles were determined. During the intervention period, there were no interactions for plasma HbA1c, fasting glucose, insulin concentrations, or fasting blood lipid concentrations ($p > .05$). Limitations of the study include inadequate description of blinding or randomization and withdrawals, as well as a small sample size and a limited patient collective, which may have allowed for the introduction of bias.
- Suppakitorn et al. conducted a randomized, single-blind, placebo-controlled trial to investigate the antidiabetic effect of cinnamon cassia powder in type 2 diabetic patients [474]. Sixty type 2 diabetic patients were randomized to receive either 1.5 g daily of cinnamon cassia powder or placebo for 12 weeks in combination with current treatments (metformin or sulfonylureal) for both groups. Measures of efficacy included HbA1c fasting plasma glucose, lipid profile, blood urea nitrogen (BUN), creatinine, liver function test, and adverse effects. After a 12-week treatment period, HbA1c decreased similarly in both groups. However the proportion of patients achieving HbA1c $\leq 7\%$ was greater in patients receiving cinnamon compared with those receiving placebo, although this was not statistically significant. No significant between-groups differences were observed for lipid profile or fasting plasma glucose, except for serum glutamic oxaloacetic transaminase (SGOT) activity, from 27.1 (8.75) to 22.1 (5) in the cinnamon group and 24.08 (8.5) to 23.63 (8.88) in the placebo group ($p = .001$). Limitations of the study include inadequate description of blinding or randomization and withdrawals.
 - Khan et al. conducted a randomized, placebo-controlled trial of 60 patients (30 men, 30 women) to determine whether cinnamon improves blood glucose and triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol levels in patients with type 2 diabetes [229]. Selection criteria for the study included the following for patients with type 2 diabetes: age > 40 years, not on insulin therapy, not taking medicine for other health conditions, and FBG levels between 7.8 and 22.2 mmol/L (140–400 mg/dL). All subjects were taking sulfonylurea drugs, i.e., glibenclamide; medications did not change during the study. The subjects were randomly divided into six groups. Groups 1, 2, and 3 consumed 1, 3, and 6 g of cinnamon daily, respectively, and Groups 4, 5, and 6 were given placebo capsules corresponding to the number of capsules consumed for the three levels of cinnamon consumed by Groups 1, 2, and 3. The cinnamon was consumed for 40 days followed by a 20-day washout period. No information is given concerning standardization of the drug. No allergies or adverse effects were reported. There were also no problems with compliance or those associated with the consumption of ≤ 6 g of cinnamon per day. No toxic effects were observed. There were no dropouts. No interactions were observed. Outcome measures were the reduction in blood glucose, triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol

levels. After 40 days, all three levels of cinnamon reduced the mean fasting serum glucose (18%–29%) and triglyceride (23%–30%), LDL cholesterol (7%–27%), and total cholesterol (12%–26%) levels ($p < .05$ for each). No significant changes were noted in the placebo groups. Changes in HDL cholesterol were not significant. Limitations of the study include inadequate description of standardization of dosing, blinding, or randomization and withdrawals, as well as failure to conduct an intention-to-treat analysis and lack of dietary standardization.

- Crawford conducted an RCT comparing treatment with cinnamon plus usual care to usual care alone for lowering HbA1c in patients with type 2 diabetes [95]. One hundred nine type 2 diabetics (HbA1c >7.0) were randomized from three primary care clinics on an air force base. Participants were randomly allocated to a usual care (with management changes) group or usual care (with management changes) in addition to 1 g daily of cinnamon capsules for 90 days. One adverse event (rash) was reported by one individual, who withdrew from the study. There were 20 dropouts in total. Cinnamon lowered HbA1c by 0.83% (95% CI: 0.46–1.20). Usual care alone lowered HbA1c by 0.37% (95% CI: 0.15–0.59). The between-groups analysis indicated a statistically significant difference ($p < .04$). The authors concluded that in addition to usual care, taking cinnamon may be useful in lowering serum HbA1c in type 2 diabetics (HbA1c >7.0). A limitation of this study was that it was not blinded.
- Solomon and Blannin conducted a randomized, controlled crossover trial in lean healthy males ($N = 7$) to assess cinnamon's effects on glucose homeostasis [460]. The doses were as follows: 5 g of a placebo (OGTTcontrol), 5 g of cinnamon (OGTTcin), or 5 g of cinnamon taken 12 hr before the oral glucose tolerance test (OGTTcin12hpre). The 5 g vegi-capsulated micronized cinnamon spice was obtained from the *C. cassia* plant (Everythingcinnamon.com, Essex, UK). Outcome measures were total plasma glucose response and insulin sensitivity. Compared with OGTTcontrol, total plasma glucose responses were found to be lower following OGTTcin and OGTTcin12hpre ($p < .05$) [–13% and –10% for OGTTcin and OGTTcin12hpre, respectively]. The effect, however, did not reach statistical significance when comparing OGTTcin with OGTTcin12hpre ($p > .05$). Serum insulin concentration for each OGTT demonstrated a statistically significant difference from baseline ($p < .01$). There was not, however, a statistically significant main effect of the trial ($p > .05$). Limitations of the study include that randomization was not discussed and blinding was not apparent.
- **Studies of lesser design quality (not included in Table 3):** Scheidegger et al. conducted a questionnaire-based study of patients ($N = 342$) with type 1 diabetes mellitus (T1DM) [424]. In addition to insulin therapy, 48 patients (14%; 13.4% adult, 18.5% pediatric; male = 20, female = 28) used CAM. The most frequently used modalities were cinnamon, homeopathy, magnesium, and “special beverages” (mostly teas). The authors conclude that collaboration between healthcare professionals of various disciplines may provide for optimal patient care.

Eye Disorders

- **Summary:** Preliminary data suggest that a combination herbal eye drop preparation (OphthaCare) may be useful in the treatment of various ophthalmic

disorders, including conjunctivitis, conjunctival xerosis (dry eye), acute dacryocystitis, degenerative conditions (pterygium or pinguecula), and disorders in postoperative cataract patients [31]. However, well-designed trials are needed before a firm conclusion can be made.

- **Evidence (combination study not included in Table 3):** Biswas et al. conducted an uncontrolled, prospective, multicenter clinical trial in patients ($N = 100$) with varying ocular disorders [31]. Diagnosed eye disorders included acute conjunctivitis (bacterial, viral, or allergic), postoperative cataract patients, acute dacryocystitis, conjunctival xerosis (dry eye), and degenerative conditions, such as pterygium or pinguecula. OphthaCare eye drops were used in the affected eye, two drops four times daily for 15 days. The outcome measures included conjunctival reactions on an ordinal (mild, moderate, or severe) scale. The eye drop preparation contains *C. camphora*, in addition to *Carum copticum*, *Terminalia bellirica*, *Embllica officinalis*, *Curcuma longa*, *Ocimum sanctum*, *Rosa damascena*, and *Melospumapum*. Acute conjunctivitis improved in 28 of 35 cases (87.5%). Dacryocystitis improved in 15 of 20 cases (88.2%). Degenerative conditions improved in 10 of 15 cases (76.5%). Conjunctival xerosis improved in four of seven cases (66.7%). Postoperative cataracts improved in 19 of 23 cases (95%). No side-effects were noted. The authors conclude that the product may be safely prescribed. Limitations of this trial include that it used a combination product, the study was not controlled or randomized, and reasons for withdrawal were not discussed. Study methods and analyses of data were suboptimal.

H. pylori infection

- **Summary:** Based on in-vitro studies, which have shown the effectiveness of cinnamon extracts against *H. pylori* [477, 478], a pilot study was conducted in order to test the activity of an alcoholic extract of cinnamon in a group of patients infected with *H. pylori*. The cinnamon extract, at a concentration of 80 mg daily as a single agent, was ineffective in eradicating *H. pylori*. However, the combination of cinnamon with other antimicrobials, or cinnamon extract at a higher concentration, may prove useful. Further studies are warranted.
- **Systematic reviews:** Dugoua et al. conducted a systematic review to examine the usefulness of common (*C. verum*, *C. zeylanicum*) and cassia cinnamon (*C. aromaticum*) in various medical conditions [121]. The authors searched nine electronic databases. One pharmacological study on antioxidant activity and seven clinical studies, including one study on *H. pylori* infection, were found [354]. The authors conclude that there is a lack of evidence to support the use of cinnamon in *H. pylori* infection eradication.
- Many different plant extracts have been tested for in-vitro antibacterial activity. A review by Martin and Ernst critically evaluated controlled clinical trials of herbal medicines with antibacterial activity [314]. Seven clinical trials met the inclusion criteria. One clinical trial conducted by Nir et al. investigated cinnamon [354].
- **Evidence:** Nir et al. conducted a controlled trial of 23 patients (18 women, 5 men) to test the activity of an alcoholic extract of cinnamon for *H. pylori* infection [354]. Patients were eligible for the study if they had a positive *Camphylobacter* urease

test (CUT) for *H. pylori*. Patients with a bleeding duodenal ulcer or poor general condition were excluded, as well as pregnant women (or women planning pregnancy); patients using nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, bismuth preparations, alcohol, or illicit drugs; or those having used antibiotics in the preceding months. Fifteen patients (11 women, 4 men) received 40 mg of cinnamon extract; eight patients (7 women, 1 man) received placebo. The extract or the placebo was administered twice daily for 4 weeks. The concentration of the major growth inhibitory component (cinnamaldehyde) was 1.68 mg/ml. The cinnamon extract was well tolerated. Five patients reported minor side-effects. No toxic effects were observed. Seven patients were excluded from the final analysis for the following reasons: negligible count on urea breath test despite presence of bacteria (1 patient), noncompliance (3 patients), and antibiotic treatment (3 patients). No interactions were observed. The amount of *H. pylori* colonization measured by the ^{13}C urea breath test served as the outcome measure. The mean urea breath test counts in the study and control groups before and after therapy were 22.1 and 23.9 versus 24.4 and 25.9, respectively. Results were not statistically significant. This pilot study was neither randomized nor double-blind.

Insect Repellent

- **Summary:** In laboratory studies, cassia oil (*C. cassia*) sprays reduced dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*) [234]. Preliminary human [65] and laboratory [90] studies suggest that cinnamon may be useful as an insect repellent. However, well-designed trials are needed before a firm conclusion can be made.
- **Evidence:** Chang et al. conducted a controlled trial comparing the efficacy of (E)-cinnamaldehyde, cinnamyl alcohol, and DEET to repel against *Aedes aegypti* (L.) female mosquitoes [65]. An “indoor test,” a patch bioassay, and a skin bioassay were evaluated ($N = 4$). In the indoor test, a 5% cassia oil cream was compared with MeiMei[®] cream (containing citronella and geranium oils) and Repellan S[®] spray (containing 19% DEET). Incremental concentrations of the products were used, and efficacy was measured over time (up to 120 min). The cassia oil cream provided 94, 83, and 61% protection against mosquito bites at 30, 50, and 70 min post application, respectively. MeiMei[®] cream appeared to be slightly more effective than the cassia oil cream. Repellan S[®] aerosol continued to provide 91% repellency at 120 min post application. In the patch bioassay tests, at 40 min post application and exposure to the mosquitoes, (E)-cinnamaldehyde (0.153 mg cm^{-2}) provided 93% protection and DEET (0.051 mg cm^{-2}) provided 89% protection. In the skin bioassay tests, at 30 min post application, (E)-cinnamaldehyde (0.051 mg cm^{-2}) provided 87% protection against mosquito bites and DEET (0.025 mg cm^{-2}) provided 95% protection. In both bioassays, (E)-cinnamaldehyde appeared to be more effective than cinnamyl alcohol. The authors conclude that products containing cassia oil merit further study as potential insect repellents. Limitations of the study include that it was not randomized, it is unclear whether between-groups analyses were conducted in separate trials, and the study population was small ($N = 4$).

Lung Cancer

- **Summary:** Preliminary study suggests that cinnamon may be useful in the treatment of lung cancer [220]. However, well-designed trials are needed before a firm conclusion can be made.
- **Evidence (combination case study not included in Table 3):** Kamei et al. conducted a case study pertaining to the treatment of a 77-year-old female with lung cancer with a combination Chinese medicine product Ninjin Yoei To (NYT; Ren-Shen-Yang-Rong-Tang; Kotaro Pharmaceutical Co., Ltd, Osaka, Japan) [220]. In total, 15 g per day of NYT was used for 7 weeks. The dried extract contained ginseng, cinnamon bark, Japanese angelica root, astragalus root, peony root, citrus unshiu peel, rehmannia root, polygala root, atractylodes rhizome, schisanda fruit, poria sclerotium, and glycyrrhiza. Outcome measures were the tumor marker levels (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9]), yin-yang, and xu-shi scores. CEA and CA19-9 before the treatment were 14.6 ng/ml and 55.0 U/ml, respectively. At the end of the seventh week, the CEA and CA19-9 scores decreased to 11.3 ng/ml and 39.2 U/ml, respectively. Yang and shi scores were based on the following: (a) a return to a natural facial complexion from pale, (b) a return to a reddish tint on the tip of tongue, (c) easily palpable pulse, (d) disappearance of a feeling of cold in limbs, (e) a change in eyes from dull to shining, (f) marked increase in abdominal tension, (g) improvement in skin color, and (h) decreased spontaneous sweating. Before treatment, yin-yang and xu-shi scores were -5 and -12.5, respectively, and +12.5 and +22.5 at the end of the 7 weeks. The patient's cough disappeared, her appetite recovered, and an increase of 6 kg in body weight was observed. Limitations of this study are that it was a case study, thus findings are not generalizable, and that a combination product was used.

Metabolic Syndrome (Coronary Heart Disease)

- **Summary:** Preliminary study suggests that cinnamon may be useful in the treatment of features of metabolic syndrome in prediabetic subjects [558]. However, well-designed trials are needed before a firm conclusion can be made.
- **Evidence:** Ziegenfuss et al. conducted a randomized, placebo-controlled, double-blind clinical trial with two parallel groups to verify the effects of a water-soluble cinnamon extract (Cinnulin PF[®]) on FBG, SBP, and body composition (i.e., characteristics of metabolic syndrome) in patients with prediabetes [558]. Subjects ($N = 22$) were randomly assigned to treatment with Cinnulin PF[®] (two capsules of 250 mg each, twice daily) or a placebo for 12 weeks. Primary outcomes included changes in FBG, SBP, and body composition. Compared with the placebo group, the treatment group noted decreases in FBG (-8.4%: from 116.3 ± 12.8 mg/dL [pre] to 106.5 ± 20.1 mg/dL [post], $p < .01$) and SBP (-3.8%: from 133 ± 14 mmHg [pre] to 128 ± 18 mmHg [post], $p < .001$), as well as increases in lean mass (+1.1%: from 53.7 ± 11.8 kg [pre] to 54.3 ± 11.8 kg [post], $p < .002$). The authors conclude that Cinnulin PF[®] may reduce FBG and SBP and improve body composition in individuals with metabolic syndrome. The authors continue that cinnamon may reduce risk factors correlated with diabetes and cardiovascular disease.

BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

- Cinnulin PF[®] [411, 558].

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this monograph.

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