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Cinnamomum Burmannii (Nees & T. Nees) Blume: A Global Evidence Review F Phytochemistry, Preclinical Pharmacology, Clinical Investigations, and Standardised Bioactive Fractions

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Kata kunci
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Abstract

Cinnamomum burmannii (Nees & T. Nees) Blume is one of the most widely traded cinnamon species globally and an increasingly investigated botanical source for metabolic, antimicrobial, anti-inflammatory, dermatological, and gastroprotective applications. Cultivated predominantly in Indonesia and distributed across tropical Southeast Asia and southern China, C. burmannii is distinguished by its high coumarin content, chemically rich and variable phytochemistry—dominated by cinnamaldehyde, A-type proanthocyanidins, D-borneol-rich essential oil, and phenolic acids—and by the emergence of standardized bioactive fractions with clinical development. This review integrates the totality of published evidence across two parallel research streams: a broad international body of phytochemical and pharmacological work from Indonesian, Chinese, Belgian, Portuguese, and other research groups, and a focused translational program from Dexa Laboratories of Biomolecular Sciences (DLBS), comprising DLBS3233—a combined C. burmannii/Lagerstroemia speciosa fraction supported by multiple Phase II–III randomized controlled trials in prediabetes, type 2 diabetes mellitus, and polycystic ovary syndrome—and DLBS2411, a bark-derived proton pump downregulator and mucoprotector with clinical trials in GERD, peptic ulcer, and functional dyspepsia. The collective evidence demonstrates robust antidiabetic activity via α-glucosidase inhibition, insulin receptor phosphorylation, PPARγ/GLUT4 upregulation, and TRPA1/GLP-1 stimulation; antioxidant and antilipidemic effects across multiple animal and human models; broad-spectrum antimicrobial activity against foodborne pathogens, Staphylococcus aureus, Aspergillus flavus, and Malassezia furfur, with characterized molecular mechanisms; anti-inflammatory action through NF-κB/IKK suppression; wound-healing promotion via M1 macrophage inhibition; and gastroprotective dual-mechanism activity.

INTRODUCTION

Cinnamomum burmannii (Nees & T. Nees) Blume is one of the most widely traded cinnamon species in the global market, valued both as a culinary spice and as a source of pharmacologically active botanical material. It belongs to the family Lauraceae and the genus Cinnamomum, which comprises approximately 250 species distributed across tropical Asia, Australasia, and the Americas. Among the four commercially dominant cinnamon species—C. burmannii, C. verum (Ceylon cinnamon), C. cassia (Chinese cassia), and C. loureiroi (Saigon cinnamon)—C. burmannii accounts for a substantial share of the global cinnamon trade. It is cultivated predominantly in Indonesia (Sumatra) and in parts of southern China and Malaysia and has been used in Indonesian, Ayurvedic, and Chinese traditional medicine for centuries.

Scientific interest in C. burmannii has accelerated substantially since 2010, driven by global demand for evidence-based complementary therapies and by its rich phytochemical profile, which generates activity across metabolic, infectious, inflammatory, dermatological, and

gastrointestinal disease domains. C. burmannii is not simply the “affordable” cinnamon of commerce; it is pharmacologically broader and more complex than its classification as cassia-type cinnamon suggests.

Two parallel research traditions now document its pharmacology. The first is a broad international literature encompassing phytochemical characterization, in vitro and in vivo pharmacological studies, food science applications, and clinical investigations conducted by research groups in Indonesia, China, Belgium, Portugal, the United States, and elsewhere. The second is a focused translational program built on standardized bioactive fractions—DLBS3233 (a combined C. burmannii and Lagerstroemia speciosa fraction) and DLBS2411 (a bark-derived gastroprotective fraction)—developed at Dexa Laboratories of Biomolecular Sciences (DLBS, PT Dexa Medica, Indonesia), which has produced one of the most clinically advanced botanical drug development programs for this species to date.

This review synthesizes both streams comprehensively, covering botany, phytochemistry (including molecular biosynthesis), preclinical pharmacology across all major activity domains, clinical evidence through Phase III randomized controlled trials, safety and toxicology, and a critical appraisal of evidence quality across therapeutic areas. The objective is to provide an integrated global evidence map for C. burmannii as a botanical pharmaceutical candidate.

METHOD

This review employed a qualitative narrative synthesis design rather than a quantitative systematic review with meta-analysis. The qualitative approach was selected because the evidence base for Cinnamomum burmannii (Nees & T. Nees) Blume spans highly heterogeneous study types, including plant genomics and transcriptomics, in vitro enzyme and antimicrobial assays, animal pharmacology, and human clinical trials. These studies used non-comparable preparations such as crude bark extracts, essential oils, and standardized fractions (DLBS3233 and DLBS2411), as well as diverse outcome measures (e.g., IC50 values, biochemical percentage changes, histopathological scores, and HOMA-IR). As a result, statistical pooling of effect sizes across such heterogeneous data would not have produced a valid or meaningful summary estimate. A qualitative, domain-by-domain synthesis was therefore considered more appropriate and is consistent with established approaches in comprehensive botanical evidence reviews.

The review integrated two parallel streams of published evidence: (i) the broader international literature on phytochemistry, preclinical pharmacology, and clinical investigation from research groups in Indonesia, China, Belgium, Portugal, the United States, and other countries; and (ii) the focused translational program on standardized bioactive fractions developed at Dexa Laboratories of Biomolecular Sciences (DLBS, PT Dexa Medica, Indonesia). The review covered the full translational continuum, including botanical identity and traditional use, phytochemical characterization (including molecular biosynthesis), preclinical pharmacology across major activity domains, clinical evidence from Phase III randomized controlled trials (RCTs), and safety and toxicology, followed by a qualitative critical appraisal of evidence quality.

RESULTS AND DISCUSSION

Botanical Identity, Distribution, and Traditional Use

1. Taxonomy and Morphology

Cinnamomum burmannii belongs to the genus *Cinnamomum* (Schaeffer, 1760), comprising ~250 species. It is an evergreen tree (7–15 m) with aromatic bark, lanceolate to elliptic 3-veined leaves (~10 × 3.5 cm), and small yellow flowers. The inner bark — the commercial part — is reddish-brown and densely secretory. Five major leaf essential-oil chemotypes are described: borneol type, 1,8-cineole type, camphor type, terpinen-4-ol type, and cymene/cineole type; the borneol type (from Meizhou, Guangdong and parts of West Sumatra) is the most pharmaceutically studied. Synonyms include: *C. kiamis* Nees, *C. dulce* (Roxb.) Nees, *Laurus burmanni* Nees & T.Nees.

2. Distribution and Production

Native to Sumatra and Java (Indonesia) and distributed across tropical Southeast Asia (Malaysia, Philippines, southern China, Thailand, India). Commercial cultivation concentrates in West Sumatra (Kerinci district) — the global epicentre — yielding the internationally traded "Korintje" grade. China (Guangdong, Guangxi, Guizhou) produces the borneol-rich chemotype used predominantly in Chinese traditional medicine and pharmaceutical extracts. Substantial inter-provincial variation in total phenolics (82–316 mg GAE/g), flavonoids (18–96 mg QE/g), cinnamaldehyde (<2 mg/g in most *C. burmannii* vs. higher in *C. cassia*), and coumarin content has been documented across Indonesian provinces (Rahayu et al., 2022; Evaluation of antioxidant and toxicity, 2023).

3. Traditional Use

Indonesian ethnomedicine: bark decoction for diarrhoea, flatulence, cold-type weakness, dysmenorrhoea, wound care. Chinese medicine (Cortex cinnamomi): yang-deficiency patterns, cold bi syndrome (arthritis/rheumatic pain), circulatory coldness. Ayurvedic medicine: prameha (diabetes-like syndrome), vata disorders, digestive complaints. Bark powder used across South and Southeast Asia for nausea, flatulent dyspepsia, coughs, and malaria.

Phytochemistry

1. Principal Bioactive Constituents

Table 1.

Principal phytochemical classes of Cinnamomum burmannii with key references.

Class	Key Constituents	Notes / Key References
Phenylpropanoids	trans-Cinnamaldehyde, cinnamic acid, cinnamyl alcohol, 2-hydroxycinnamaldehyde, methyl cinnamate	Dominant bark oil compounds; cinnamaldehyde up to 98% of bark EO; lower in C. burmannii bark (<2 mg/g) vs. C. cassia; principal antidiabetic and antimicrobial agents (Cao et al., HPLC fingerprint)
Coumarins	Coumarin (1,2-benzopyrone), cinnamate esters	Highest coumarin content among traded cinnamons; EFSA TDI 0.1 mg/kg/day; hepatotoxic risk at high chronic doses; DLBS extracts standardised to 0.07% coumarin (MECB safety study)

Proanthocyanidins	A-type oligomers, procyanidins B2, catechin, epicatechin, flavan-3-ol heterodimers	Confirmed by LC-HRMS (Muhammad et al., 2021); catechin 51 µg/g, procyanidin B2 1,396 µg/g; primary contributors to α-glucosidase inhibition (IC50 0.50 µg/mL) in water extract (Risna et al., 2019)
Flavonoids	Kaempferol glycosides, quercetin, quercitrin, anthocyanins	Quercetin 18.76 mg/g, quercetin equivalent from Bogor bark; total flavonoid 18–96 mg QE/g across Indonesian provinces (Rahayu et al., 2022; Sandhiutami et al., 2023)
Phenolic acids	Gallic acid, protocatechuic acid, chlorogenic acid, cinnamic acid 934 µg/g, 3,4-dihydroxybenzaldehyde	Confirmed by LC-HRMS (Muhammad et al., 2021); gallic acid linked to hepatoprotective and antioxidant actions
Volatile terpenes (EO)	D-borneol (dominant in borneol-type; 28.40% in CBLEO Shi et al., 2024), camphene, α-terpineol, β-caryophyllene, linalool, 1,8-cineol, p-cymene, spathulenol	GC-MS: 32–78 volatile compounds identified (Zhang et al., 2024; Wang et al., 2025); 5 chemotypes confirmed; 6 terpene synthases (CbTPS1–7) characterised (Ma et al., 2022); MVA + MEP pathway expression profiled (Hou et al., 2023)
Other	Alkaloids, steroids, butanolides, lignans, pectin, crude fats, tannins, saponins	Secondary metabolites confirmed by qualitative phytochemical analysis (Delfira et al., 2024)

2. Molecular Biology of Terpene Biosynthesis (Recent Advances)

A significant body of Chinese molecular biology work has characterised the biosynthesis of *C. burmannii*'s essential oil at the genomic level. Ma et al. (2022, *Plant Science*) characterised six terpene synthase genes (CbTPS2–7) via RNA-seq and enzyme assays, demonstrating that CbTPS1–3 (TPS-b subfamily) produce monoterpenes, CbTPS4–6 (TPS-a) produce mixed mono/sesquiterpenes, and CbTPS7 (TPS-g) shows linalool/nerolidol synthase activity — collectively accounting for 13 monoterpenoids and 12 sesquiterpenoids in leaf EO. Hou et al. (2023, *Front Genet*) used Oxford Nanopore full-length transcriptomics across four leaf developmental stages, identifying 44 DEGs in terpenoid synthesis, with the MEP pathway dominant from stage CBS2 onward, underpinning the observed GC-MS increases in borneol, camphene, and caryophyllene with leaf maturation. A parallel study used full-length transcriptomics combined with RNA-Seq to analyse 76 terpenoid-related genes, providing a comprehensive map for directed breeding of high-borneol cultivars (MDPI Genes, 2022).

3. DLBS Fractions: Phytochemical Standardisation

DLBS3233 (C. burmannii + Lagerstroemia speciosa combined fraction): the C. burmannii component contributes A-type proanthocyanidin oligomers and cinnamaldehyde derivatives; the L. speciosa component contributes corosolic acid and ellagitannins. Together these synergise the IRS-1 phosphorylation and PPARγ/GLUT4 axis. DLBS3233 preclinical characterisation: Tandrasasmita et al. (2011, *Int J Gen Med*); Nailufar et al. (2011, *Biomed Prev Nutr*). US Patent 9,345,731 documents the preparation process.

DLBS2411 (C. burmannii bark fraction): standardised for H^+/K^+-ATPase inhibitory activity. Active constituents include phenolic acids and terpenoid compounds; mechanism fully characterised by Tjandrawinata, Nailufar, Arifin (2013, *Int J Gen Med*) and Wulandari, Tandrasasmita, Tjandrawinata (2016, *Int J Pharm Pharm Sci*). Patent held: "Cinnamomum burmanii Extract, Extraction Process and Its Use as Proton Pump Down-regulator, Enzyme Inhibitor, and Mucoprotector."

Preclinical Pharmacology

1. **Antidiabetic and Insulin-Sensitising Activity**

a. In Vitro: Enzyme Inhibition and Receptor Activation

Water extract of C. burmannii bark optimised via factorial design (temperature, concentration, time) yielded IC50 of 0.50 µg/mL for α-glucosidase inhibition and IC50 3.45 µg/mL for DPPH radical scavenging, with total phenolics 259 µg GAE/mg; optimum extract confirmed by LC-MS as A-type proanthocyanidin polymers and flavan-3-ol heterodimers (Risna et al., Biocatalysis and Agricultural Biotechnology, 2019). Cinnamaldehyde activates 3T3-L1 adipocyte IRS-1/PI3K/Akt, upregulates GLUT4 membrane translocation, and stimulates enteroendocrine TRPA1 channels to release GLP-1 (incretin mechanism).

Bahtiarsyah et al. (2023, Indonesian Biomedical Journal) demonstrated synergistic α-glucosidase inhibition when C. burmannii was combined with Aquilaria malaccensis extract, with the combination producing greater inhibition than either plant alone, supporting combinatorial phytotherapy approaches for T2DM.

b. DLBS3233: Molecular Mechanism (Preclinical)

Tandrasasmita, Wulan, Nailufar, Sinambela, Tjandrawinata (2011, *Int J Gen Med*) characterised three parallel mechanisms of DLBS3233: (1) tyrosine phosphorylation of insulin receptor substrate-1, enhancing downstream signal transduction; (2) PPARγ upregulation promoting adipocyte differentiation and insulin sensitivity; and (3) GLUT4 upregulation and membrane translocation increasing glucose uptake. Nailufar, Tandrasasmita, Tjandrawinata (2011, *Biomed Prev Nutr*) additionally demonstrated PPARδ upregulation by DLBS3233, extending the nuclear receptor mechanism. These parallel actions place DLBS3233 between a natural thiazolidinedione (PPARγ) and an insulin receptor sensitiser, without the fluid retention and weight gain of thiazolidinediones.

c. In Vivo: STZ and HFD Models

In STZ-induced (60 mg/kg) Wistar rats, cinnamaldehyde (20 mg/kg × 45 days) reduced plasma glucose by 63.3% ($p < 0.05$) with dose-dependent HbA^{1c}, TC, TG reduction and increased plasma insulin, hepatic glycogen, and HDL-C (LD^{50} 1,850 ± 37 mg/kg). Preliminary study at Universitas Muhammadiyah Prof. Dr. HAMKA (2024) found significant fasting blood glucose reduction and body weight reduction

in Sprague-Dawley STZ-T2DM rats treated with C. burmannii bark extract, with the highest dose showing significant between-group differences.

Jafar et al. (2020, Open Access Maced J Med Sci) conducted a quasi-experimental randomised pre-test study in 28 adult prediabetics in Makassar City: cinnamon stew (10 g C. burmannii + education for 14 days) vs. education alone. Fasting blood glucose (GDP) levels were significantly lower in the intervention group (Wilcoxon/Mann-Whitney analysis), supporting translational use in community health centres.

Delfira et al. (2024, Int J Research and Review) evaluated C. burmannii bark extract in a streptozotocin-induced type-1 diabetes-like rat model, confirming secondary metabolite profile (flavonoids, phenolics, alkaloids, saponins, steroids, triterpenoids) and significant blood glucose lowering activity.

2. Antioxidant Activity

DPPH, FRAP, and ABTS antioxidant assays across multiple studies consistently demonstrate strong activity. Rahayu, Hakim, Mawarni, Satriani (2022, Cosmetics) characterised Indonesian C. burmannii extraction for flavonoid content, antioxidant activity, and stability in the presence of ascorbic acid — a cosmetic formulation stability study confirming robust antioxidant properties under acidic conditions. Qarani, Husna, Yulia et al. (2023, Narra J, PMID 38454977) compared C. burmannii with Michelia champaca (both endemic Aceh plants) by GC-MS, DPPH, and tyrosinase inhibition: C. burmannii showed higher total phenolics (66.34 vs. 24.71 mg GAE/g) and flavonoids (80.52 vs. 60.20 mg QE/g), with strong antioxidant activity. In hepatoprotective models, C. burmannii ethanolic extract (125–500 mg/kg BW) normalised hepatic MDA, SOD activity, and lipid parameters in HFD + PTU-challenged Sprague-Dawley rats (Susilowati et al., Vet World, 2022, PMID 35698494).

3. Antilipidemic and Cardiovascular Effects

a. Single-Plant Studies

Sandhiutami, Iskandar et al. (2023, Open Access Maced J Med Sci) evaluated cinnamon bark extract (CBE) at 300, 400, and 500 mg/kg BW in dyslipidaemic mice (HFD-induced). After 7 days of treatment: TC decreased 20.1–35.8%, TG 4.1–12.5%, LDL 38.2–68.0%; HDL increased significantly; MDA decreased dose-dependently; SOD activity improved; bleeding time and coagulation time normalised — indicating antiplatelet aggregation activity. The 500 mg/kg BW group showed MDA reduction most effectively. CBE activity was comparable to atorvastatin on TC and LDL endpoints.

Susilowati and Setiawan (2022, *Vet World*, PMID 35698494) evaluated C. burmannii ethanolic extract in HFD + propylthiouracil (PTU) dyslipidaemic rats, demonstrating reductions in TG (all doses, $p < 0.05$), TC and LDL (125 mg/kg dose), and MDA (500 mg/kg). The 12.4% cinnamaldehyde and 15.1% transcinnamaldehyde identified in Bogor-origin bark alcohol extract, with IC50 antioxidant of 1.273 ppm, were identified as mechanistic contributors.

b. Combination Studies

Susilowati and Setiawan (2020, *Vet World*, PMID 32848317) investigated combination of *C. burmannii* and *Eleutherine palmifolia* (red onion grass, rich in quercetin) in HFD-induced hyperlipidaemic mice across five concentration ratios.

Results showed that *E. palmifolia* proportion correlated with antilipidaemic effect ($p < 0.05$), while *C. burmannii* proportion correlated with cardiac MDA reduction ($p < 0.05$) — confirming a mechanistic division: cinnamaldehyde-dominant *C. burmannii* primarily counteracts lipid peroxidation/oxidative cardiac stress, while quercetin-dominant *E. palmifolia* primarily lowers circulating lipids. The E225:C75 ratio showed the highest overall therapeutic potential.

4. Antimicrobial Activity

a. Antibacterial: Bark Extract

Shan, Cai, Brooks, Corke (2007, JAFAC) — the foundational antibacterial study: methanol branch extract at 100 µg/mL inhibited B. cereus (15.4 ± 0.3 mm zone) and S. aureus (15.7 ± 0.4 mm), with moderate activity against L. monocytogenes, E. coli, S. anatum. Principal active: cinnamaldehyde.

b. **Antibacterial: Essential Oil — Molecular Mechanism**

Shi, Lin, Cai, Chen, Zhang, Liang, Xiu, Lin, He (2024, *Int J Mol Sci*, DOI: 10.3390/ijms25053078): most mechanistically detailed antibacterial study to date. *C. burmannii* leaf EO (CBLEO; borneol 28.40%; 37 volatile compounds) against *S. aureus*: inhibition zone 28.72 mm; MIC 1.0 µg/mL; MBC 2.0 µg/mL. Dynamic time-kill, material leakage, ROS formation, protein oxidation, cell morphology (SEM), and DNA-interaction assays were conducted at doses 1/2–2×MIC over 0–24 h. CBLEO-induced oxidative stress suppressed transcription of virulence regulators RsbU, SigB, and their target genes (agrA, sarA, icaA, cidA), increasing protease production and disrupting biofilm formation. This is the first comprehensive molecular mechanism map for *C. burmannii* EO antibacterial action.

Wang, Cai, Wang, Tan, Xu, Xiong (2025, Microorganisms, DOI: 10.3390/microorganisms13061241) extended the antimicrobial scope to Malassezia furfur (cutaneous pathogen causing dandruff, pityriasis versicolor, seborrhoeic dermatitis). GC-MS identified 78 constituents in CBEO (D-borneol predominant, from steam molecular distillation after D-borneol crystallisation). MIC 0.88 mg/mL; MFC 1.75 mg/mL; 85.6% biofilm suppression at 2×MIC ($p<0.01$). Synergistic effect with ketoconazole (FICI = 0.5). Mechanism: enhanced membrane permeability → cytoplasmic leakage of proteins, nucleic acids, ions; ergosterol binding disruption (8-fold MIC increase in ergosterol-supplemented media); UPLC-confirmed dose-dependent suppression of ergosterol synthesis via squalene epoxidase inhibition. SEM revealed surface invaginations and pore structures.

c. Antibiofilm and Anti-Pseudomonas

Earlier studies documented CBEO activity against Pseudomonas aeruginosa PAO1 and S. aureus biofilm through sarA regulatory suppression and cinnamaldehyde-mediated killing of planktonic and biofilm-embedded cells (biofilm study, ResearchGate, 2015). The cinnamaldehyde-S. aureus biofilm mechanism was confirmed across multiple studies: sarA encodes a central regulatory element for virulence factors and biofilm development.

d. Antifungal: Aspergillus flavus and Aflatoxin

Liang, Lv, Xian, Luo, Zhang, Yang, Li, Zhao (2025, Foods, DOI: 10.3390/foods14040682) characterised C. burmannii leaf EO inhibition of

Aspergillus flavus and aflatoxin production: mechanisms include cell membrane disruption, ergosterol biosynthesis interference, and intracellular ROS generation — a multi-target antifungal strategy relevant to food preservation and mycotoxin control.

5. Anti-inflammatory Activity

The ethyl acetate fraction of *C. burmannii* methanol bark extract exhibits the highest anti-inflammatory activity among tested fractions via SLO inhibition assay; preparative HPLC yielded coumarin and 2-hydroxycinnamaldehyde as active principals, with 2-hydroxycinnamaldehyde IC^{50} = 60 μM (SLO inhibition). Cinnamaldehyde suppresses NF-κB by inhibiting IKK, blocking IκB degradation, reducing transcription of TNF-α, IL-1β, IL-6, COX-2, and iNOS in LPS-macrophage models. Water extract of *C. burmannii* was shown to decrease pro-inflammatory cytokine mRNAs (IL-6, IL-1β, COX-1, TNF-α) and suppress IL-8, TLR-2, TLR-4 expression (data cited in Susilowati et al., 2022). Hepatoprotection of bark ethanolic extract in Sprague-Dawley rats confirms systemic anti-inflammatory activity through MDA/SOD/GPX normalisation.

6. Wound Healing

Zhang, Lin, Cao, Xie, Yang, Liu, Xu, Cheng, Chen, Pang (2024, *Molecules*, DOI: 10.3390/molecules29092080): first systematic wound-healing characterisation of *C. burmannii* EO (borneol type; 32 main GC-MS components). Network pharmacology predicted TNF, IL-6, TP53, AKT1, VEGFA as core wound-healing targets. CCK-8 assay confirmed keratinocyte and fibroblast proliferation support in vitro. In BALB/c full-thickness 8 mm punch wound model: 20% (v/v) EO approached EGF reference performance in wound closure rate. Mechanism: M1 macrophage polarisation suppression → reduced pro-inflammatory cytokine secretion → accelerated transition from inflammatory to proliferative healing phase.

7. Gastroprotective Activity — DLBS2411

a. H+/K+-ATPase Inhibition

Tjandrawinata, Nailufar, Arifin (2013, *Int J Gen Med*): DLBS2411 decreased H^+/K^+-ATPase mRNA expression in HEK293 cells and rat gastric parietal cells in dose-dependent manner (in vitro and ex vivo). DLBS2411 was a competitive H^+/K^+-ATPase inhibitor across pH range. In indomethacin-induced and ethanol-induced gastric ulcer models: significant petechiae reduction.

b. Mucoprotective Mechanisms

Wulandari, Tandrasasmita, Tjandrawinata (2016, *Int J Pharm Pharm Sci*): DLBS2411 upregulated MUC5AC (gastric mucin 5AC) gene expression in gastric epithelial cells; stimulated COX-2/PGE^2 synthesis promoting submucosal blood flow, mucus/bicarbonate secretion, and endothelial NO formation. This dual mechanism (antisecretory + mucoprotective) is pharmacologically distinct from conventional PPIs.

c. Anti-ulcer In Vivo Models

Nailufar and Tjandrawinata (2017, *Am J Pharmacol Toxicol*): acetic acid-induced gastric ulcer in rats; DLBS2411 at 25 and 50 mg/kg BW reduced ulcer size

by 36.5% and 54.8% vs. controls; comparable to omeprazole (2 mg/kg) and sucralfate (100 mg/kg). Tjandrawinata and Nailufar (2020, *J Exp Pharmacol*, PMID 32256127): ethanol-induced ulcer model; DLBS2411 50 mg/kg BW comparable to sucralfate 100 mg/kg BW by ULI, cure ratio, lesion area, histopathology; clean haematology.

8. **Anticancer / Cytotoxic Activity**

Cinnamaldehyde induces mitochondrial-pathway apoptosis in MCF-7, HCT-116, and HeLa cell lines via caspase-3/9 activation, Bax/Bcl-2 ratio shift, and cytochrome c release. This body of work largely uses cinnamaldehyde from multiple Cinnamomum sources; C. burmannii-specific anticancer investigation remains less developed than other activity domains and warrants dedicated study.

9. **Cosmetic and Dermatological Applications**

Rahayu et al. (2022, Cosmetics) evaluated extraction and flavonoid stability for cosmetic use: C. burmannii flavonoid content and antioxidant activity are stable in the presence of ascorbic acid under acidic conditions, supporting cosmetic formulation. Priani, Nurhasanah, Suparman (2022, Res J Pharm Tech) developed an antiacne nanogel containing C. burmannii bark oil and olive oil; the nanogel system improved delivery of cinnamaldehyde's antibacterial activity against Propionibacterium acnes and Staphylococcus epidermidis, with reduced skin irritation due to olive oil co-formulation.

Peel-off facial mask formulations from C. burmannii bark extract, combining PVA and HPMC gelling agents, were evaluated for DPPH antioxidant activity and physicochemical properties — demonstrating anti-photoageing applications through radical scavenging at the dermal level.

10. **Food Science Applications**

Muhammad, Tuenter, Patria, Foubert, Pieters, Dewettinck (2021, *Food Chem*, PMID 32919354): LC-HRMS phytochemical profiling of *C. burmannii* extracts and their incorporation into white chocolate nanoparticles. Key phenolics identified: catechin 51 µg/g, epicatechin 53 µg/g, procyanidin B2 1,396 µg/g, quercitrin 13 µg/g, 3,4-dihydroxybenzaldehyde 1,138 µg/g, protocatechuic acid 228 µg/g, cinnamic acid 934 µg/g. Phenols up to 310 mg EE/g; antioxidant activity up to 260 mg TAE/g. Ultrasonic-assisted extraction superior to traditional methods.

Muhammad, Lemarcq, Alderweireldt et al. (2020, *J Food Sci Tech*): antioxidant activity and quality attributes of white chocolate incorporating *C. burmannii* EO at various concentrations; sensory, physicochemical, and antioxidant endpoints confirmed value-added functional food applications.

Zhang, Lai, Dai, Huang, Guan, Wen (2025, *Foods*, DOI: 10.3390/foods14173139): sodium alginate / gelatin / zein / gum arabic matrix combined with CBEO for biodegradable fish fillet preservation film. Demonstrated strong bacteriostatic activity (borneol + cinnamaldehyde); extended shelf life of *Squaliobarbus curriculus* filets beyond conventional methods; eco-friendly packaging alternative.

Summary of Global Preclinical Evidence

Table 2.

Summary of global preclinical and applied evidence for Cinnamomum burmannii and its fractions.

Domain	Model / Assay	Key Outcome	Key Reference(s)
Antidiabetic — α-glucosidase	In vitro, factorial optimisation	IC50 0.50 µg/mL; A-type proanthocyanidins confirmed by LC-MS	Risna et al. (2019) Biocatal Agric Biotechnol
Antidiabetic — insulin signalling (DLBS3233)	3T3-L1 adipocytes; PPARγ, GLUT4 assays	IRS-1 tyrosine phosphorylation + PPARγ/δ + GLUT4 upregulation; increased adiponectin, decreased resistin	Tandrasasmita et al. (2011) Int J Gen Med; Nailufar et al. (2011) Biomed Prev Nutr
Antidiabetic — in vivo	STZ rats; HFD mice; prediabetes (human, quasi-exp)	63.3% plasma glucose reduction (cinnamaldehyde); FBG reduction + body weight; GDP reduction in prediabetes	Muhammadiyah HAMKA (2024); Jafar et al. (2020)
Synergistic antidiabetic	In vitro α-glucosidase; STZ rats	C. burmannii + A. malaccensis synergistic; C. burmannii + Zingiber synergistic insulin increase	Bahtiarsyah et al. (2023) Inabj; combination study (2022) MMJ
Antilipidemic	HFD mice; HFD + PTU rats	TC −35.8%, LDL −68%, TG reduced; antiplatelet; cardiac MDA reduced; comparable to atorvastatin	Sandhiutami et al. (2023); Susilowati et al. (2020; 2022)
Antioxidant	DPPH, FRAP, ABTS; hepatic OS model	Strong scavenging (IC50 1.273 ppm Bogor bark); normalised GPX/SOD; phenolics 82–316 mg GAE/g	Multiple Indonesian studies; Rahayu et al. (2022); Qarani et al. (2023)
Antibacterial — EO mechanism	S. aureus; disc diffusion; MIC; ROS; SEM; transcriptomics	MIC 1.0 µg/mL; MBC 2.0 µg/mL; ROS-mediated virulence gene (sigB/agrA/sarA/icaA/cidA) suppression; biofilm disruption	Shi, Lin et al. (2024) Int J Mol Sci
Antifungal — Malassezia furfur	In vitro; SEM; UPLC ergosterol	MIC 0.88 mg/mL; 85.6% biofilm suppression; ergosterol synthesis suppressed; synergy with ketoconazole (FICI=0.5)	Wang, Cai et al. (2025) Microorganisms
Antifungal — Aspergillus + aflatoxin	In vitro; food safety	A. flavus growth + aflatoxin production inhibited; membrane disruption + ergosterol interference + ROS	Liang et al. (2025) Foods

Anti-inflammatory	SLO inhibition; LPS-macrophage; NF-κB	2-OH-cinnamaldehyde IC50 60 μM; NF-κB/IKK suppression; IL-6/TNF-α/COX-2 reduced	PMC3459454 (Al-Dhubiab 2012); Susilowati 2022
Wound healing	BALB/c punch; CCK-8; network pharmacology	Wound closure ~EGF; M1 macrophage suppression; proliferative phase acceleration	Zhang et al. (2024) Molecules
Gastroprotective (DLBS2411)	H+/K+ATPase inhibition; acetic acid / ethanol ulcer; MUC5AC qPCR	Ulcer size −54.8%; comparable to omeprazole/sucralfate; MUC5AC + COX-2/PGE2 upregulated	Tjandrawinata & Nailufar (2013; 2017; 2020); Wulandari et al. (2016)
Antiaging / cosmetic	DPPH; tyrosinase inhibition; GC-MS	Strong antioxidant; phenolics 66.34 mg GAE/g; skin application potential	Qarani et al. (2023) Narra J; Rahayu et al. (2022)
Food preservation	Fish fillet packaging; white chocolate nanoparticles	Extended shelf life; antioxidant functional food enrichment	Zhang et al. (2025) Foods; Muhammad et al. (2021) Food Chem

Clinical Evidence

1. DLBS3233 Programme — Full Clinical Summary

a. Phase I — Safety and Pharmacodynamics

Tjandrawinata, Suastika, Nofiarny (2011, *Int J Diabetes Metab*): established safety, tolerability, and insulin-sensitising pharmacodynamic effect in healthy volunteers. Negligible hypoglycaemia risk confirmed — critical differentiator from sulphonylureas enabling prediabetes indication.

b. Phase II — Prediabetes (IGT), RCT

Manaf, Tjandrawinata, Malinda (2016, *Drug Des Devel Ther*, PMID 27099473): 80 IGT adults (2-hr PPBG 140–199 mg/dL); DLBS3233 50–100 mg/day vs. placebo; 12 weeks; double-blind RCT. HOMA-IR: −27.04% ± 29.41% vs. −4.90% ± 41.27% (P = 0.013). Preserved first-phase and second-phase insulin secretion. Improved oral disposition index. Clinically significant as one of few botanical-agent RCTs in IGT population using validated IR endpoints.

c. Phase II/III — Add-on T2DM

Tjokroprawiro, Murtiwi, Tjandrawinata (2016, *J Complement Integr Med*): open prospective, T2DM inadequately controlled (HbA^{1c} >7.0%) on ≥2 OADs for ≥3 months; DLBS3233 100 mg/day add-on × 12 weeks. Significant reductions in HbA^{1c}, FBG, 1-hr PPBG, HOMA-IR; increased adiponectin (consistent with PPARγ mechanism); improved lipid profile. Safe and tolerable with metformin and other OADs.

d. Phase III — Newly Diagnosed T2DM, RCT

12-week double-blind, randomised, placebo-controlled trial; 104 newly diagnosed T2DM subjects (Acta Med Indonesiana, 2024): effective glycaemic control; effect onset from Week 6 (consistent with PPARγ/GLUT4 induction kinetics requiring adipose tissue remodelling). Safe and well-tolerated as insulin-sensitising first-line option.

e. PCOS — Three-arm Study

Hidayat, Mulyantoro, Damas, Tjandrawinata (2023, *Int J Womens Health*, PMID 37424700): randomised, double-blind, 3-arm, double-dummy, non-inferiority, controlled trial at Dr. Cipto Mangunkusumo Hospital Jakarta (RSCM). Arms: DLBS3233 alone; metformin alone; DLBS3233 + metformin combination. Primary: HOMA-IR. Secondary: glycaemic indicators, lipid profiles, reproductive parameters. DLBS3233 produced significant HOMA-IR improvement; glycaemic control from Week 6; improved lipids. Mechanistically rational for PCOS as insulin sensitiser addressing root metabolic defect (hyperinsulinaemia-driven hyperandrogenism → anovulation).

f. PCOS — Non-Inferiority vs. Metformin-XR, RCT

Hestiantoro, Permadi, Tjandrawinata, Wiweko, Ritonga et al. (2024, *Int J Fertil Steril*, PMID 39033369; NCT01733459): 2-arm, double-blind, non-inferiority RCT; 124 insulin-resistant PCOS women; DLBS3233 100 mg/day vs. metformin-XR 750 mg BID × 6 months. HOMA-IR: DLBS3233 −1.03 ± 0.50 vs. metformin-XR −1.19 ± 0.50 (difference 0.16; 95% CI −1.24, 1.56; P = 0.317) — within non-inferiority margin, though formally inconclusive. Critical finding: DLBS3233 more tolerable than metformin-XR — directly relevant to GI-intolerant PCOS patients. Both groups showed significant within-group HOMA-IR improvement.

2. DLBS2411 Programme — Full Clinical Summary

a. Intragastric Acidity Study (Healthy Volunteers)

Tjandrawinata (*Ina-JGHE*): demonstrated effective H^+/K^+-ATPase inhibitory pharmacodynamic effect on intragastric acidity in healthy volunteers — clinical translation of in vitro enzyme inhibition data. Safety confirmed.

b. Registered Phase II–III Trials

NCT05248802 — Functional dyspepsia: DLBS2411 antisecretory + mucoprotective vs. standard management.

NCT03367195 — GERD: DLBS2411 vs. standard of care; 258 subjects (129/arm); 8-week treatment; dual mechanism of acid suppression and mucosal defence.

NCT02262169 — Non-bleeding peptic ulcer healing: DLBS2411 vs. comparator; 140 subjects (70/arm); ulcer healing primary endpoint.

The GERD and peptic ulcer trials position DLBS2411 as a novel plant-derived pharmacotherapy for acid-related disorders. Its dual mechanism — anti-secretory (H+/K+-ATPase inhibition + mRNA downregulation) combined with mucoprotection (MUC5AC upregulation + COX-2/PGE2 + endothelial NO) — offers a potentially superior safety profile to long-term PPI monotherapy, which is associated with hypomagnesaemia, C. difficile predisposition, microbiome disruption, and vitamin B12 depletion.

3. **Non-DLBS Clinical Studies**

a. Prediabetes — Community Clinical Trial, Indonesia

Jafar, Qalbi, Thaha, Hadju et al. (2020, Open Access Maced J Med Sci): quasi-experimental randomised pre-test study; 28 adult prediabetics at Pampang and Antara Community Health Centres, Makassar. Intervention: cinnamon stew (10 g C. burmannii + nutrition education) × 14 days vs. education alone. Fasting blood glucose (GDP) significantly lower in intervention group (Wilcoxon/Mann-Whitney); first clinical study to demonstrate C. burmannii benefit at community health centre level in Indonesian prediabetic population.

b. Postprandial Glucose — RCT, Portugal/Indonesia

NCT05145673 (2022): 36 T2DM adults; randomised, blinded; aqueous extract C. burmannii bark (6 g/100 mL, Indonesia origin via Sucrame Portugal); single dose post-OGTT. No significant difference in postprandial iAUC ($p = 0.834$) or maximum glucose. Negative result is interpretively important: consistent with DLBS3233 clinical finding that insulin sensitisation requires chronic dosing (receptor-level adaptation) — a single acute dose does not represent the mechanism of action.

c. Prediabetes, CGM — 4-week RCT, USA

Hayward, McDougall et al. (2024, Am J Clin Nutr): crossover RCT in obese prediabetic adults using continuous glucose monitoring (CGM) × 4 weeks with C. burmannii (Indonesian cinnamon) identified as the study species. C. burmannii was noted as having among the highest polyphenol content (618 µg/mg GAE) of traded species. Species-specific CGM results provide real-world glycaemic response data for C. burmannii in prediabetes. Limitations: obesity-specific population, limited generalisability.

d. Meta-Analysis Context

Deyno et al. (2019, Complement Ther Med): meta-analysis of 16 cinnamon trials (n = 1,025 participants): significant reductions in TC, LDL-C, and TG; modest HDL increase. Species-specific subgrouping for C. burmannii not available, but given its global market dominance, the majority of 'cinnamon' used in North American and European trials is likely C. burmannii.

Comprehensive Clinical Evidence Summary

Table 3.

Comprehensive clinical evidence for Cinnamomum burmannii (DLBS and non-DLBS studies).

Study / Author (Year)	Design	n	Intervention	Key Outcome
Tjandrawinata et al. 2011 (Phase I DLBS3233)	Phase I	Healthy volunteers	DLBS3233 50–100 mg/day	Safe, negligible hypoglycaemia risk, insulin-sensitising PD confirmed
Manaf, Tjandrawinata,	DB RCT	80 IGT	DLBS3233 50–100 mg/day × 12 wks	HOMA-IR −27.04% vs. −4.90% (P=0.013); β-cell preserved; oral disposition index improved

Malinda 2016 PMID 27099473				
Tjokroprawiro, Murtiwi, Tjandrawinata 2016	Open prosp.	T2DM inadequate control	DLBS3233 100 mg/day add-on × 12 wks	HbA1c, FBG, PPBG, HOMA-IR reduced; adiponectin increased; lipids improved; safe with combination OADs
Acta Med Indones 2024	DB RCT	104 new T2DM	DLBS3233 × 12 wks	Effective glycaemic control from Week 6; safe
Hidayat, Tjandrawinata et al. 2023 PMID 37424700	3-arm DB RCT	PCOS + IR	DLBS3233 vs. metformin vs. combination	Significant HOMA-IR improvement; glycaemic control from Week 6; lipids improved; mechanistically addresses PCOS root cause
Hestiantoro, Tjandrawinata et al. 2024 PMID 39033369 (NCT01733459)	2-arm DB NI RCT	124 PCOS + IR	DLBS3233 100 mg/day vs. metformin-XR 750 mg BID × 6 months	HOMA-IR comparable to metformin-XR; non-inferiority inconclusive; DLBS3233 more tolerable
Tjandrawinata (Ina-JGHE) — DLBS2411	PD study	Healthy volunteers	DLBS2411 oral	Effective intragastric acid suppression; safe; H+/K+ATPase inhibition confirmed in humans
NCT03367195 — DLBS2411 GERD	Phase II/III RCT	258	DLBS2411 × 8 wks	Anti-secretory + mucoprotective; registered, results pending publication
NCT02262169 — DLBS2411 peptic ulcer	Phase II/III RCT	140	DLBS2411, ulcer healing endpoint	Registered trial; natural PPI alternative with cytoprotective advantage
Jafar et al. 2020 (Makassar, prediabetes)	Quasi-exp RCT	28	C. burmannii stew 10 g × 14 days	GDP significantly lower (Wilcoxon); first community-level C. burmannii prediabetes study, Indonesia
NCT05145673 2022 (T2DM, Portugal/Indonesia)	RCT blinded	36 T2DM	Aqueous extract 6 g/100 mL single dose post-OGTT	No postprandial iAUC effect (p=0.834); confirms acute single-dose is insufficient for insulin-sensitisation mechanism
Hayward et al. 2024 AJCN (USA, prediabetes CGM)	RCT crossover	Prediabetes + obesity	C. burmannii powder × 4 wks, CGM	Glycaemic response modulation by CGM; C. burmannii highest polyphenol content among traded species

Safety, Toxicology, and Regulatory Considerations

1. Preclinical Safety of Generic Extracts

MECB (methanol extract; 0.07% coumarin, 0.20% trans-cinnamaldehyde w/w): NOAEL ≥ 2,000 mg/kg in acute (14-day) and sub-chronic (28-day) Sprague-Dawley studies; no mortality, no organ/haematological abnormalities. Indonesian inter-provincial antioxidant and toxicity evaluation (2023): extracts from five Indonesian provinces

classified as relatively safe for consumption within reasonable limits; variability in coumarin content noted as requiring management.

2. **DLBS Safety Data**

DLBS3233 — acute and subchronic toxicity (Sukandar, Sigit, Adnyana, ITB, 2008 study reports); teratogenicity study: no adverse effects. Across Phase I through Phase III trials (2011–2024): no significant hypoglycaemia, no hepatic/renal/cardiac adverse effects, excellent GI tolerability (superior to metformin-XR in PCOS non-inferiority trial). DLBS2411 — acute and subchronic toxicity (Sukandar, Sigit, Adnyana, ITB, 2010 study reports): no adverse findings. Clinical intragastric acidity study: safe.

3. **Coumarin Risk Management**

C. burmannii has the highest coumarin of traded cinnamons. EFSA TDI: 0.1 mg/kg/day. At conventional culinary doses (1–6 g/day bark powder) and at DLBS therapeutic doses (50–100 mg DLBS3233; 25–50 mg/kg DLBS2411), coumarin exposure remains below TDI. German BfR has issued cautions for high-dose chronic use of cassia-type cinnamon. Long-term PPI alternative studies with DLBS2411 will need to address cumulative coumarin exposure over years. Standardised fractionation — the DLBS approach — is the scientifically sound solution to coumarin risk management without sacrificing therapeutic efficacy.

4. **Drug Interactions and Contraindications**

Contraindications: hypersensitivity to cinnamon or Peru balsam (cinnamate cross-reactivity). Contact dermatitis documented with topical application. Drug interactions: monitor for additive hypoglycaemic effect with antidiabetics (sulphonylureas, insulin) in combination with DLBS3233 at high doses. Theoretical anticoagulant interaction given antiplatelet activity; no human pharmacokinetic interaction data published for C. burmannii specifically.

Global Translational Positioning of Cinnamomum burmannii

The global significance of C. burmannii as a botanical pharmaceutical candidate rests on the convergence of three distinguishing features that are rarely found together in a single plant species.

First, high-volume commodity availability. Unlike many medicinal plants confined to small cultivation areas or protected habitats, C. burmannii is produced at scale as a global commodity (principally from Sumatra, Indonesia, and parts of southern China), with consistent supply chains, established post-harvest processing infrastructure, and multiple commercial grades available for pharmaceutical-grade extraction.

Second, chemically rich and variable phytochemistry with characterised biosynthesis. The species possesses a layered bioactive architecture — phenylpropanoids, A-type proanthocyanidins, coumarins, and a terpene-rich essential oil — with five described chemotypes and recently characterised biosynthetic gene families (CbTPS1–7). This chemical complexity generates pharmacological breadth (metabolic, antimicrobial, anti-inflammatory, gastroprotective, wound healing) that exceeds most botanicals studied for a single indication. Variability in chemotype provides an opportunity for chemotype-targeted cultivation and standardisation rather than representing a liability.

Third, the emergence of standardised fractions with clinical development. The DLBS programme demonstrates that the plant's pharmacological complexity is amenable to fractionation into defined, reproducible preparations with characterised mechanisms and clinical

efficacy. This transforms C. burmannii from a crude botanical into a platform for multiple pharmaceutical products addressing distinct clinical indications. This third feature — clinical developability — is what elevates C. burmannii above the many plants with preclinical data but no translational progress.

Comparatively, *C. verum* (Ceylon cinnamon) has a better coumarin safety profile but lower cinnamaldehyde and proanthocyanidin content, and lacks an equivalent clinical development programme. *C. cassia* has been used in more Chinese medicine clinical studies but carries similar coumarin risk and has not produced standardised fractions with equivalent RCT evidence. The global evidence reviewed here positions *C. burmannii* as pharmacologically broader and clinically more developable than either of its major commercial competitors.

Critical Appraisal: Evidence Maturity by Therapeutic Domain

A critical appraisal of evidence quality across therapeutic domains is essential for any global review. The following framework distinguishes: (A) evidence from human RCTs; (B) open or quasi-experimental human studies; (C) in vivo animal models; (D) in vitro mechanistic studies; and (E) formulation/application studies without clinical endpoints.

Table 4. Evidence maturity framework for Cinnamomum burmannii across therapeutic domains. Evidence types: A = human RCT; B = open/quasi-experimental human study; C = in vivo animal model; D = in vitro mechanistic; E = formulation/application study.

Therapeutic Domain	Evidence Type	Highest Evidence Level	Main Limitation	Translational Readiness
Antidiabetic / insulin sensitisation (DLBS3233)	A — multiple RCTs (Phase I–III)	Phase III RCT (T2DM, IGT, PCOS); non-inferiority vs. metformin	Long-term cardiovascular outcome data absent; non-inferiority in PCOS inconclusive	HIGH — registered drug product; multiple completed trials
Gastroprotective (DLBS2411)	A+D — in vitro mechanism + Phase I human PD + registered RCTs	Phase I human intragastric acidity study; Phase II/III trials registered (GERD, peptic ulcer)	Phase II/III results not yet published; long-term PPI-comparative safety data needed	MODERATE–HIGH — strong mechanism; clinical results pending
Antidiabetic — crude extracts (non-DLBS)	A+B+C+D	Small quasi-experimental community trials (Indonesia); 4-week CGM crossover RCT (USA)	Heterogeneous preparations, species confirmation, small sample sizes; single-dose acute studies uninformative	MODERATE — supportive but not sufficient; standardised fraction needed for regulatory pathway
Antilipidemic / cardiovascular	C+D	HFD-induced dyslipidaemia mouse and rat models;	No dedicated human lipid RCT for C. burmannii specifically;	MODERATE — strong preclinical; human data needed

		antiplatelet activity	species confirmation in meta-analysis absent	
Antioxidant	C+D+E	Multiple in vitro assays + hepatoprotective rat models	No dedicated clinical antioxidant outcome trial; biomarker-only endpoints	MODERATE — consistent across studies; mechanistic underpinning of other activities
Antibacterial — molecular mechanism	D	In vitro disc diffusion, MIC/MBC, transcriptomic virulence gene mapping (Shi et al., 2024)	Entirely in vitro; no clinical infection trial; food-contact application not yet regulated	MODERATE — mechanistically strong; pre-clinical stage for clinical indications
Anti-Malassezia / antifungal skin	D	In vitro MIC/MFC, SEM, ergosterol biosynthesis mapping (Wang et al., 2025)	No clinical dermatological trial; in vitro-to-skin pharmacokinetics unmapped	EARLY–MODERATE — promising mechanism; Phase I/II dermatology trial warranted
Wound healing	C+D	In vivo BALB/c full-thickness punch model + network pharmacology + CCK-8 (Zhang et al., 2024)	No clinical wound healing trial; borneol-type chemotype specific; topical formulation not optimised	EARLY–MODERATE — strong in vivo signal; clinical translation feasible
Antiaging / cosmetic	D+E	DPPH antioxidant, tyrosinase inhibition, peel-off mask formulation; nanogel antiacne	No clinical skin aging or acne RCT; regulatory cosmetic claims not validated	EARLY — formulation science mature; clinical evidence absent
Food preservation	D+E	Antimicrobial packaging film, chocolate fortification, essential oil application studies	No human food safety clinical study; food-contact regulatory status varies by jurisdiction	EARLY — application science mature; regulatory pathway needed
Anticancer / cytotoxic	D	Cell line data (MCF-7, HCT-116, HeLa) for cinnamaldehyde	Species-specific C. burmannii data limited; no animal tumour model or clinical data	EARLY — exploratory; dedicated C. burmannii programme needed

Research Gaps and Future Directions

1. **DLBS3233 long-term cardiovascular outcome RCTs.** HbA1c and HOMA-IR endpoints established; macrovascular (MACE) and microvascular outcome data over ≥2 years are the critical next step for T2DM guideline consideration.
2. **DLBS3233 vs. GLP-1 agonists and SGLT-2 inhibitors.** The TRPA1/GLP-1 mechanism and PPARγ/GLUT4 profile position DLBS3233 as a mechanistically relevant comparator to newer antidiabetic drug classes; head-to-head trials are warranted.
3. **DLBS2411 published trial results.** NCT03367195 (GERD) and NCT02262169 (peptic ulcer) should be published; long-term microbiome and safety comparisons with omeprazole/pantoprazole needed.
4. **Species-specific subgroup analyses in meta-analyses.** Given C. burmannii's market dominance, existing meta-analyses should sub-analyse C. burmannii vs. C. verum vs. C. cassia outcomes.
5. **Pharmacokinetics and pharmacogenomics.** Oral bioavailability of cinnamaldehyde and proanthocyanidins from C. burmannii preparations in humans is unmapped; CYP2A6 and PPARγ polymorphism-stratified responses for DLBS3233 would optimise personalised dosing.
6. **PCOS non-inferiority: powered confirmatory trial.** A larger (n ≥ 200), longer (≥12 months) PCOS RCT powered for formal non-inferiority vs. metformin is needed to resolve the inconclusive HOMA-IR result.
7. **Anti-Malassezia / anti-acne: clinical dermatological trials.** Wang et al. (2025) CBEO anti-Malassezia data and the antiacne nanogel (Priani et al., 2022) both merit Phase I/II clinical dermatological validation.
8. **Wound healing translation.** Zhang et al. (2024) in vivo data support topical application trials in diabetic foot ulcer management — a high-unmet-need indication in Indonesia and globally.
9. **Food preservation: regulatory pathway.** Zhang et al. (2025) fish fillet film and Muhammad et al. white chocolate data support a food-grade CBEO preservative application; safety-for-use regulatory assessment for food contact applications is needed.
10. **Geographical standardisation.** A pharmacopoeial monograph for C. burmannii bark standardised to cinnamaldehyde and coumarin content, grounded in DLBS fractionation experience and Indonesian inter-provincial data, would benefit global regulation and research reproducibility.

CONCLUSION

Cinnamomum burmannii is globally significant not because of its geographic origin but because of a convergence of three features: high-volume availability as a commodity species, a chemically rich and variable phytochemical profile that generates activity across multiple therapeutic domains, and the emergence of standardized fractions with clinical-stage development. These features distinguish it from the majority of botanicals that remain confined either to traditional use or preclinical pharmacology.

The international non-DLBS literature—spanning Indonesian, Chinese, Belgian, Portuguese, American, and other research groups—has consistently documented α-glucosidase inhibitory activity from A-type proanthocyanidins; insulin-sensitizing effects through

cinnamaldehyde-mediated IRS-1/GLUT4 signaling; antilipidemic and cardiovascular protective effects in high-fat diet (HFD) animal models; broad antimicrobial activity, including mechanistic insights into Staphylococcus aureus virulence suppression (Shi et al., 2024) and Malassezia furfur ergosterol disruption (Wang et al., 2025); anti-inflammatory activity via NF-κB/IKK suppression; wound-healing effects through M1 macrophage polarization inhibition; and applied uses in food preservation and cosmetics. The molecular biology of terpene biosynthesis has also been characterized through transcriptomic and enzymatic studies (Ma et al., 2022; Hou et al., 2023), providing a foundation for targeted breeding of pharmacologically optimized chemotypes.

Among available C. burmannii-derived preparations, DLBS3233 and DLBS2411 currently represent the most clinically advanced standardized fractions. DLBS3233 has progressed from preclinical mechanistic characterization (PPARγ/GLUT4/IRS-1 phosphorylation) through Phase I and multiple Phase II–III randomized controlled trials across three clinical indications (prediabetes, type 2 diabetes mellitus, and polycystic ovary syndrome), demonstrating consistent insulin-sensitizing effects, minimal risk of hypoglycemia, and superior gastrointestinal tolerability compared with metformin extended-release formulations. DLBS2411 has demonstrated dual-mechanism gastroprotective activity (H+/K+-ATPase inhibition and mucosal defense enhancement), supported by in vivo studies and multiple registered clinical trials. The critical appraisal framework presented in Table 4 of this review indicates that evidence maturity varies substantially across therapeutic domains, with several applications—wound healing, anti-Malassezia, anticancer activity, and food preservation—remaining at early to moderate translational stages and requiring further clinical validation.

The central scientific conclusion of this review is that C. burmannii is pharmacologically broader and more clinically developable than its commoditized classification as cassia cinnamon suggests. Its full translational potential will depend on long-term outcome trials, pharmacokinetic characterization, pharmacogenomic stratification, and strengthened international regulatory engagement—advances that are both scientifically justified and economically feasible given the plant's abundance, existing safety profile, and demonstrated clinical signals.

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