Postprint: Chemical Constituents of Cinnamomi Ramulus

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Abstract

Cinnamomi Ramulus is a traditional Chinese medicine commonly used in clinical practice. Our research group previously discovered that the ethanol extract of Cinnamomi Ramulus exhibits inhibitory activity against programmed necrosis. To further elucidate the chemical constituents of Cinnamomi Ramulus and better exploit its medicinal resources, this study investigated the 75% ethanol extract of Cinnamomi Ramulus using various methods including macroporous adsorption resin, silica gel column chromatography, Sephadex LH-20 column chromatography, and preparative high-performance liquid chromatography. This report describes the isolation of 13 monomeric compounds from the extract, whose structures were identified through spectroscopic data analysis and literature comparison as abscisic acid (1), grasshopper ketone (2), 2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (3), erythro-1,2,3-trihydroxyphenylpropane (4), 1-phenyl-1,3-propanediol (5), coumarin (6), cinnamic acid (7), p-hydroxycinnamic acid (8), o-hydroxycinnamic acid (9), o-methoxycinnamic acid (10), cinnamaldehyde (11), ferulic acid (12), and ethyl caffeate (13). Among them, compounds 1-5, 12, and 13 were isolated from Cinnamomi Ramulus for the first time.

Full Text

Preamble

Chemical Constituents of Cinnamomi Ramulus

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Abstract

Cinnamomi Ramulus is a traditional Chinese medicine commonly used in clinical practice. Our research group previously discovered that the ethanol extract of Cinnamomi Ramulus exhibits physiological activity in inhibiting programmed necrosis (necroptosis). To further elucidate its chemical constituents and facilitate the development and utilization of this medicinal resource, we investigated the 75% ethanol extract of Cinnamomi Ramulus using various methods including macroporous adsorption resin, silica gel column chromatography, Sephadex LH-20 column chromatography, and preparative high-performance liquid chromatography. This report describes the isolation and identification of 13 compounds: abscisic acid (1), grasshopper ketone (2), 2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (3), erythro-type-1,2,3-trihydroxyphenylpropane (4), 1-phenyl-1,3-propanediol (5), coumarin (6), cinnamic acid (7), p-hydroxycinnamic acid (8), o-hydroxycinnamic acid (9), o-methoxycinnamic acid (10), cinnamaldehyde (11), ferulic acid (12), and ethyl caffeate (13). Among these, compounds 1–5, 12, and 13 were isolated from Cinnamomi Ramulus for the first time.

Keywords: Cinnamomi Ramulus; 75% ethanol extract; chemical constituents; isolation; identification

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Cinnamomi Ramulus, the dried tender twigs of *Cinnamomum cassia* (Lauraceae), is a pungent and warm traditional Chinese medicine commonly used to induce sweating, relieve muscle tension, dispel cold, and alleviate pain. According to *Compendium of Materia Medica*, it "treats all wind-cold and wind-dampness conditions, joint contracture and pain, relaxes muscles and opens the interstitial spaces, suppresses liver qi, supports spleen earth, and warms yin bi syndrome." Current pharmacological research on Cinnamomi Ramulus has primarily focused on its volatile oils, with fewer studies investigating non-volatile components. Literature reports indicate that Cinnamomi Ramulus possesses various pharmacological effects including antibacterial, anti-inflammatory, antitumor, antiviral, anti-allergic, and antipyretic-analgesic activities. Necroptosis, a form of programmed cell death discovered in recent years, is closely associated with the progression of many inflammatory diseases including cancer, metabolic disorders, and neurodegenerative conditions. Inhibition of necroptosis can reduce damage from these diseases. Our group previously reported for the first time that the non-volatile extract of Cinnamomi Ramulus exhibits inhibitory activity against necroptosis. To further clarify its chemical constituents and better develop its medicinal resources, we conducted a systematic chemical investigation of the 75% ethanol extract. This report describes 13 compounds isolated from the petroleum ether and dichloromethane fractions: abscisic acid

(1), grasshopper ketone (2), 2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (3), erythro-type-1,2,3-trihydroxyphenylpropane (4), 1-phenyl-1,3-propanediol (5), coumarin (6), cinnamic acid (7), p-hydroxycinnamic acid (8), o-hydroxycinnamic acid (9), o-methoxycinnamic acid (10), cinnamaldehyde (11), ferulic acid (12), and ethyl caffeate (13). Their structures are shown in Figure 1 [Figure 1: see original paper]. Compounds 1–5, 12, and 13 were obtained from Cinnamomi Ramulus for the first time.

1 Materials and Instruments

The medicinal material was purchased on May 14, 2015, from Zhangshu, Jiangxi Province, and authenticated by Professor Lai Xuewen of Jiangxi University of Traditional Chinese Medicine as the dried tender twigs of *Cinnamomum cassia*. A voucher specimen is deposited in the herbarium of Jiangxi University of Traditional Chinese Medicine.

Instruments: Inova-600 superconducting NMR spectrometer (Varian, USA); 1525 preparative HPLC system equipped with a Lichrospher C18 preparative column (30 mm × 250 mm, 10 m) (Waters, USA); AE100 electronic analytical balance (Mettler-Toledo, Switzerland); WFH-203 (ZF-1) three-purpose UV analyzer (Shanghai Jingke Industrial Co., Ltd.).

Reagents and Materials: ODS column chromatography packing (50 m, YMC, Japan); Sephadex LH-20 (GE Healthcare, Sweden); silica gel for column and thin-layer chromatography (200 mesh, Qingdao Marine Chemical Plant). All extraction and isolation reagents were analytical grade; methanol for preparation was chromatographic grade; water was triple-distilled.

2 Extraction and Isolation

Dried Cinnamomi Ramulus (20 kg) was pulverized and extracted by cold maceration with 75% ethanol (7 days per extraction, repeated four times). The combined extracts were concentrated under reduced pressure to obtain the total crude extract. The 75% ethanol extract was dissolved in methanol, mixed with diatomaceous earth, and concentrated under vacuum before column packing. The material was sequentially extracted with petroleum ether, dichloromethane, ethyl acetate, and methanol. After solvent recovery under reduced pressure, four fractions were obtained: petroleum ether fraction (Fraction A, 260 g), dichloromethane fraction (Fraction B, 100 g), ethyl acetate fraction (Fraction C, 120 g), and methanol fraction (Fraction D, 120 g).

Fraction A (260 g) was re-extracted with methanol:water (9:1) and subjected to silica gel column chromatography (200–300 mesh) using a petroleum ether–ethyl acetate gradient (200:1 to 0:1) as eluent. Thin-layer chromatography (TLC) monitoring yielded six subfractions (A-1 to A-6). Subfraction A-6 was purified by preparative HPLC to afford compound **7** (300 mg). Subfractions A-1 and A-2 were further separated on a 300–400 mesh silica gel column us-

ing petroleum ether–ethyl acetate (200:1 to 0:1) gradient elution, followed by preparative HPLC to yield compounds **11** (6.5 mg), **10** (9 mg), and **6** (5 mg).

Fraction B (100 g) was chromatographed on a D101 macroporous adsorption resin column with an ethanol–water gradient to obtain five fractions: water eluate (B1), 30% ethanol eluate (B2), 50% ethanol eluate (B3), 70% ethanol eluate (B4), and 90% ethanol eluate (B5).

- **Fraction B2 (80 g)** was subjected to silica gel column chromatography (200–300 mesh) using a dichloromethane–methanol gradient (500:1 to 0:100) to yield eight subfractions (B2-1 to B2-8) based on TLC analysis. Subfraction B2-3 (11 g) was further separated on a 300–400 mesh silica gel column with dichloromethane–methanol (500:1 to 0:100) to give seven subfractions (B2-3-1 to B2-3-7). B2-3-1 was purified by Sephadex LH-20 column chromatography (methanol elution) and preparative HPLC to afford compounds **8** (20 mg), **9** (20 mg), and **12** (20 mg). B2-3-4 yielded compounds **1** (18.4 mg) and **5** (38 mg) after gel column chromatography and preparative HPLC. B2-3-5 was separated by combined Sephadex LH-20 and preparative HPLC to give compound **2** (33 mg). B2-3-6 and B2-3-7 were subjected to Sephadex LH-20 (methanol elution) followed by preparative HPLC to afford compounds **4** (42 mg) and **3** (10 mg), respectively.
- **Fraction B3 (85 g)** was chromatographed on silica gel (200–300 mesh) using dichloromethane–methanol (500:1 to 0:100) to yield four subfractions (B3-1 to B3-4). Subfraction B3-3 was separated on a 300–400 mesh silica gel column with dichloromethane–methanol (500:1 to 0:100) gradient elution to obtain three subfractions (B3-3-1 to B3-3-3). B3-3-2 was further purified by silica gel column chromatography, followed by combined Sephadex LH-20 and preparative HPLC, to afford compound **13** (62.5 mg).

3 Structural Identification

Compound 1 was obtained as colorless transparent crystals (methanol). HR-ESI-MS *m/z*: 263.1281 $[M-H]^-$, 527.2617 $[2M-H]^-$, indicating a molecular weight of 264. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.78 (dd, J = 16.1, 0.5 Hz, 1H, H-5), 6.24 (dd, J = 16.1, 0.4 Hz, 1H, H-4), 5.92 (m, 1H, H-8), 5.74 (s, 1H, H-2), 2.53 (d, J = 16.9 Hz, 1H, H-10b), 2.18 (d, J = 16.9 Hz, 1H, H-10a), 2.04 (d, J = 1.3 Hz, 3H, H-15), 1.93 (d, J = 1.4 Hz, 3H, H-14), 1.06 (s, 3H, H-13), 1.03 (s, 3H, H-12). ^{13}C-NMR (150 MHz, CD_3OD) δ: 18.2 (C-15), 19.8 (C-14), 22.2 (C-12), 23.3 (C-13), 41.5 (C-11), 49.3 (C-10), 79.2 (C-6), 118.2 (C-2), 125.2 (C-8), 128.0 (C-4), 135.5 (C-5), 149.7 (C-7), 165.1 (C-3), 168.0 (C-1), 199.6 (C-9). These data are consistent with literature values (Wu et al., 2012), identifying compound **1** as abscisic acid. This represents the first isolation of a sesquiterpenoid compound from Cinnamomi Ramulus.

Compound 2 was isolated as a colorless transparent oily solid (methanol). HR-ESI-MS *m/z*: 247.1309 $[M+Na]^+$, corresponding to a molecular weight of 224.

^{1}H-NMR (600 MHz, CD_3OD) δ: 5.83 (s, 1H, H-8), 4.21 (tt, J = 11.4, 4.1 Hz, 1H, H-3), 2.21 (dd, J = 4.1, 2.1 Hz, 1H, H-4a), 2.19 (s, 3H, H-10), 1.96–1.89 (m, 1H, H-2a), 1.40 (d, J = 7.3 Hz, 1H, H-2b), 1.38 (s, 6H, H-12, H-13), 1.37–1.34 (m, 1H, H-4b), 1.15 (s, 3H, H-11). ^{13}C-NMR (150 MHz, CD_3OD) δ: 211.68 (C-7), 200.98 (C-9), 120.09 (C-6), 101.29 (C-8), 72.58 (C-5), 64.54 (C-3), 50.09 (C-4), 49.88 (C-2), 37.13 (C-1), 32.42 (C-12), 30.95 (C-13), 29.47 (C-11), 26.68 (C-10). These data match literature values (Ren et al., 2013), identifying compound **2** as grasshopper ketone. This is also the first sesquiterpenoid derivative isolated from Cinnamomi Ramulus.

Compound 3 was obtained as a white powder (methanol), sparingly soluble in methanol. HR-ESI-MS m/z: 241.0728 $[M-H]^-$, indicating a molecular weight of 242. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 0.04 (dd, J = 5.4, 3.4 Hz, 1H, H-8), 3.64 (dd, J = 11.6, 5.4 Hz, 1H, H-9a), 3.71 (dd, J = 11.6, 3.4 Hz, 1H, H-9b), 7.28 (s, 2H, H-2, H-6). ^{13}C-NMR (150 MHz, DMSO-d_6) δ: 198.44 (C-7), 147.51 (C-3, C-5), 141.10 (C-4), 125.46 (C-1), 106.58 (C-2, C-6), 73.79 (C-8), 64.45 (C-9), 56.14 (C-3,5-OMe$×$2). These data are consistent with literature values (Hui et al., 2015), identifying compound **3** as 2,3-dihydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone. This compound was obtained from Cinnamomi Ramulus for the first time.

Compound 4 was isolated as a colorless transparent oily solid, readily soluble in methanol. HR-ESI-MS m/z: 191.0680 $[M+Na]^+$, corresponding to a molecular weight of 168. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.46–7.37 (m, 2H, H-5, H-9), 7.34 (dd, J = 10.4, 4.8 Hz, 2H, H-6, H-8), 7.29–7.23 (m, 1H, H-7), 4.63 (d, J = 6.3 Hz, 1H, H-3), 3.77 (td, J = 6.5, 3.8 Hz, 1H, H-1a), 3.67 (dd, J = 11.3, 3.8 Hz, 1H, H-2), 3.5 (dd, 1H, H-1b). ^{13}C-NMR (150 MHz, CD_3OD) δ: 143.46 (C-4), 129.18 (C-6, C-8), 128.53 (C-7), 128.32 (C-5, C-9), 76.77 (C-3), 76.32 (C-2), 64.48 (C-1). These data match literature values (Miao et al., 2015), identifying compound **4** as erythro-type-1,2,3-trihydroxyphenylpropane. This compound was isolated from Cinnamomi Ramulus for the first time.

Compound 5 was obtained as colorless transparent needle crystals (methanol). HR-ESI-MS m/z: 175.0730 $[M+Na]^+$, corresponding to a molecular weight of 152. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.36 (d, J = 7.2 Hz, 2H, H-2 , H-6), 7.32 (t, J = 7.2 Hz, 2H, H-3 , H-5), 7.24 (t, J = 7.0 Hz, 1H, H-4), 4.83–4.76 (m, 1H, H-1), 3.72–3.56 (m, 2H, H-3), 2.11–1.73 (m, 2H, H-2). ^{13}C-NMR (150 MHz, CD_3OD) δ: 146.56 (C-1), 129.46 (C-3 , C-5), 128.39 (C-4), 127.07 (C-2 , C-6), 72.48 (C-1), 60.24 (C-3), 42.97 (C-2). These data are consistent with literature values (Miao et al., 2015), identifying compound **5** as 1-phenyl-1,3-propanediol. This compound was isolated from Cinnamomi Ramulus for the first time.

Compound 6 was obtained as colorless transparent needle crystals (methanol). HR-ESI-MS m/z: 147.0437 $[M+H]^+$, corresponding to a molecular weight of 146 and molecular formula $C_9H_6O_2$. ^{1}H-NMR (600 MHz, CD_3OD) δ: 6.44 (d, J = 9.5 Hz, 1H, H-3), 7.96 (d, J = 9.5 Hz, 1H, H-4), 7.70–7.56 (m, 2H, H-5, H-7), 7.41–7.32 (m, 2H, H-6, H-8). ^{13}C-NMR (150 MHz, CD_3OD) δ: 162.94 (C-2), 117.72 (C-3), 145.79 (C-4), 129.60 (C-5), 125.97 (C-6), 133.32 (C-7), 117.28 (C-

8), 155.46 (C-9), 120.55 (C-10). These data match literature values (Jung et al., 2007), identifying compound **6** as coumarin.

Compound 7 was isolated as colorless transparent flaky crystals (methanol) that showed severe tailing on TLC silica plates, suggesting it is an organic phenolic acid. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.66 (d, J = 16.0 Hz, 1H, H-7), 7.59–7.53 (m, 2H, H-2, H-6), 7.40–7.36 (m, 3H, H-3, H-4, H-5), 6.47 (d, J = 16.0 Hz, 1H, H-8). ^{13}C-NMR (150 MHz, CD_3OD) δ: 170.49 (C-9), 146.47 (C-7), 135.87 (C-1), 131.54 (C-4), 130.12 (C-3, C-5), 129.31 (C-2, C-6), 119.41 (C-8). These data are consistent with literature values (He et al., 2015), identifying compound **7** as cinnamic acid.

Compound 8 was obtained as colorless transparent flaky crystals (methanol) that gave a positive ferric chloride-potassium ferricyanide reaction. HR-ESI-MS m/z: 163.0418 $[M-H]^-$, corresponding to a molecular weight of 164. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.60 (d, J = 15.9 Hz, 1H, H-7), 7.52–7.37 (m, 2H, H-2, H-6), 6.88–6.75 (m, 2H, H-3, H-5), 6.28 (d, J = 15.9 Hz, 1H, H-8). ^{13}C-NMR (150 MHz, CD_3OD) δ: 171.17 (C-9), 161.3 (C-4), 146.79 (C-7), 131.22 (C-2, C-6), 127.4 (C-1), 116.9 (C-3, C-5), 115.7 (C-8). These data match literature values (Zhu et al., 2018), identifying compound **8** as p-hydroxycinnamic acid.

Compound 9 was isolated as colorless transparent flaky crystals (methanol) that gave a positive ferric chloride-potassium ferricyanide reaction. HR-ESI-MS m/z: 163.0404 $[M-H]^-$, corresponding to a molecular weight of 164. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.96 (d, J = 16.1 Hz, 1H, H-7), 7.47 (dd, J = 8.0, 1.6 Hz, 1H, H-6), 7.28–7.15 (m, 1H, H-4), 6.91–6.73 (m, 2H, H-3, H-5), 6.55 (d, J = 16.1 Hz, 1H, H-8). ^{13}C-NMR (150 MHz, CD_3OD) δ: 171.54 (C-9), 158.34 (C-2), 142.53 (C-7), 132.66 (C-4), 130.13 (C-6), 122.81 (C-1), 120.89 (C-5), 118.88 (C-8), 117.12 (C-3). These data are consistent with literature values (Ding et al., 2016), identifying compound **9** as o-hydroxycinnamic acid.

Compound 10 was obtained as colorless transparent needle crystals (methanol). HR-ESI-MS m/z: 177.0571 $[M-H]^-$, corresponding to a molecular weight of 178 and molecular formula $C_{10}H_{10}O_3$. ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 7.08 (dd, J = 8.4 Hz, 1H, H-3), 7.40 (td, J = 7.8 Hz, 1H, H-4), 6.98 (td, J = 7.5 Hz, 1H, H-5), 7.67 (dd, J = 7.6 Hz, 1H, H-6), 7.84 (d, J = 16.1 Hz, 1H, H-7), 6.51 (dd, J = 16.1, 1.0 Hz, 1H, H-8), 12.32 (s, 1H, H-9), 3.86 (s, 3H, H-C10). ^{13}C-NMR (150 MHz, DMSO-d_6) δ: 122.44 (C-1), 157.73 (C-2), 111.72 (C-3), 131.80 (C-4), 119.17 (C-5), 128.44 (C-6), 138.75 (C-7), 120.72 (C-8), 167.81 (C-9), 55.63 (C-10). These data match literature values (Yang et al., 2010), identifying compound **10** as o-methoxycinnamic acid.

Compound 11 was isolated as a yellow oily liquid with an aromatic odor, showing a faint purple-dark spot under 254 nm UV light. Co-TLC with an authentic cinnamaldehyde standard using three different solvent systems showed identical Rf values, confirming compound **11** as cinnamaldehyde.

Compound 12 was obtained as colorless transparent needle crystals (methanol). HR-ESI-MS m/z: 193.0510 $[M-H]^-$. ^{1}H-NMR (600 MHz, CD_3OD)

δ: 7.59 (d, J = 15.8 Hz, 1H, H-7), 7.17 (d, J = 1.9 Hz, 1H, H-2), 7.06 (d, J = 8.1, 1.9 Hz, 1H, H-6), 6.81 (d, J = 8.0 Hz, 1H, H-5), 6.31 (d, J = 15.8 Hz, 1H, H-8), 3.89 (s, 3H, -OCH_3). ^{13}C-NMR (150 MHz, CD_3OD) δ: 171.28 (C-9), 150.60 (C-3), 149.49 (C-4), 146.94 (C-7), 127.96 (C-1), 124.10 (C-6), 115.74 (C-8), 116.21 (C-5), 111.80 (C-2), 56.57 (-OCH_3). These data are consistent with literature values (Rho & Yoon, 2017), identifying compound **12** as ferulic acid. This compound was isolated from Cinnamomi Ramulus for the first time.

Compound 13 was obtained as colorless transparent needle crystals (methanol) that gave a positive ferric chloride-potassium ferricyanide reaction, indicating the presence of phenolic hydroxyl groups. HR-ESI-MS m/z: 207.0657 $[M-H]^-$, corresponding to a molecular weight of 208 and molecular formula $C_{11}H_{12}O_4$. ^{1}H-NMR (600 MHz, CD_3OD) δ: 7.03 (d, J = 1.8 Hz, 1H, H-2), 6.77 (d, J = 8.2 Hz, 1H, H-5), 6.92 (dd, J = 8.2, 1.8 Hz, 1H, H-6), 7.52 (d, J = 15.9 Hz, 1H, H-7), 6.23 (d, J = 15.9 Hz, 1H, H-8), 4.20 (q, J = 7.1 Hz, 2H, H-10), 1.29 (t, J = 7.1 Hz, 3H, H-11). ^{13}C-NMR (150 MHz, CD_3OD) δ: 123.03 (C-1), 115.23 (C-2), 146.86 (C-3), 149.66 (C-4), 116.62 (C-5), 127.86 (C-6), 146.93 (C-7), 115.39 (C-8), 169.47 (C-9), 61.55 (C-10), 14.76 (C-11). These data match literature values (Zhu et al., 2018), identifying compound **13** as ethyl caffeate. This compound was isolated from Cinnamomi Ramulus for the first time.

Discussion

Cinnamomi Ramulus is a versatile traditional Chinese medicine with functions including inducing sweating, relieving muscle tension, warming the channels, and assisting yang transformation. Through long-term clinical practice, physicians of past dynasties have developed numerous classical formulas using Cinnamomi Ramulus as the principal or ministerial herb, such as Guizhi Fuling Pill, Huangqi Guizhi Wuwu Decoction, Guizhi Shaoyao Zhimu Decoction, and Baihu Jia Guizhi Decoction, for treating wind-cold dispersion, cough, and joint pain. Current chemical studies on Cinnamomi Ramulus have primarily focused on volatile oils and low-polarity components, with reported compounds mainly being small molecules dominated by phenylpropanoids, along with flavonoids, phenolic acids, and minor terpenoids and steroids.

In this study, 13 compounds were isolated from the petroleum ether and dichloromethane fractions of the ethanol extract, among which 11 were phenylpropanoids and 7 were obtained from Cinnamomi Ramulus for the first time. These results not only align with current research identifying phenylpropanoids as major chemical constituents of Cinnamomi Ramulus, but also enrich the structural diversity of its chemical components through the isolation of two sesquiterpenoids. In addition to cinnamaldehyde, which demonstrates anti-inflammatory and antiviral activities, we also obtained substantial amounts of cinnamic acid. Cinnamic acid is a natural, low-toxicity compound that effectively inhibits proliferation of human hepatoma cells and induces apoptosis, while also promoting differentiation of gastric adenocarcinoma cells, making it a potential tumor differentiation inducer. Abscisic acid,

a plant hormone isolated from Cinnamomi Ramulus for the first time in this study, can inhibit proliferation of various cancer cells and was patented as an anticancer agent in the United States in the 1970s. Ethyl caffeate exhibits anti-inflammatory, immunomodulatory, and antitumor activities as a specific inhibitor of the NF- B signaling pathway, showing promising clinical potential. Whether phenylpropanoid compounds such as abscisic acid, cinnamaldehyde, cinnamic acid, and ethyl caffeate are the principal components responsible for the inhibitory effect of Cinnamomi Ramulus on necroptosis requires further systematic investigation.

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Note: Figure translations are in progress. See original paper for figures.