PHYTOCHEMICAL AND BIOLOGICAL STUDIES ON
CINNAMOMUM GRIFFITHII

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ABSTRACT

The stem barks of *Cinnamomum griffithii* was extracted using methanol, filtered and evaporated to dryness to give 552.84 g (23.03 % weight / dry weight) crude extract. Solvent partition was performed using solvent with increasing polarities and resulted in four partitions which are hexane (8.12 g), dichloromethane (0.76 g), ethyl acetate (5.91 g) and methanol partition (10.4 g). Further purification of hexane partition and ethyl acetate partition were resulted in one pure compound (greenish crystal from H27 combined fraction) and four semi pure compounds (isolated from H15, H15b, H16, E2 and E5b). The pure compound showed the Rf value of 0.8 in chloroform-ethyl acetate (3:2) and exhibited the molecular mass of 256 g/mol corresponded to molecular formula of C15H11O4 with melting point of 195.0°C - 195.8°C. Infrared spectra showed an absorbance bands at 3390 cm⁻¹ (OH group), 1629 cm⁻¹ (C=O group), 1603cm⁻¹ (C=C aromatic) and 1300 cm⁻¹ (presence of C-O). Based on information from the mass spectrum, infrared, melting point and comparison with published data, the pure compound has been identified as pinocembrin. Meanwhile, the semi pure compounds were identified as 1, 2-dimethoxy-4-(2-propenyl)-benzene, 3-phenylmethyl-2-propanoic acid, 5-ethyl-3, 5-dimethylloxazolidione and 1, 2-benzenedicarboxylic acid. Toxicity test against larvae of *Artemia salina* was performed and hexane partition showed inhibitory activity against the larvae of *Artemia salina* with LC₅₀ value of 82.54 µg/mL.

**Keywords:** *Cinnamomum griffithii*; chromatography analyses; spectroscopy analyses; pinocembrin; 1,2-dimethoxy-4-(2-propenyl)-benzene; 3-phenylmethyl-2-propanoic acid; *Artemia salina*
ABSTRAKS

Bahagian kulit batang pokok Cinnamomum griffithii telah diekstrak dengan menggunakan pelarut metanol, dituras dan dikeringkan bagi memberikan 552.84 g (23.03 % berat kering) ekstrak kasar. Pempartisan pelarut menggunakan pertambahan kepolaran pelarut telah dijalankan dan proses ini telah menghasilkan empat partisi dengan nilai berat hasil tertentu iaitu partisi heksana sebanyak 8.12 g, partisi diklorometana sebanyak 0.76 g, partisi etil asetat sebanyak 5.91 g dan partisi metanol sebanyak 10.4 g. Pemisahan ke atas partisi heksana dan partisi etil acetat telah berjaya memisahkan satu sebatian tenu (kristal kehijauan dari fraksi H27) dan empat sebatian hampir tenu (dari fraksi H15, H15b, H16, E2 dan E5b). Sebatian tenu yang telah berjaya dipisahkan memberikan nilai R, 0.8 dalam sistem pelarut kloroform-etil asetat (3:2) dan memberikan berat molekul 256 g/mol berpadanan dengan jisim formula C17H22O3 dan takat lebunya berada dalam julat 195.0°C-195.8°C. Maklumat sinar infra merah memunjukkan penyerapan yang kuat pada frekuensi 3390 cm\(^{-1}\) (kumpulan OH), 1629 cm\(^{-1}\) (kumpulan C=O), 1603 cm\(^{-1}\) (C=C aromatik berkonjugat) dan frekuensi 1300 cm\(^{-1}\) (kumpulan C-O). Berdasarkan maklumat spektroskopi, sinar inframerah, takat lebur dan perbandingan dengan data yang pernah diterbitkan, kemungkinan besar sebatian tenu ini adalah pinosembrin. Sebatian separa tenu yang diperolehi telah dienalpasti sebagai 1, 2-dimetoksi-4-(propenil)-benzena, asid 3-fenilmetyl-2-propanoik, 5-etil, 5-dimetiloxalidiona dan asid 1,2-dibenzenakarbosilik. Ujian ketoksikan terhadap larva Artemia salina telah dijalankan dan partisi heksana telah menunjukkan kesan perencatan ke atas larva Artemia salina iaitu dengan nilai LC\(_{50}\) sebanyak 82.54 µg/mL manakala partisi-partisi lain tidak menunjukkan sebarang kesan ketoksikan.

Katakunci: Cinnamomum griffithii, analisa kromatografi, analisa spektroskopi, pinosembrin, 1,2-dimetoksi-4-(propenil)-benzena, asid 3-fenilmetyl-2-propanoik, ujian ketoksikan Artemia salina.
CHAPTER 1
INTRODUCTION

1.1 Lauraceae

The Lauraceae family is a green medium size tree found in the tropics especially in India, China, East Africa and South Asian Countries like Malaysia, Indonesia and the Philippines. It is a big family consisting of more than 32 genus and 2000 to 2500 species (Thomson, 1993; Wiart, 2000, 2002). Some of the genuses in Lauraceae family are Cinnamomum, Litsea, Aniba, Lindera, Cryptocarya and Nathaphoea (Burkill, 1966; Davies-Coleman and Revett, 1989). The members of Lauraceae family can be found in tropical rain forest and grow at various altitudes from highlands slopes to lowland forest and occurs in both marshy places and on well-drained soils. However, in latitudes with seasonal climatic conditions, they become exceedingly rare (Lawrence, 1967; Kochummen, 1989).

The Lauraceae families, which are commercially used in traditional medicine, have drawn attention by natural product chemists and medicinal clinicians as they have been used for treatment of various ailments (Burkill, 1966; Mat Salleh and Latiff, 2002). Various biologically active compounds have been isolated from the Lauraceae family for example alkaloids, terpenes, flavanoids, polyphenol, and others (Hanaraka et al., 1985; Zhang et al., 2003; Chen et al., 2005; Fang et al., 2005; Kuo et al., 2005; Lee et al., 2005; Simic et al., 2004; Wang et al., 2005). These secondary metabolite shows numerous biological activities such as anti-diabetic agent, anti-inflammatory agent, anti-tumor, anti-virus, anti-fungal, anti-helmentic activities and other biological activities.
(Hanaraka et al., 1985; Zhang et al., 2003; Yang et al., 2004; Chen et al., 2005; Fang et al., 2005; Kuo et al., 2005; Lee et al., 2005; Simic et al., 2004; Verspohl et al., 2005; Wang et al., 2005).

Some of the biologically active compounds isolated from Lauraceae family includes litseaverticillols A (1), litseaverticillols B (2), litseaverticillols C (3), litseaverticillols D (4), litseaverticillols E (5), litseaverticillols G (6) and litseaverticillols H (7) which belongs to the sesquiterpenes and were isolated by bioassay directed fractionation from the leaves of *Litsea verticillata*. All of the compounds inhibited HIV-1 replication in HOG R5 cells (Zhang et al., 2003).
Riparin III (8) isolated from the unripe fruit of *Aniba riparia* showed broad-spectrum anti-microbial activity, effects on central nervous system and has potent smooth muscle relaxant activity. It also produces an inhibition of Ca$^{2+}$ influx and release of intracellular Ca$^{2+}$ (Sousa *et al.*, 2004).
Various butanolide (γ-lactone) such as akalactone A (9), akalactone B (10), litseakolide A (11) and litseakolide B (12) have been isolated from the stem bark of *Litsea akoensia*. These butanolides showed *in-vitro* cytotoxic activity against P-388, KB 16, A 549 and HT-29 cancer cell lines (Chen *et al.*, 1998).

![Chemical structure of Butanolides](image)

Studies on the constituents from the leaves of *Dehaasia triandra* resulted in the isolation of five novel alkaloid which were identified as socoxanthoplanine (13), dehydroisocorydione (14), (8, 8'-R)-bisisocorydine (15), (8, 8'-S)- bisisocorydine (16) and 11, 8'-O- bisisocorydine (17) (Lee *et al.*, 1996).
Naturally occurring 6-[ω-arylalkenyl]-5,6-dihydro-α-pyrones, cryptomoscatones D2, E1, E2, E3 and F1 and cryptopyranmoscatones A1, A2, A3, B1, B2 and B4, including goniothalamin (18) and cryptofolione (19) have been isolated from stem bark of Cryptocarya moschata, Cryptocarya latifolia and Cryptocarya myrtifolia (Sehlapelo et al., 1994; Cavalheiro and Yoshida, 2000).

The discovery of large number of natural bioactive compounds from the tree of Lauraceae family give large impact to the medicinal purposes in order to further research and study to reveal and discovered the natural drug resources.
1.2 Cinnamomum

*Cinnamomum* is one of the most well known genera in Lauraceae family. It contains about 250 species and distributed throughout China, India, East Africa and South Asian Country like Malaysia, Indonesia and Philippine (Ridley, 1924; Kochummen, 1989; Ibrahim et al., 1995). According to Ibrahim et al., (1995), *C. verum* J.S Presl, *C. pubescens* Kochummen, *C. javanicum* Bl, *C. iners* Reinw., *C. impressicostatum* Kosterm., *C. moliissimim* Hk.f., *C. porrectum* (Roxb.) koster., *C. camphora* (L.) J.S Presi., *C. sintoc* Bl., *C. aureofulvum* Gamb., *C. microphyllum* Ridl., *C. scortechinii* Gamb., *C. subavanim* Miq. and *C. altissimum* Kosterm are the most well known species. In Malaysia, 30 species of *Cinnamomum* have been recorded (Mawardi et al., 2000) and *C. inners*, *C. moliissimim* and *C. sintoc* are widely distributed (Burkill, 1966). Table 1.1 shows the *Cinnamomum* species found in Malaysia and their local names (Burkill, 1966; Mat Salleh and Latiff, 2002; Wiart, 2002).
Table 1.1: *Cinnamomum* species found in Malaysia and their local names (Burkill, 1966; Mat Salleh and Latiff, 2002; Wiart, 2002).

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Local Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. altissimum</em> Kosterm</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. burmanni</em></td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. camphora</em> (L.) J.S. Presl</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. cassia</em> J.S. Presl</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. celebicum</em> Miq</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. culitlawan</em> (L.) Kosterm</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. deschampsii</em> Gamble</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. eugenoliferum</em> Kosterm</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. grandiflorum</em> Kosterm</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. grandis</em> Kosterm</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. iners</em> Reinw. ex Blume</td>
<td>Teja, Teja Lawang, Medang Teja, Kemangi, Teja Badak, Abau</td>
</tr>
<tr>
<td><em>C. japonicum</em> Sieb ex Nees.</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. javanicum</em> Blume</td>
<td>Medang Kayu Manis, Kura Bengkak, Lawang</td>
</tr>
<tr>
<td><em>C. loureirii</em> Nees</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. mercadoi</em> S. Vidal</td>
<td>Medang, Kalinngag, Samiling, Tagalog, Kaningag</td>
</tr>
<tr>
<td><em>C. mollissimum</em> Hook.f.</td>
<td>Medang Lawang, Medang Wangi, Pialu</td>
</tr>
<tr>
<td><em>C. nees</em> ex Blume</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. pendulum</em> Cammerl.</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. politum</em> Miq.</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. poirectum</em> (Roxb.) Kosterm</td>
<td>Medang serai, Medang Gatal, Kayu Gadis, Medang Benar, Medang Losoh, medang Lilin, Medang Lawas</td>
</tr>
<tr>
<td><em>C. puberulum</em> Ridley</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. rhynchophyllum</em> Miquel</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. scortechinii</em> Gamble</td>
<td>Not known</td>
</tr>
<tr>
<td><em>C. sintoc</em> Blume</td>
<td>Kayu Sintok, Teja Lawang</td>
</tr>
</tbody>
</table>
Table 1.1: (continued).

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Local Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. subavenium Miq</td>
<td>Not known</td>
</tr>
<tr>
<td>C. subcuneatum Miq.</td>
<td>Not known</td>
</tr>
<tr>
<td>C. subtetramerum Miq.</td>
<td>Not known</td>
</tr>
<tr>
<td>C. schaeffer</td>
<td>Not known</td>
</tr>
<tr>
<td>C. verum J.S. Presl</td>
<td>Kayu Manis</td>
</tr>
<tr>
<td>C. zeylanicum Blume</td>
<td>Kayu Manis, Pattai</td>
</tr>
</tbody>
</table>

In Malay communities, the **Cinnamomum** species are well known as Kayu Manis and Tejur. It has been used as medicinal plants in order to treat the health problems (Cornel, 1951). For examples the roots of C. *iners* or commonly known as Teja, Teja Lawang, Medang Teja, Kemangi, Teja Badak or Abau by the Bidayuh community is used to reduce and calm down fever, cough, asthma and as a tonic which used by women after giving birth (Mat Salleh and Latiff, 2002). Meanwhile the leaves, strip and bark are used to reduce toxin and painful in body and as tonic by women after giving birth (Mat Salleh and Latiff, 2002; Wiart, 2002). Besides, the root of C. *javanicum* or locally known as Medang Kayu Manis, Kura Bengkak, Lawang Kecil, Kayu Kapur and Kerak Bengkah is used to treat the spleen problem and ‘meroyan’ (Burkill 1966; Mat Salleh and Latiff, 2002).

The bark of C. *mercadai* or a locally known as Medang, Kalinngag, Samiling (Tagalog) and Kaningag is used to reduce headache and treat intestinal problem such as diarrhea and stomachache while the root and bark of C. *mollissimum* or known as Medang Lawang, Medang Wangi or Pialu by the Malay’s community is used by
‘Temuan’ people to reduce fever and eaten with *Piper betle* and tobacco as a tonic (Burkill 1966; Mat Salleh and Latiff, 2002).

In addition, the barks and seeds of *C. porrectum* is used as tonic especially for female teenagers during menstrual or after giving birth or to improve an internal energy and to reduce and treat rheumatism (Ridley, 1924; Burkill 1966; Mat Salleh and Latiff, 2002). The dried bark of *C. sintoc* or locally known as Sintok or Teja Lawang is used as an antiseptic and to treat gastrointestinal problem such as stomachache and diarrhea (Ridley, 1924; Burkill 1966; Mat Salleh and Latiff, 2002; Wiart, 2002). It also used as a tonic by women after giving birth (Burkill, 1966; Wiart, 2002). Meanwhile, the barks and leaves of *C. verum* and *C. zeylanicum* or known as Kayu Manis and Pattai by Tamil’s community are used as tonic, anti-toxin and also used to treat skin problem caused by fungal infection (Ridley, 1924; Burkill 1966; Mat Salleh and Latiff, 2002; Wiart, 2002). It also used in order to reduce scar, menstrual and as a flavoring agents in food, perfume and pharmaceutical industry (Burkill, 1966; Mat Salleh and Latiff, 2002). Table 1.2 shows the summary of some of the uses of some *Cinnamomum* species found in Malaysia.
Table 1.2: The uses of some *Cinnamomum* species found in Malaysia.

<table>
<thead>
<tr>
<th>Species</th>
<th>Medicinal Use(s)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. iners</em></td>
<td>Fever, cough and asthma</td>
<td>Mat Salleh and Latiff, 2002;</td>
</tr>
<tr>
<td></td>
<td>Tonic and anti-toxin</td>
<td>Wiart, 2002</td>
</tr>
<tr>
<td><em>C. javanicum</em></td>
<td>Spleen problem</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latiff, 2002</td>
</tr>
<tr>
<td><em>C. mercadai</em></td>
<td>Headache and intestinal problem</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latiff, 2002</td>
</tr>
<tr>
<td><em>C. mollissimum</em></td>
<td>Fever and as tonic (eaten with <em>Piper betle</em> and tobacco)</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latiff, 2002</td>
</tr>
<tr>
<td><em>C. porrectum</em></td>
<td>Tonic and rheumatism</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latiff, 2002; Wiart, 2002</td>
</tr>
<tr>
<td><em>C. sintoc</em></td>
<td>Tonic and stomachache</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latiff, 2002</td>
</tr>
<tr>
<td><em>C. verum</em></td>
<td>Antiseptic, intestinal problem and constipation</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latiff, 2002</td>
</tr>
<tr>
<td><em>C. zeylanicum</em></td>
<td>Tonic and anti-toxin, skin and scar treatment, intestinal problem,</td>
<td>Burkill 1966; Mat Salleh and</td>
</tr>
<tr>
<td></td>
<td>constipation, insomnia and flavoring agent</td>
<td>Latiff, 2002; Wiart, 2002</td>
</tr>
</tbody>
</table>

*Cinnamomum* species are the source of cinnamon bark which has been used since ancient time. For instead, the barks of *C. zeylanicum*, *C. loureirii*, *C. burmanni*, and *C. cassia* are the four principal *Cinnamomum* species entering the trade market as cinnamon. Cinnamon has been known in Southern Europe for well over a thousand years, but become more widely known in other parts of Europe during the Middle Ages when the Islamic World extended its influence to the Orient and East to the Siberia starting in the eighth century A.D. (Smith *et al.*, 1992).
In mediaval times, cinnamon was distilled to produce cordials, ostensibly to aid in digestion. In the Orient, cinnamon and its near relatives are still widely used for local remedies, particularly for gastrointestinal and respiratory disorders. Meanwhile, in Philipine and the Pacific, cinnamon is taken to relieve headaches while in the West, it is used mainly for flavouring food, as an ingredient in perfumes and in the case of Mexico, to enhance the flavour of coffee. In Columbia, however, cinnamon sticks are chewed to speed parturition (Smith et al., 1992).

The studies on phytochemical and biologically active compounds on a wide number of Cinnamomum species have resulted in the isolation and characterization of valuable biological active compounds. The Cinnamomum species are rich in essential oils, tannin (Morimoto et al., 1986; Namba, 1986; Yazaki and Okuda, 1990; Buckingham, 1992), alkaloids (Kretovitch, 1966; Gellert and Summuns, 1969; Kechummen, 1972), terpenoids and terpene (Yang et al., 2005), lignans (Wu et al., 1994), flavanoids (Pesry and Metzger, 1950; Chopra et al., 1956; Said, 1969; Egan et al., 1981; Nohara et al., 1985; Vincieri et al., 1988; Evans, 1989; Fang et al., 2005) and benzylic compounds (Thomson, 1993).

These various compound especially phenolics, terpenoids and alkaloids, which existed in plants shows repellent activities to animals (Harding, 1985; Hansson, 1988; Harbone, 1993). Cinnamaldehyde is the main compounds which responsible for the aroma of the cinnamomum species and other aromatic plants (Ibrahim et al., 1995) and it also known for the anti-fungal properties (Thompson, 1989), anti-bacterial properties (Lee and Ahn, 1998) and anti-mutagenic effects (Kakinuma et al., 1984).
Cinnamophilin (20), a natural compound isolated from *C. philipinense* (Wu *et al.*, 1994), possesses both thromboxane A_2_ synthesis inhibitory and thromboxane A_2_ receptor antagonist properties (Wu *et al.*, 1994; Yu *et al.*, 1994). Cinnamophilin is also effective in the reduction of reperfusion-induced arrhythmia (Su *et al.*, 1999) and it also acts as a novel antioxidant and cytoprotectant against oxidative damage (Hsiao *et al.* 2001).

![Chemical structure of Cinnamophilin (20)](image)

Studies on *C. osmophlocrum* (Taiwan endemic tree) has resulted in the isolation of four kaempferol glycosides named as kaempferitrin (21), kaempferol 3-0-β-D-glucopyranosyl-(1,4)-α-l-rhamnopyranosyl-7-0-α-l-rhamnopyranoside, kaempferol 3-0-β-D-apiofuranosyl-(1,2)-α-l-arabinofuranosyl-7-0-α-l-rhamnopyranoside and kaempferol 3-0-β-D-apiofuranosy-(1,4)-α-l-rhamnopyranosyl-7-0-α-l-rhamnopyranoside. These compounds were evaluated as inhibitors of some macrophage functions involved in the inflammatory process and inhibited lipopolysaccharide (LPS) and interferon (IFN)-γ-induced nitric oxide (NO). Besides, they also inhibited cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-12 in a dose-dependent manner. However, kaempferol 3-0-β-D-glucopyranosyl-(1,4)-α-l-rhamnopyranosyl-7-0-