A review of the phytochemical compounds and pharmacological activities of *Eurycoma longifolia*

Insanu M, Pratiwi S N E*, Fidrianny I

Department of Pharmaceutical Biology, School of Pharmacy, Bandung Institute of Technology, Bandung-40132, Indonesia

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**ABSTRACT**

*Eurycoma longifolia* belongs to Simaroubaceae family. It is a tall tree and has different local names from many countries and this review consisted of traditional usage, phytochemical compounds and pharmacological activity. A systematic review was conducted to study the scientific work of *E. longifolia* which published in the last 10 years and minimum 20 articles that published in the last 2 years, published in Pubmed, Scopus etc. also has a digital object identifier (DOI). *E. longifolia* was a popular traditional medicine. The leaves were used as a supplement for giving birth, its bark as anthelmintic and its roots as antimalaria, laxative, antidiabetic etc. Due to high demand of this plant there are various formula of *E. longifolia* available in health food market. Many studies have been performed to determine the active constituents and pharmacological activities of *E. longifolia*. Alkaloid, quassinoid, polyphenols, flavonoid, polysaccharide, triterpenoid were found in *E. longifolia*. Quassinoids is a major phytochemical compound in *E. longifolia* which has various types like eurycumanone, eurycomanol, eurycomadilactone and eurylactone. Quassinoids has bitter taste and often found in Simaroubaceae family. Pharmacological activities of *E. longifolia* such as anti-inflammatory, analgesic, antioxidant, antimicrobial, antidiabetic, anti-osteoporotic activities. The literature review results showed that *E. longifolia* can be considered as medicinal plant for human. In the future, further studies on mechanism of pharmacology activity of *E. longifolia* are warranted.

*Corresponding Author
Name: Pratiwi S N E
Phone: +62-82218747914
Email: sausanpratiwi17@gmail.com

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**INTRODUCTION**

*Eurycoma longifolia* is one of the species in Eurycoma genus and belong to Simaroubaceae family. This plant is originated from the Southeast Asia so can be found in Malaysia, Laos, Cambodia, Myanmar, Indonesia, Vietnam and Thailand. *E. longifolia* also called as bidaralaut and pasakbumi (Indonesia), tongkatali, lempedupahit, bedaramerah (Malaysia), Ian-don, piak and tung saw (Thailand), Cay babenh and bhabinh (Vietnam), tho nan (Laotian) ([Jiraungkoorskul and Khanijo, 2016](https://www.jiraungkoorskul.org/journals/japa/vol16/issue2/46.pdf)). *E. longifolia* is a slender, shrubby, tall and slow-growing tree and well known as herbal medicine ([Chen et al., 2019](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6511937/)). Since old time, *E. longifolia* has been used as traditional medicine and nowadays this plant has been sold in the market with various form. Their leaves, barks and roots have been used as traditional medicine for different diseases. Many studies have been performed to determine
the active constituents and pharmacology activities of *E. longifolia*. Several parts of *E. longifolia* have been used to treat some diseases. The most commonly used part is the roots because it has many active constituents. The extract also has been studied and proved that contain many active substances to treat various diseases (Li *et al.*, 2013). Active substances such as quassinoids, alkaloids, squalene derivatives, triterpenes were found in *E. longifolia*. The major active substance of *E. longifolia* was quassinoids with various type and biological activities. Quassinoids has bitter taste and often found in Simaroubaceae family (Ebrahimii *et al.*, 2016). Eurycomanone is the most bioactive of quassinoids found in *E. longifolia* (Nhan and Loc, 2017). Some of pharmacological activities of *E. longifolia* were antimicrobial, antidiabetic, cytotoxicity against cancerous cells, drug for sexual insufficiency, immunomodulator, anti-inflammation, etc. (Abubakar *et al.*, 2018). In this article review, we aimed to examine the chemical substances and pharmacological activities of *E. longifolia*.

**MATERIALS AND METHODS**

The article review was conducted by collecting the scientific work about chemical compound, and pharmacology activity of *E. longifolia* which published in the last 10 years and minimum 20 articles that published in the last 2 years, published in Pubmed, Scopus etc., also has a DOI. The scientific work search by using keyword “*Eurycoma longifolia*”.

**RESULTS AND DISCUSSION**

**Traditional Uses**

In Malaysia, decoction of *E. longifolia* have been used to treat depression, high blood pressure, malaria and fatigue (Talbott *et al.*, 2013). Based on cultural beliefs, the traditional uses of *E. longifolia* have been passed from generation to generations. The taste of the decoction is bitter and it is assumed more bitter passed from generation to generation. The taste of *E. longifolia* is popular for its aphrodisiac effect that can enhancing libido due to its ability to stimulate the production of androgen hormones (Ezzat *et al.*, 2019a).

Due to high demand of this plant there are various formula of *E. longifolia* are available in health food market, in crude drug powder form or capsules which contain crude drug powder or *E. longifolia* extract (Effendy *et al.*, 2012). It can be found as health supplements in capsules, tablets and beverages (Fadzil *et al.*, 2018). Nowadays, root extract of *E. longifolia* used as pre-mixed in tea, coffee and carbonated drink which sales in commercial market (Low *et al.*, 2013).

**Phytochemical Compounds**

Several major phytochemical compounds have been determined in *E. longifolia* such as quassinoid, squalene-type triterpenes, canthin-6-one alkaloids, and tirucallane-type triterpenes (Bräuer *et al.*, 2019). Quassinoidswas the most phytochemical compound identified in *E. longifolia*, mostly C18-C22 quassinoids (Chua *et al.*, 2011). Besides that, polyphenols, high molecular weight polysaccharides and glycoprotein were also found in root of *E. longifolia* (Tsai *et al.*, 2020). Polar to semipolar saponins have been founded in *E. longifolia* roots (Chua *et al.*, 2019).

Flavonoids was discovered in ethyl acetate, chloroform, methanol and acetone extracts of stem and root of *E. longifolia*. Alkaloids was only detected in chloroform, ethyl acetate and petroleum ether extracts of the stem. Terpenoids was observed in all the extracts except acetone extract. All the extracts of *E. longifolia* stem except petroleum ether and chloroform have been discovered the presence of protein (Khanam *et al.*, 2015). Eurylophenolosides A and B, eurylolignanosides A and B which were four new phenolic acid along with 12 known isolates were detected from 70% ethanol extract of the roots (Ruan *et al.*, 2019).

Quassinoid has many various types with biological activity. Phytochemical studies of this *E. longifolia* have led to the discovery of quassinoids type which promising various biological activities (Yang *et al.*, 2020). Five quassinoids, eurycomanone, 13α,21-epoxyeurycomanone, eurycomanol, eurycomanol-2-O-β-d-glucopyranoside and 13,21-dihydroeurycomanone were observed using electrospray ionization (ESI) and atmospheric pressure chemical (APCI) in positive and negative ion modes (Teh *et al.*, 2011). Other five new quassinoids, eurylactone E, eurylactone F, eurylactone G, eurycomalide D, and eurycomalide E were identified along with 10 known quassinoids (Park *et al.*, 2014). Meanwhile study by Meng *et al.* (2014) exposed that Δ4,5,14-hydroxyglaucarubol, 1463
Figure 1: Structure of chemical compounds in *E. longifolia*
Table 1: Anti-inflammatory activity of isolated compound

| Compound                        | IC50 (µM) | CI95 (µM) |
|--------------------------------|-----------|-----------|
| Eurycomalide C                  | 18.4      | 16.9–20.1 |
| Eurycomalactone                 | 0.5       | 0.3–0.7   |
| 7α-hydroxyeurycomalactone       | 1.5       | 1.3–1.6   |
| 5,6-dehydroeurycomalactone     | 6.2       | 5.3–7.4   |
| Eurycolactone E                 | 3.8       | 3.2–4.5   |
| Longlactone                     | 4.7       | 3.7–5.9   |
| 14,15β-dihydroxyklaieanone      | 1.0       | 0.8–1.2   |
| 11-dehydroklaieanone            | 1.9       | 1.8–2.1   |
| Eurycomanone                    | 2.4       | 2.0–2.9   |
| 13,21-dehydroeurycomanone      | 0.7       | 0.6–0.9   |
| 1-methoxycarbonyl-β-carboline   | 29.3      | 20.3–42.4 |
| 9-hydroxycanthin-6-one          | 3.8       | 3.3–4.4   |
| 9-methoxycanthin-6-one          | 7.4       | 6.6–8.2   |
| 9,10-dimethoxycanthin-6-one     | 19.5      | 13.0–29.4 |
| 3,5,6,7,8,3′,4′-heptamethoxyflavone | 23.3   | 18.4–29.4 |
| Parthenolide (positive control) | 1.5       | 1.3–1.8   |

Table 2: Antimicrobial activity of E. longifolia

| Microorganism    | Methanol extract | Acetone extract | Ethyl acetate extract | Chloroform extract | Petroleum ether extract |
|------------------|------------------|-----------------|-----------------------|--------------------|------------------------|
|                  | Stem | Root | Stem | Root | Stem | Root | Stem | Root | Stem | Root |
| E. coli          | +    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| P. aeruginosa    | -    | -    | -    | -    | -    | +    | -    | -    | -    | -    |
| S. Virchow       | -    | -    | -    | -    | -    | -    | -    | -    | -    | -    |
| B. cereus        | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| S. aureus        | +    | +    | +    | +    | +    | +    | +    | +    | +    | +    |
| A. A. niger      | -    | -    | -    | -    | +    | -    | -    | -    | -    | -    |

Note: + = present; - = absent

5-iso-eurycomadilactone, eurycomadilactone, 13-epi-eurycomadilactone was found as four new quassinoids. The structure of chemical compounds in E. longifolia was shown in Figure 1.

Pharmacological Activities

E. longifolia had many pharmacological activities. The activities were described below:

Antioxidant Activity

Administration of 70% ethanol extract of E. longifolia root proved increase SOD (Super Oxidant Dismutase) levels and reducing MDA (Malondialdehyde) levels. E. longifolia contained flavonoid, alkaloid, phenols and glycoside which were known to have antioxidant activity (Triawanti et al., 2020). Flavonoid has a role as free radical scavenger and stimulating antioxidant enzymes. Alkaloid has a role as scavenger of superoxide radical. The activity of antioxidant and SOD enzymes would increase but superoxide anion level decrease (Edyson et al., 2019).

The other research by Oboh et al. (2018) presented that E. longifolia inhibited PDE-5, arginase and angiotensin-converting enzyme(ACE) as pro-oxidant-induced lipid peroxidation in a concentration dependent. The inhibitory activity showed with half maximum inhibitory concentration (IC50). The result on PDE-5 (IC50 = 251.8 µg/ml), ACE (IC50 = 96.07 µg/ml) and arginase (IC50 = 48.28 µg/ml).

Anti-inflammatory and Analgesic Activity

All of the alkaloids from E. longifolia roots displayed potential nitric oxide(NO) inhibitory activities on lipopolysaccharide (LPS)-stimulated RAW264.7 cells. Many compounds such as 4,9-dimethoxy-5-hydroxycanthin-6-one, 1-hydroxy-canthin-6-one,
4-methoxycanthin-6-one, 5-methoxy-canthin-6-one, 8-hydroxy-9-methoxy-canthin-6-one, 4,9-dimethoxycanthin-6-one, 5,9-dimethoxycanthin-6-one and 9,10-dimethoxycanthin-6-one inhibited NO release from LPS-stimulated RAW264.7 (Zhang et al., 2020).

Some of quassinoids and alkaloids showed the most potent NF-κB inhibitory effect with IC₅₀ displayed in the Table 1 (Tran et al., 2014). Recent study identified new anti-inflammatory β-carboline, 7-methoxy-(9H-β-carbolin-1-il)-(E)-1-propenoic acid from E. longifolia hairy roots which had strong inhibitory effect on NO release and decrease cyclooxygenase-2 (COX-2) expression induced by LPS RAW264.7 (Ngoc et al., 2016). E. longifolia extract discovered anti-inflammatory activity on carrageenan-induced paw edema. It inhibits the expression of COX-2 induced by LPS through blocking the NF-κB translocation. The extract also showed analgesic effect on heat-induced (hot plate test) and chemical-induced pain (acetic acid induced writhing). The analgesic effects were time and dose dependent and the analgesic activity of 400 mg/kg E. longifolia was higher than aspirin at 2 and 3 h after administration in heat-induced pain but lesser at 1 h. Thus, the onset time of E. longifolia is slower than aspirin (Han et al., 2016).

Immunomodulatory and Cytotoxic Activity
Polysaccharide from E. longifolia roots could activate macrophages by improving pinocytic and phagocytic activities in concentrations <250 µg/ml, promote NO and cytokine secretion. The polysaccharide contained uronic acid and its backbone composed of β-1,4-xylose which enhanced its immunomodulatory activity (He et al., 2019). sd

The compounds TAF273, F3 and F4 from methanolic extract of E. longifolia roots found had cytotoxic activity at IC₅₀ 19±3, IC₅₀ 55±2 and IC₅₀ 62±7µg/ml. The TAF273, F3 and F4 were tested on K-562 cells (Al-Salahi et al., 2014). The extract have been reported able to increase immunological parameters such as T cells, CD4⁺ T cells and lymphocytes (George et al., 2016).

Antitumor Activity
Extract of E. longifolia root enhanced the apoptotic level of adenocarcinoma cells. The higher the dose of E. longifolia extract showed the higher the apoptotic level of adenocarcinoma cells. After 24 h given the extract, the percentage of DNA damaged cells increased 39.4% and 43.5% after 48 h with highest concentration (100 µg/ml) (Rahman et al., 2020).

The treatment with TAF273 compound induced apoptotic in K-562 cells in dose and time dependent. The TAF273 compound at concentration 25 and 50 µg/ml enhanced apoptotic index (AI) from 10% (untreated) to 30 and 41%. Eurycomanone at concentration of 6 and 12 µg/ml also enhanced the apoptotic index to approximately 28 and 39%. The apoptotic index were calculated from the mean from at least three experiments (Al-Salahi et al., 2014).

Anti-osteoporotic
Shuid et al. (2011) revealed that E. longifolia had a potential in treating androgen deficient osteoporosis in men by alternative agent to testosterone replacement. Based on histomorphometry, quassinoids in E. longifolia extract effective as testosterone in the ORX + EL25, DGX + EL50, and DGX + EL100 groups to reduce degenerative changes of bone structure by enhancing bone volume and trabecular number. The extract also reduced percentage of osteoclast and increased percentage of osteoblast (Jayusman et al., 2018). Other than that E. longifolia suppressed the high of C-terminal telopeptide of type I collagen to prevent the enhancement of bone resorption rate after orchiectomy (Chinnappan et al., 2020). Based on recent study, E. longifolia showed anti-osteoporotic effect in six samples which improved fracture bones by increasing bone volume (Meng et al., 2014).

Sexuality Drug for Men
Thu et al. (2017) demonstrated that E. longifolia was detected to increase male sexual libido, male fertility, penile erection and testosterone level. The conventional way to treat TDS (testosterone deficiency syndrome) is TRT (testosterone replacement therapy). E. longifolia showed improving sexual health by restoring testosterone levels and naturally used as TRT (George and Henkel, 2014).

Studies showed eurypeptides activate CYP17(17α-hydroxylase/17,20 lyase), an enzyme that enhancing the conversion of pregnolone and 17-OH-pregnolone to produce more dehydroepiandrosterone and the metabolism of pregnolone and 17-OH-pregnolone to testosterone and 4-androstenedione (Erasmus et al., 2012). Aqueous extract of E. longifolia found to inhibit ROCK-II which has a role for inhibiting smooth muscle contraction. Trans-coniferyl aldehyde, eurycomanone and scopoletin exhibited maximum inhibition of ROCK-II at 82.1±0.63, 78.3±0.38 and 77.1±0.11 % (Ezzat et al., 2019b).

Anticancer and Antiproliferative
Eurycomanone had ability to affect the expression of cellular protein that have multifunctional roles in proliferation and associated with cancer development. This compound will affect cell replication that
involving in p53 tumor suppressor gene, cancer cells with hnRNP A2/B1 markers, annexin I, prohibitin and inhibit lung cancer proliferation (Wong et al., 2012). SQ40 contain 40% of the total quassinoids showed inhibitory activity against LNAp human prostate cancer cells. SQ40 detected to inhibit LNCaP cell growth at IC₅₀ 5.97 µg/ml. In lower dose, SQ40 inhibited LNCaP cell growth and in higher dose SQ40 can cause cleavage in LNCaP cells (Tong et al., 2015).

**Antimicrobial activity**

Methanol, acetone, ethyl acetate, chloroform and petroleum ether extract of E. longifolia roots were found active against Gram positive bacteria but inactive against Gram negative bacteria. The chloroform extract of the root exhibited highest activity among Gram positive bacteria with inhibition zone of 11.67 ± 1.53 mm against S. aureus followed by acetone extract with inhibition zone of 11.00 ± 1.00 mm at 200 µg/ml.

Stem extracts were found active against Gram positive bacteria and showed low to moderate activity against Gram negative bacteria with inhibition zone of 9.33 ± 0.58 mm against P. aeruginosa and 3.33 ± 5.77 mm against E. coli. The ethyl acetate extracted the highest activity among all tested extracts with inhibition zone of 11.00 ± 1.73 mm against Aspergillus niger at 200 µg/ml (Khanam et al., 2015). The antimicrobial activity of E. longifolia root and stem were presented in Table 2.

Research by Lee et al. (2018) study regarding influence of E. longifolia against tuberculosis. Treatment tuberculosis with E. longifolia and rifampicin found increasing in TNF-α production by promoting autophagy through ERK1/2 and NF-Kb signal to suppress intracellular Mycobacterium tuberculosis growth. Pasakbumin play a role in this activity. It was also enhanced levels of pro-inflammatory cytokine and NO via ERK1/2 and NF-Kb.

**Antidiabetic**

E. longifolia root was capable in modulating glucose and lipid metabolism. It enhanced insulin sensitivity and suppressed lipid production in 3T3-L1 adipocytes simultaneously. Also increase uptake glucose up to more than 200% with a dose of 50 µg/mL (Lahrita et al., 2015).

As said above, E. longifolia has been used to treat erectile dysfunction that one of the complications cause by diabetes. More than half men having diabetic also experiencing erectile dysfunction led to impotency (Thorve et al., 2011). E. longifolia 800 mg/kg showed reducing in omentum fat weight and body weight of 31.9% and 5.7%. Opponently the serum testosterone concentration increased by 30.2% (Solomon et al., 2014).

**Ant-obsogenic**

E. longifolia root expressed strong potential lipolysis enhancement but low pancreatic lipase inhibitory and reduced lipid accumulation in 3T3-L1 adipocytes. The roots contained eurycomanone and 13β,21-epoxyeurycomanone which increased lipolysis with EC₅₀ of 14.6 and 8.6 µM (Ruangaram and Kato, 2020). The standardized quassinoid and eurycomanone fraction was found affected in 3Y3-L1 preadipocyte cells. Both compounds decreased body weight, epididymal and perianal fat. Besides that, standardized quassinoids-enriched fraction (SQEL) also increased glucose clearance, reduced elevated total cholesterol and serum triglycerides levels (Balan et al., 2018).

**Antigout**

Quassinoids in E. longifolia had human urate transporter 1 (URAT1) inhibition activity by reducing blood uric acid levels in induced hyperuricemia animal model (Bao et al., 2019). Study by Liu et al. (2019) presented that E. longifolia reduced ankle swelling caused by gout in low and medium doses which indicated that E. longifolia has anti-gout effect.

**CONCLUSION**

This review summarized the traditional usage, phytochemical compound and pharmacology activity. Based on the literature review was reported the most compound that gave pharmacology activity on E. longifolia were quassinoids especially eurycomanone. This review showed E. longifolia has potential as medicinal plant which can be developed into traditional medicine for human. In the future, further study about mechanism of pharmacology activity of E. longifolia is needed.

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**Conflict of Interest**

The authors declare that there is no conflict of interest for this study.

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