Relationships For The Utilization Of Pasak Bumi Plants (eurycoma longifolia Jack.) As A Traditional Medicine And Its Bioactivity

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A R T I C L E  I N F O

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A B S T R A C T

Pasak bumi (Eurycoma longifolia Jack.) is a species belonging Simaroubaceae has been long used as traditional medicine, which known very well as aphrodisiac. The studies have been conducted to reveal the benefits of E. longifolia through ethnobotany, phyto-chemical, and bioessay approaches, but the review articles on the its utilization and bioactivity limited. This article is based on scien- tific articles published on line or off line, then synthesized so that to be information the relationship between use and bioactivity. Ethno- botany of E. longifolia have been used as a medicine for fever, ma- laria, improve stamina, diabetic, cancer, aphrodisiac, erectile dys- function. Bioactivity of E. longifolia is antiosteoporotic, antimicro- bial, aphrodisiac, anticancer, angiogenesis, and hepatoprotective. Eurycomanone is secondary metabolites in E. longifolia has activi- ty as an antimalaria, antipyretic, aphrodisiac, and cytotoxic. The quassinoids, coumarin and glycosides of El have activity increase the production, quality, totality, synthesis and release of spermatozoa. Eurycoma longifolia is very potential to be developed as an antiosteoporotic and aphrodisiac drug, but until now most of it is harvested directly from the forest, so to preserve it, we need to study the cultivation method.

1. Introduction

*Eurycoma longifolia* (El) is a plant that has long been used as a traditional medicine, especially for people living in Southeast Asia (de Padua et al. 1999) and South Asia (Razak et al. 2012), including Indonesia. The vernacular names El among others: stick ali, bitter antidote, bitter powder, stick king, earth petala, earth peg, earth support, cay ba binh and plaa-lai-pueak (Chan et al. 2013). For Indonesians, El is better known as peg bumi because it has roots that resemble pegs / poles with little or no branching, while for Malaysians it is known as Tongkat ali, which has a connotation similar to male genitalia.

Silalahi and Nisyawati (2015) state that the existence of El has begun to be difficult to find in North Sumatra due to trade or over exploitation, however, the Batak Toba sub-ethnic group in Peadungdung village has started planting it in their yards so that it is easier to access this plant. All parts or organs of El are used as medicine from the roots to the seeds (Silalahi and Nisyawati 2015; Silalahi 2014), which has implications for their sustainability. For the Toba Batak ethnic community in North Sumatra, El is also used as a bioindicator, namely as an indication of infertile land so that it is not suitable for use as agricultural land (Silalahi and Nisyawati 2015; Silalahi 2014).

The North Sumatra Batak ethnic group has long used El as drugs for malaria, fever, energy booster (Silalahi 2014), drugs for dysentery, fever, malaria, sexual disorders including male infertility for local communities in Malaysia (Chan et al. 2013),
antimalarials, antidiabetic, anticancer and aphrodisiac (Abubakar et al. 2018). El can be consumed by combining its extracts in food or in drinks such as tea and coffee for the people of Malaysia (Ahmad et al. 2018) and also the Batak ethnic group in Peadundung village is used as "tea" after activities in the fields (Silalahi and Nisyawati 2015). El root is used to restore energy and vitality, increase blood flow and is used for postpartum mothers (de Padua et al. 1999). Although local communities in Indonesia have long used El (de Padua 1999), their research is mostly carried out by researchers in Malaysia so that El is often called “Malaysian ginseng”.

The use of plants as medicine is related to their bioactive compounds and most plants produce bioactive compounds that vary from one organ to another. El root contains the main content of eurycomanone (Ahmad et al. 2018), quassinoids, coumarin and glycosinate (Chan et al. 2013), phenolic compounds, tannins, eurycomanone, eurycomanol, eurycomalactone, canthine-6-one al-caloid 9-hydroxy canthin-6-one, 14,15β dihydroxyklaneanone, quanissoinds and triterpenes (George et al. 2018). El has bioactivity as antiosteoporosis, anticancer, antiproliferasi, antimalarial, antimicrobial, antioxidant, aprosidiac, anti-inflammatory, antidiabetic, antirheumatic and antiallergic (Thu et al. 2018).

Empirically, it can be seen that there are still many people who are confused about the efficacy and effectiveness of traditional medicines. This is related to the assumption that the efficacy of traditional medicinal plants is only based on empirical evidence without being supported by scientific evidence, even though scientific research is also being carried out to develop traditional medicinal plants. This article will discuss the relationship between the use of EL and its bioactivity so that it becomes information for the development and use of EL as a traditional medicine as well as a modern medicine.

2. Result and Discussion

Botanical Eurycoma longifolia

Eurycoma longifolia is one of the species used as medicine that comes from the Simaroubaceae family. Eurycoma distribution is limited in Southeast Asia (de Padua et al. 1999), however some researchers claim it is also found in South Asia. E. longifolia and E. apiculata are two species that are widely used as medicine, with relatively the same distribution. However, El is found up to an altitude of 1000 m asl while E. apiculata is found up to an altitude of 1200 m asl (de Padua et al. 1999). This plant is actually easily found in primary and secondary forests on the island of Sumatra, including North Sumatra (Silalahi 2014; Silalahi and Nisyawati 2015; de Padua et al. 1999). The local Toba Batak ethnic community in Peadundung El Village is used as a bio-indicator to show acidic soils with good drainage (de Padua et al. 1999). Physta is an exclusive product containing freeze-dried water extract from El, which is traditionally used as an energy booster and aposidic in Malaysia (Udani et al. 2014). Aprosidiacs are compounds used to increase libido.

The Batak ethnic group knows El as bulung besan (Karo), tongkat ali (Phakpok), horis kotala (Simalungun), tengku ali (Toba), and ampahan gunjo (Angkola-Mandailing) (Silalahi and Nisyawati 2015). El is distributed in parts of South Burma (Myanmar), Indo-China (Cambodia, Laos and Vietnam), Thailand, Peninsular Malaysia, Sumatra, Kalimantan, and the Philippines (de Padua et al. 1999).

El can grow to be up to 10 m tall with very few branches. The leaves are up to 100 cm long and green in color. The leaves are pinnate (paired) and lanceolatus to ovate or obovate (Figure 1). Dioecus flowers with ovoid-shaped fruit that turn dark brown when the fruit ripens (George et al. 2018; de Padua et al. 1999).

For the people of Malaysia, El is one of the most important among many medicinal plants and has been developed into a variety of easy-to-use medicines. Although, El is one that has been bought and sold in Malaysia and is declared an aprosidiac drug. Abubakar et al. (2018) reported that herbal medicinal products (HBP) which were stated to contain El extract, turned
out that 27% of the 37% HBP studied were fake. Furthermore Abubakar et al. (2018) stated that DNA bar-coding with ITS2 barcodes can be used as the first screening step for HBP testing containing El.

**Benefits and Bioactivity**

*Eurycoma longifolia* has long been used as a traditional medicine, therefore *herbal medicinal products* (HMP) containing El are easily found in the market in the form of *raw crude root powder* (root powder) or capsules, tablets, or a mixture of tea with coffee in Malaysia (Rehman et al. 2016) and markets in North Sumatra (Silalahi et al. 2015b: Silalahi 2014). Ethnobotanically El is used as a medicine for malaria (Silalahi 2014; Abubakar et al. 2018), fever, aprodissiak (Silalahi et al. 2015; Abubakar et al. 2018; Al-Sahali et al. 2014; Al-Sahali et al. 2014), antidiabetic mellitus (Abu-Bakr et al. 2018; Al-Sahali et al. 2014), anticancer (Abubakar et al. 2018), overcome erectile dysfunction, improve sexual function (Low and Tan, 2007) and increase spermatogenesis (Wahab et al. 2010). Based on the results of research in the El laboratory, it has bioactivity as antiosteoporosis, anticancer, hepatoprotective, antimicrobial, antiaging and aprodissiak.

**Antiosteoporosis**

Osteoporosis is a serious health problem associated with aging which is characterized by a decrease in bone density or density (Jayusman et al. 2018). Steroid sex hormones are thought to play an important role in the development and maintenance of the bone system in humans and animals (Vanderschueren et al. 2014), so that hormone reduction is directly or indirectly related to osteoporosis in humans. Decrease in estrogen in women leads to a rapid reduction in bone density, while a decrease in the hormone estrogen in men induces osteopenia (Jayusman et al. 2018).

Hypogonadism or reduced androgen levels is associated with lower bone mineral density and an increased risk of fracture (Kenny et al. 2000). The main causes of osteoporosis in men are divided into primary causes (age-related and idiopathic osteoporosis) and secondary causes (alcohol abuse, excess glucocorticoids, and hypogonadism) (Orwoll et al. 1995). Various drugs used in the treatment of osteoporosis, especially estrogen replacement therapy with bisphosphonates, selective estrogen receptor modulators, and calcitonin, however, have side effects, such as breast cancer, hypercalcemia, and hypertension (Thu et al. 2017).

*Eurycoma longifolia* can be used as an alternative treatment to prevent and treat male osteoporosis without causing side effects associated with testosterone (Effendy et al. 2012). Research on the use of El extract as antosteoporosis has been carried out, including Thu et al. (2017), Jayusman et al. (2018) and (Ramli et al. 2012). Chidectomised male mice (castrated using chemical compounds) were used as animal models for the study of male osteoporosis associated with androgen deficiency (Blouin et al. 2008). The absence of estrogens causes menopause, thus increasing osteoclast formation and activity (de Villiers 2009; Wensel et al. 2011). Osteoclasts play a key role in bone loss (de Villiers 2009), therefore, inhibiting osteoclast formation and function is one strategy for osteoporosis therapy (Thu et al. 2017).

Improving bone regeneration on the one hand and suppressing osteoclast differentiation on the other hand may have great therapeutic value in treating osteoporosis and other erosive bone diseases such as rheumatoid arthritis and metastases associated with bone loss (Thu et al. 2017). El extract supplementation increases testosterone levels (Tong et al. 2015; Jayusman et al. 2018) which may contribute to reducing bone damage (Jayusman et al. 2018). El bioactive compounds that inhibit El include eurypeptides, glycosaponins, and eurycomanone (Jayusman et al. 2018). Based on the histomorphometric index, the standardized extract of quassinoid El has the same effectiveness as testosterone in reducing degenerative changes in osteoporosis model of bone caused by androgen deficiency (Jayusman et al. 2018), through inhibition differentiation, maturation, and osteoclast function (Thu et al. 2017).

The use of El as an antiosteoporosis drug is
associated with its ability to act as an aprosidial which directly or indirectly affects the hormone testosterone (Jayusman et al. 2018). Eurycomanone is thought to be a compound that is responsible for antioestrophorotic activity, which in laboratory experiments used male rats lacking in gonadal hormones (Jayusman et al. 2018). High doses of El (90 mg / kg) may have the potential to maintain bone microarchitecture in orchidec-tomised mice, but lower doses can further exacerbate changes in osteoporosis (Ramlı et al. 2012).

**Anti cancer**

Cancer is the uncontrolled growth of cells and is one of the main causes of human death. Various compounds extracted directly from plants and some of them have been commercialized such as taxol, vinblastine and vincristine. Even so, the exploration of plants that have the potential to act as anticancer continues (Silalahi et al. 2015b), including El. The basic principle of anticancer compounds is compounds that can inhibit cell division. Eurycomanone is the main compound in EL affecting the expression of various cellular proteins and many of these proteins have multiple functions in cell proliferation and survival and are associated with cancer development and metastasis (Wong et al. 2012).

Eurycomanone induces apoptosis (Al-Sahali et al. 2014; Zakaria et al. 2009) and decreases antiapoptotic protein (Zakaria et al. 2009). Based on the bioessay conducted by Wong et al. (2012) stated that El extract has activity as an anticancer compound, especially lung cancer with multi-target activity in inhibiting the proliferation of lung cancer cells. El root extract induces apoptosis in a dose and time dependent manner (Al-Sahali et al. 2014). Eurycomanone inhibits the proliferation of lung cancer A549 cells ranging from 5 to 20 µg / ml (Wong et al. 2012). The concentration that inhibits 50% cell growth (GI50) is 5.1µg / ml (Wong et al. 2012), however the antiproliferative effect was not completely reversible following removal of eurycomanone.

**Flow cytometry** was used to measure apoptosis and cell cycle resistance (Al-Sahali et al. 2014). The El root extract showed various levels of growth inhibition with IC50 values of 19.55 and 62 mg / ml, respectively. Root extracts hold the cell cycle in the G1 and S phases (Al-Sahali et al. 2014). Administration of El extract intraperitoneally (50 mg / kg) resulted in significant growth inhibition of subcutaneous tumors compared to control mice. The El root extract showed strong antiproliferative activity in in vitro and in vivo models of K-562 leukemia cell line (Al-Sahali et al. 2014).

**Hepatoprotective**

Various chemicals cause liver damage and to protect the structure and function of the liver, a hepatoprotective compound is needed. In laboratory experiments carbon tetrachloride (CCl₄) was used to induce acute hepatotoxicity in rats (Al-Faqeh et al. 2010). El is not hepatotoxic and has hepatoprotective activity against CCl₄-induced hepatotoxicity and does not result in side effects such as anorexia, hypodypsia or weight loss (Al-Faqeh et al. 2010).

In mice given El at low (300 mg / kg) and moderate (750 mg / kg) doses, CCl₄ was found to induce moderate inflammation, fatty acid changes and transient hepatic necrosis at high doses (1500 mg / kg), CCl₄ induces severe inflammation, fatty acid changes and hepatocyte necrosis. The increase in serum total bilirubin (moment) caused by CCl₄ was not significantly reduced by all El doses. Animals treated with CCl₄ alone and in groups treated with CCl₄ and dose El had decreased body weight, diet and water intake. In the El 750 mg / kg treatment group, there was no reduction in body weight, dietary and water intake. EL administered alone does not cause liver toxic effects but, in combination with CCl₄, appears to synergize the CCl₄-induced hepatotoxicity which increases as the El dose is increased.

**Antimicrobial**

Various types of diseases and food damage are caused by bacteria, fungi (Khanam et al. 2015) and protozoa (Kavitha et al. 2012). Antimicrobial compounds are compounds that inhibit microbial growth, through the destruction of cell walls and inhibit protein synthesis. Various types of plants have long been used as an antimicrobial including El. Methand
extract, acetone, ethyl acetate, chloroform and petroleum ether extract from the stem and roots of El have antimicrobial activity (Khanam et al. 2015). El extract at a concentration of 12.5-200 µg/µl with the disc diffusion method inhibited the growth of gram-positive bacteria, gram-negative bacteria and fungi (Khanam et al. 2015).

The antibacterial activity of root and stem extracts El depends on the dose, but in general, the highest anti-bacterial activity against Gram positive bacteria (Khanam et al. 2015). The difference in antibacterial activity in bioactive compounds is influenced by the structure of the bacterial cell wall. Gram-negative bacteria have lipopolysaccharides in the outer membrane which acts as a permeability barrier and limits the diffusion of active compounds (Niv and Yechiel 2005). Gram positive bacteria allow direct contact of the extract constituents with the phospholipid bilayer of the cell membrane, causing either increased ion permeability, leakage of vital intracellular constituents, or damage to the bacterial enzyme system (Zhao et al. 2001). The ability of El extracts to inhibit microbial growth depends on the concentration, organs and materials used in the extraction (Kavitha et al. 2012). El stem extract was stronger than root extract against Bacillus cereus and Staphylococcus aureus. Ethyl acetate extract from the stem showed moderate activity against gram-negative bacteria, Pseudomonas aeruginosa and high activity against the fungus, Aspergillus niger (Khanam et al. 2015). El root extract has activity against Toxoplasma gondii (Kavitha et al. 2012). Toxoplasma gondii given El extract showed cell wall changes with invagination followed by wall damage and decreased cytoplasmic volume, structural disorganization of cell cytoplasm and destruction of organelles since 12 hours after administration of the extract (Kavitha et al. 2012).

Aprosidiak

The use of El as aprosisi is more prominent than other uses. For the people of Southeast Asia have long used El to overcome sexual dysfunction and infertility (Tong et al. 2015) and South Asia (Razak et al. 2012). El root extract has been recognized for its aphrodisiac and anabolic properties (Faisal et al. 2017). The decrease in testosterone concentration usually occurs in adult men aged 40 years and over (Tambi et al. 2012). The glycopeptides in the aqueous extract of El are responsible for the aphrodisiac and fertility enhancing effects (Tambi et al. 2012). Mice given the El extract (8 mg / kg - 500 µg / kg bw) intramuscular showed significantly higher sperm count and sperm motility when compared to the control group (Wahab et al. 2016).

Twenty-four adult male albino rats Wistar strain were divided into 3 groups; control, group A and group B. Group A received 5 mg / kg twice daily from pure El root extract, while group B received 10 mg / kg twice daily from the same extract for 6 weeks. The serum testosterone level was significantly higher in group B than in control and group A, while group A did not show any statistically significant difference compared to control. El root extract can significantly reduce serum leptin levels due to an increase in serum testosterone levels. Consumption of El also causes a significant reduction in total body weight which points to a possible reduction in body fat content (Faisal et al. 2017).

Standardized and water-soluble extracts of El root increased male fertility associated with higher semen volume, sperm concentration, percentage of normal sperm morphology and mate sperm motility of subfertile male partners with idiopathic infertility. A total of 350 patients were given 200 mg of El extract and analyzed for daily semen and follow-up was done every 3 months for 9 months. Of these 350 patients, 75 patients completed a full 3 month cycle. Follow-up semen analysis in this patient showed significant improvement in all semen parameters. El's extract significantly improved sperm quality in these patients, allowing 11 (14.7%) spontaneous pregnancies (Tambi and Imran 2010). El is known as an aphrodisiac and drug to increase male libido (Ismail et al. 2012). The 12-week study in 109 men between the ages of 30 and 55 were given 300 mg of an aqueous extract of El root. The group given El showed higher scores in overall erectile function, sexual libido (14% at week 12), SFA with 44.4% sperm motility, and 18.2% semen volume at the
end of treatment (Ismail et al. 2012).

Angiogenesis

Apoptosis is a programmed cell death process and one of the biological mechanisms involved in the aging process and cell degeneration. Caspase3 is an enzyme that plays a role in activity in cellular apoptosis (Cohen 1997). Angiogenesis is an excellent strategy to combat angiogenesis-dependent pathophysiology such as cancer, rheumatism, obesity, systemic lupus erythematosus, psoriasis, proliferative retinopathy and atherosclerosis (Al-Salahi et al. 2013). El root can be used as an alternative medicine to prevent and treat angiogenesis-related diseases (Al-Salahi et al. 2013).

The quassinoid-rich El extract caused significant suppression in budding of small blood vessels in the rat aorta with IC50 (11.5 μg / ml). The quassinoid-rich El extract (50 μg / ml) showed remarkable inhibition (63.13%) of neo-vascularization in the allantoic chorion of the chicken embryo membrane. In vitro, quassinoid-rich El extracts significantly inhibited major angiogenesis steps such as proliferation, migration and differentiation of human umbilical venous endothelial cells (HUVEC) (Al-Salahi et al. 2013). Elangiogenic activity may be due to its inhibitory effects on endothelial cell proliferation, differentiation, and migration that can be attributed to quassinoids (Al-Salahi et al. 2013).

Figure 1. The shoot (shoot) of Eurycoma longifolia Jack with compound leaves.

3. CONCLUSION

Eurycoma longifolia produces various secondary metabolites, eurycomanone, coumarin and quassinoids. Eurycomanone has activity as an antimalarial drug, antipyretic, aphrodisiac, and cytotoxic activity, while quasinoids and coumarin and glycosides can increase the production and quality of spermatozoa in the form of morphology and motility and also increase the synthesis and release of testosterone in male cells. To overcome infertility El can be consumed orally. The bioactivity of El has been tested as antiosteoporosis, antimicrobial, afrosi-deac, anti-cancer, angiogenesis and hepatoprotective.

4. REFERENCES


