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Review Article
Torch Ginger (*Etlingera elatior*): A Review on its Botanical Aspects, Phytoconstituents and Pharmacological Activities

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Abstract

In order to propose a prospective candidate for novel complementary phytopharmaceuticals, one of Zingiberaceae family plant, *Etlingeraelatior* or torch ginger, was being evaluated. The aim of this review was to provide a comprehensive literature research focused on the botanical aspects, nutritional quality, phytoconstituents and pharmacological activities of *E. elatior*. Researches on this particular plant were conducted in Malaysia (55.5%), Indonesia (33.3%), Thailand (8.3%) and Singapore (2.7%). This review article has revealed that the most prominent pharmacological activities were anti-microbial, anti-oxidant and anti-tumor activities in consistent with the dominated levels of flavonoids, terpenoids and phenols. However, extended and integrated research should be converged towards intensive investigations concerning to isolated phytoconstituents and its bioactivities, pharmacokinetics, bioavailability, molecular mechanism of its specific pharmacological activities, safety and efficacy studies for further development.

Key words: *Etlingeraelatior*, flavonoids, kaempferol, quercetin, zingiberaceae

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The empirical use of medicinal herbs for hundreds of years indicates that Indonesia possesses an enormous opportunity to support the development of indigenous medication. One of the famous Indonesian original plant is *Etlingera elatior* (Jack) R. M. Smith (Zingiberaceae family).In Indonesia, the inflorescence bud is cultivated especially for culinary purpose to add flavor in traditional dishes and as a nutritional sources[1]. Interestingly, *E. elatior* is potentially used as a source of alternative medicine due to its afford ability, availability and compatibility as plant-derived drugs. This plant contains secondary metabolites such as phenols, flavonoids, glycosides, saponins, tannins, steroids, terpenoids, which revealed its bioactivities[2,3]. Therefore, *E. elatior* has been reported of its broad range of pharmacological activities including anti-hyperglycemic[4], anti-hyperuricemic[5], anti-inflammatory[4], anti-microbials[6], anti-oxidant[7] and anti-tumor activity[8]. Moreover, for commercial used as natural ingredient in cosmetic formulation, inflorescence of torch ginger is also used for skin whitening[9], anti-aging[9] and lipstick preparation[10].

This review article provides a comprehensive literature research focused on the botanical aspects, nutritional quality, phytoconstituents and pharmacological activities of *E. elatior* (Table 1).

Botanical aspects: The morphological characters of mature *E. elatior* were presented in Table 2.

The reproductive phase of this plant starts once the inflorescence shoot emerges from the rhizome. The major phases of the *E. elatior* developments are peduncle elongation, inflorescence occurrence, flowering and senescent stage. At the initial growth, peduncle elongation stage takes place 20 days to grow. The elongation of peduncle will slow down when the inflorescence bud is established during the blooming stage. After 30 days of shoots occurrence, the inflorescence bud starts to establish. *E. elatior* inflorescence consists of floral and involucral bracts. The floral bract of mature inflorescence at a full bloom may contain up to 20-25 layers, while the involucral bracts are only 3-4 layers. The seven development growth stages of inflorescence bracts are observed throughout the innermost layer (stage one to four) to the outermost layer (stage five to seven). The floral bracts are tender and smaller than involucral bracts. The purpose of involucral bracts is essentially for defense mechanism. The inflorescence proposes the flowering phase after 50 days of development. At the initial of the blooming phase, the outermost of involucral bract begins to disclose. By day 60, all of the involucral bracts will be completely disclosed and the bracts will be opened. During this phase, the first ring of the individual flowers will be opened gradually. From stage one to five, actual flowers were in the developing process. Through the 6th stage, the yellow margin of labellum appeared. Within stage seven, full blooming flowers arriving senesced stage and the labellum will be shut. The involucral bracts will dry slowly and the color become brown as the opening of true flowers continued[17].

Phytoconstituents: *E. elatior* is widely used empirically as a traditional medicine because of its high level of secondary metabolites such as phenols, flavonoids, glycosides, saponins, tannins, steroids, terpenoids[2,3]. Total phenolic and flavonoids contents within *E. elatior* were found in high amounts in the leaves, flowers, stems and rhizome[28]. Flavonoids contained in *E. elatior* are quercetin, apigenin, kaempferol, luteolin, myricetin[8]. Kaempferol 3-glucuronide, quercetin 3-rhamnoside, quercetin 3-glucoside and quercetin 3-glucuronide were identified in the leaves[37]. Quercetin, kaempferol-3-O-glucoside and kaempferol were found in the flowers and stems[16]. The high content of kaempferol played a role as an anti-inflammatory agent and might help in decreasing risk of various types of brain disorders[38]. High level of anthocyanin was also found in this plant and had been shown to have cytotoxic activity against ovarian cancer cell lines[31].However, anthocyanin is very susceptible to degradation due to increasing heating temperature[39]. Interestingly, anthocyanin in *E. elatior* extract had been proven to be more resistant to heating during food processing or pasteurization[31].

Moreover, essential oils are found considerably rich in *E. elatior*, which had been identified in the leaves, stems, flowers and rhizome extracts. The essential oils were dominated by monoterpenes hydrocarbons whereas miscellaneous compounds were contained more in the flowers, oxygenated monoterpene derivates and oxygenated sesquiterpene derivatives were abundantly detected in the stems, while the sesquiterpene hydrocarbons were highly quantified in the leaves[21]. Based on the classification of essential oils, the most commonly compounds were β-pinene, caryophyllene, (E)-β-farnesene, 1,1-dodecanediol diacetate, (E) -5-dodecane, cyclododecane, 1-dodecanol, dodecanal, 17-pentatriacontene, dodecanoic acid, myrcene, α-humulene, camphene, β-pinene, Z-11-pentadecanol[3,21,12,35].

Eight isolates of secondary metabolites derivatives of steroids, diarylheptanoids and labdane diterpenoids had been identified and isolated from ethyl acetate, n-hexane, chloroform rhizome extracts, which revealed potent

Table 1: Most important results of the main *E. elatior* articles

References	Site of study	Plant part	Extract	Assay methods	Main results
Abdelwahab *et al.*[11]	Malaysia	Whole parts	Aqueous	GC-MS, DPPH, disc diffusion, agar disc,	20 compounds in essential oils Antioxidant and antibacterial activities
Adliani *et al.*[10]	Indonesia	Flowers	Ethanol	Melting point, breaking point, stability, pH	Coloring agent in lipstick formulation
Anzian *et al.*[12]	Malaysia	Unopened and opened flowers	Ethanol	GC-MS, DPPH, FRAP	16 compounds in unopened flowers 18 compounds in opened flowers Antioxidant activity
Chan *et al.*[13]	Malaysia	Leaves	Methanol	DPPH, FRAP, FIC, BCB, disc diffusion	Antioxidant and antibacterial activity
Chan *et al.*[14]	Malaysia	Leaves	Methanol	CC, TLC, ^{1}H-NMR, ^{13}C-NMR, molybdate, folin-ciocalteu, HPLC, sulforhodamine B	3 compounds in the leaves extract No cytotoxic effect WRL-68 and Vero cells
Chan *et al.*[6]	Malaysia	Leaves	Aqueous	GC, GC-MS, disc diffusion method	15 essential oils in the leaves extract Antibacterial activity
Chan *et al.*[15]	Malaysia	Leaves	Ethanol	Molybdate, RP-HPLC, folin-ciocalteu, DPPH, disc-diffusion, dopachrome	Antioxidant and antibacterial activities
Chang *et al.*[16]	Singapore	Flowers and stems	Methanol	LC-MS	3 compounds in the flowers and stems
Choon and Ding[17]	Malaysia	Whole plant	-	-	155 days to grow gradually developed into four phonological stages
Dewi *et al.*[5]	Indonesia	Flowers	Aqueous	Uric acid kit	Antihyperuricemic activity
Ghasemzadeh *et al.*[8]	Malaysia	Flowers	Aqueous and ethanol	UHPLC, DPPH, FRAP, MTT, agar-well diffusion	High amount of total phenolic and flavonoid compounds Antioxidant, anticancer and antibacterial activities
Habsah *et al.*[18]	Malaysia	Rhizomes	Hexane, chloroform, ethyl acetate, methanol	CC, HPLC, ^{1}H-NMR, ^{13}C-NMR, EI-MS, EBV activation, MTT	8 compounds isolates in rhizomes Cytotoxic and antitumor-promoting activities
Handayany *et al.*[19]	Indonesia	Leaves	Ethanol	-	Wound healing activity of leaves gel preparations
Haw *et al.*[20]	Malaysia	Not mentioned	Not mentioned	SOD, GPx, PCC, ELISA kits, H and E staining	Increased SOD and GPx, lowered PCC in the testis and lowered testosterone serum level Repaired testis histology alterations Antioxidant activity
Jaafar *et al.*[21]	Malaysia	Leaves, stems, flowers and rhizomes	-	GC-MS	Monoterpenes hydrocarbons compounds dominated
Jackie *et al.*[2]	Malaysia	Flowers	Ethanol	Total antioxidant, LPO, PCC, SOD, GPx, GST	Antioxidant activity
Khalid and Azman[22]	Malaysia	Stems, midribs, leaves, flowers	Methanol, n-hexane	GC-MS,	11 compounds in the leaves, stems, midribs and flowers
Koraag *et al.*[23]	Indonesia	Leaves, flowers	Ethanol	Not mentioned	Anti-larvae of Aedes aegypti
Krajarng *et al.*[24]	Thailand	Flowers	Hydroglycol	MTT, phosphatidylserine exposure, caspase-Glo* 3/7, 8 and 9 kits, western blot	Antitumor activity
Kusumawati *et al.*[25]	Indonesia	Leaves	Ethanol	Disc diffusion	Antibacterial activity
Lachumy *et al.*[7]	Malaysia	Flowers	Methanol	Disk diffusion, broth dilution, BSLT, DPPH	Antibacterial and antioxidant activities
Lestari and Ruswanto[26]	Indonesia	Flowers	Methanol, ethyl acetate, n-hexane	MTT	Anticancer activity
Mackeen *et al.*[27]	Malaysia	Flower-shoots	Ethanol	Disk diffusion, cytotoxicity	Antimicrobial and cytotoxic activities
Mai *et al.*[28]	Malaysia	Rhizomes, leaves, flowers	Ethanol and acetone	MTT, phosphatidylserine apoptosis kit	Anti-proliferative and apoptotic activities
Maimulyanti and Prihadi[3]	Indonesia	Flowers	Methanol, ethyl acetate and n-hexane	GC-MS, DPPH	39 compounds in the flowers Antioxidant activity
Naufalin *et al.*[29]	Indonesia	Flowers	Ethanol, ethyl acetate, hexane	Disc diffusion	Antibacterial activity

Table 1: Continue

Reference	Site of study	Plant part	Extract	Assay methods	Main results
Nithitanakool *et al.*[9]	Thailand	Flowers	Propylene glycol	DPPH, anti-tyrosinase, anti-collagenase, spectrophotometry	Anti-oxidant, anti-tyrosinase and anti-collagenase activities (skin whitening and anti-aging)
Angin[30]	Indonesia	Flowers	-	GC-MS, FTIR, disc diffusion	3 compounds of essential oils Anti-microbial activity
Srey *et al.*[4]	Thailand	Rhizomes	Ethanol	α-glucosidase, α-amylase inhibitory activity, DPPH, FRAP, NO inhibitory activity in RAW264.7 cell line	Anti-hyperglycemic, anti-inflammatory and antioxidant activities
Ramasamy *et al.*[31]	Malaysia	Flowers	Methanol	NRU cytotoxicity, DPPH, FRAP	High amount of anthocyanin and phenolic contents Antioxidant and cytotoxicity activities
Rusanti *et al.*[32]	Indonesia	Seeds	Methanol, ethyl acetate and n-hexane	Spectrophotometry UV-Visible, FTIR, LCMS, TLC, BSLT, MTT	7 compounds in the seeds Cytotoxic activity
Suryanto *et al.*[33]	Indonesia	Roots	Methanol, ethyl acetate and n-hexane bacterial cell extract	Endophytic bacterial cell extraction, antifungal assay of endophytic bacterial isolates and bacterial cell extract	Antifungal activity 11 endophytic bacterial isolates in the roots
Susanti *et al.*[34]	Malaysia	Flowers	-	GC-MS, disc diffusion, invisible growth of microorganism on culture plates	22 compounds in the essential oil Antimicrobial activity
Wijekoon *et al.*[1]	Malaysia	Flowers	Not mentioned	GC-FID, ICP-OES	High amounts of crude protein, fat, fiber content, fatty acids, amino acids and major minerals in the inflorescences Below limits of heavy metals Nutritional sources
Wong *et al.*[35]	Malaysia	Leaves, rhizomes, roots	-	GC, GC-MS, Preparative GC	Monoterpenoids and sesquiterpenoids compounds in the essential oil 37 compounds of the oils in the leaves 55 compounds of the oils in the rhizomes and roots

*GC-MS: Gas chromatography mass spectrometry, DPPH: 2,2-diphenyl-1-picrylhydrazyl, FRAP: Ferric-reducing antioxidant power, FIC: Ferrous-ion chelating, BCB: β-carotene bleaching, CC: Column chromatography, TLC: Thin layer chromatography, H- and C-NMR: Nuclear magnetic resonance, HPLC: High-performance liquid chromatography, RP-HPLC: Reversed-phased HPLC, LC-MS: Liquid chromatography-mass spectrometry, MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide, EI-MS: Electron ionization MS, EBV: Epstein-Barr virus, SOD: Superoxide dismutase, PCC: Protein carbonyl content, GPx: Glutathione peroxidase, GST: Glutathione S-transferase, H and E: Hematoxylin and Eosin, NO: Nitric oxide, BSLT: Brine shrimp lethality test, NRU: Neutral red uptakes, FTIR: Fourier-transform infrared spectroscopy, GC-FID: GC with flame ionization detector, inductively coupled plasma optical emission spectrophotometry (ICP-OES)

Table 2: Morphology and physiology of *E. elatior*[36]

Traits	Values/characteristics
Plant height	Up to 6 m tall
Stem	Pseudostems (leaf shoots)
Length	3-6 m tall
Shape	Short
Leaves	Numerous, dark green
Length	38-85 cm long
Width	8-18 cm wide
Arrangement	Lanceolate, hairless
Shape	Ligule to 1.5 cm long, lobed, glabrous
Flowers	Inflorescence, terminal, ovoid shaped of head consisting spirally overlapping flowers. The base is surrounded by showy crimson-pink bracts
Size	60-150 cm long and 0.8-1.5 cm wide
Color	Inflorescence has bright red or pink bracts, the labellum have yellow or white margins
Fruit	Green or red with many and black seeds
Size	2-2.5 cm in diameter
Color	Greenish or reddish
Shape	Short-pubescent, globose

cytotoxic activity[18]. Additionally, caffeoylquinic acids isomers, which are esters of caffeic and quinic acids were also isolated from *E. elatior* leaves due to the high amounts of chlorogenic acids (CGA) and caffeoylquinic acids (CQA)[14]. The phytoconstituents isolated from this plant are presented in Table 3[14].

Nutritional quality: In traditional dishes, *E. elatior* flower, inflorescence and fruit are widely used as a food ingredient because of the bright red shaped, distinctive taste and smell, which can increase the taste of the dishes. The consumption of *E. elatior* in foods is considered to have high nutritional value such as unsaturated fatty acids, proteins, amino acids and other mineral compounds as well as low contaminants of heavy metals. The composition of protein, fat and fiber in the dried flower were 12.6, 18.2 and 17%, respectively[1]. The high level of fiber content in this plant can potentially reduce blood cholesterol levels, hypertension, heart disease risk and constipation[40]. It was proven that the high content of saturated fatty acids were: Myristic acid>palmitic acid>stearic acid, whereas for the unsaturated were: Palmitoleic acid>linoleic acid>oleic acid[1]. Monounsaturated fatty acid and polyunsaturated acid contents were quantified up to 22.4 and 19.8%, respectively. In this basis, *E. elatior* could be used as an alternative source of fatty acids that is essential for various physiological processes and protection against various disease[41].

Furthermore, the amino acid profiles of *E. elatior* inflorescence revealed the presence of non-essential amino acids higher than the essential amino acids, which supports the pharmacological activity to treat inflammation, as immune stimulating agents, anti-oxidant and anti-microbials agent[42,43]. The non-essential amino acids were dominated by glutamic acid and aspartic acid, while the essential amino acids were dominated by lysine, leucine, valine, threonine, isoleucine and phenylalanine. The inflorescence also contained high levels of major minerals like potassium, calcium, magnesium and phosphor, which are very fundamental for extracellular and intracellular roles and as building blocks of physical components in human body. Also interestingly, heavy metal contents are found at a lower concentration thus making it safer for daily diet consumption[1].

Pharmacological activities: Table 4 listed all of the pharmacological activities articles of *E. elatior* accompanied with the inhibitory activity, which are anti-microbial, anti-oxidant, anti-tumor, anti-hyperglycemic, anti-hyperuricemic, anti-inflammatory, anti-larvae, skin whitening and anti-aging and wound healing.

Anti-microbial activity: *E. elatior* has been reported to having significant capability as anti-bacterial agent in responding to the symptoms caused by pathogenic microbes. Leaves, rhizome and inflorescence extracts of this plant were found to have anti-bacterial and anti-fungal activity against various microbes (Table 5).

The highly potential anti-microbials activity possessed by *E. elatior* against microbial infections is due to its elevated contents of flavonoids, phenolic and terpenoids compounds. A study by Xu and Lee *et al.*[44] showed inhibitory activity against MRSA by four flavonols such as datiscetin, kaempferol, quercetin, myricetin and two flavones such as flavone and luteolin[44]. Flavonoids mechanism in defeating microorganism pathogen is by targeting membrane cell wall due to its capability to composite with extracellular and soluble proteins[45,46]. Furthermore, flavonoids with more hydroxyl

Table 3: Chemical compounds isolated from *E. elatior*

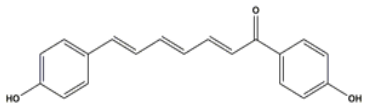
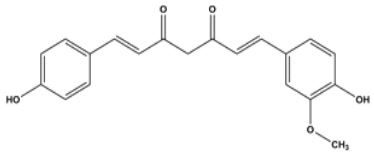
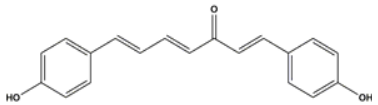
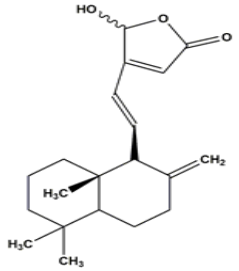
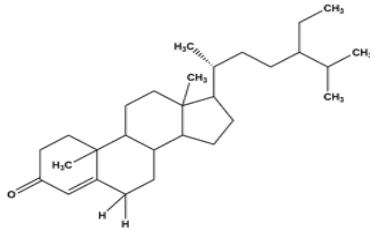
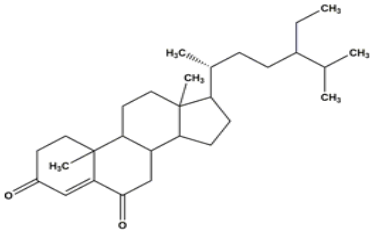
References	Chemical structures	IUPAC name, Formula	Molecular weight (MW)	Potential pharmacological activity
Habsah *et al.*[18]		1,7-bis(4-hydroxyphenyl)-2,4,6-heptatrienone $C_{19}H_{16}O_3$	292.33	Antioxidant
Habsah *et al.*[18]		Demethoxycurcumin $C_{20}H_{18}O_5$	338.3	Antioxidant
Habsah *et al.*[18]		1,7-bis(4-hydroxyphenyl)-1,4,6-heptatriene-3-one $C_{19}H_{16}O_3$	292.33	Antioxidant
Habsah *et al.*[18]		16-Hydroxylabda-8(17),11,13-trien-15,16-olide $C_{20}H_{28}O_3$	316.44	Antioxidant
Habsah *et al.*[18]		Stigmast-4-en-3-one $C_{29}H_{48}O$	412.70	Antitumor
Habsah *et al.*[18]		Stigmast-4-ene-3,6-dione $C_{29}H_{46}O_2$	426.69	Antitumor

Table 3: Continue

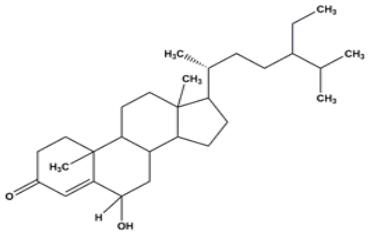
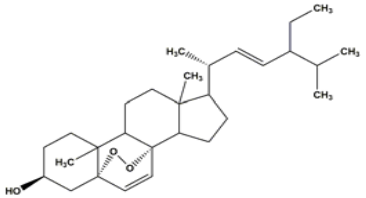
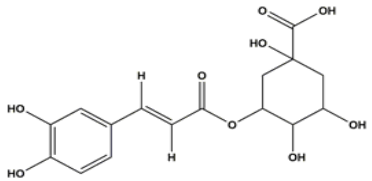
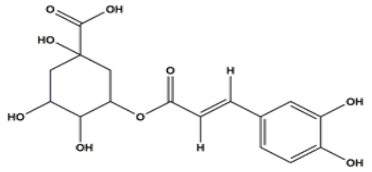
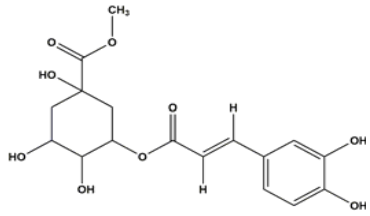
References	Chemical structures	IUPAC name, Formula	Molecular weight (MW)	Potential pharmacological activity
Habsah *et al.*[18]		Stigmast-4-en-6-ol-3-one $C_{29}H_{48}O_2$	428.70	Antitumor
Habsah *et al.*[18]		5,8-Epidioxyergosta-6,22-dien-3-ol $C_{28}H_{44}O_3$	428.66	Antitumor
Chan *et al.*[14]		3-O-Caffeoylquinic acid $C_{16}H_{18}O_9$	354.31	Antioxidant and antibacterial
Chan *et al.*[14]		5-O-Caffeoylquinic acid $C_{16}H_{18}O_9$	354.31	Antioxidant and antibacterial
Chan *et al.*[14]		5-O-Caffeoylquinic acid methyl esters $C_{17}H_{20}O_9$	368.34	Antioxidant and antibacterial

Table 4: Pharmacological activity studies of *E. elatior*

Pharmacological activity	References	Study design	Extract dose	Inhibitory activity
Anti-microbial	Abdelwahab *et al.*[11]	*In vitro*	100 mg mL^{-1}	MIC to *S. aureus*: 10 mg mL^{-1}
	Chan *et al.*[6]	*In vitro*	Not mentioned	MIC to *B. cereus*: 25 mg mL^{-1}, *M. luteus*: 6.30 mg mL^{-1}, *S. aureus*: 50 mg mL^{-1}
	Ghasemzadeh *et al.*[8]	*In vitro*	10 mg mL^{-1}	MIC to *S. aureus*: 40 g mL^{-1}, *B. subtilis*: 80 g mL^{-1}, *L. monocytogenes*: 40 g mL^{-1}, *S. typhimurlum*: 50 g mL^{-1}, *P. aeruginosa*: 60 g mL^{-1}
	Kusumawati *et al.*[25]	*In vitro*	200, 400, 600, 800, 1000 mg mL^{-1}	Inhibition zone to *S. typhi*, 20%: 3.9 mm, 40%: 6.5 mm, 60%: 6.76 mm, 80%: 7.45 mm, 100%: 9.28 mm
	Lachumy *et al.*[7]	*In vitro*	100 mg mL^{-1}	MIC to *S. aureus*: 1.563 mg mL^{-1}, *B. thuringiensis*: 6.250 mg mL^{-1}, *E. coli*: 12.5 mg mL^{-1}, *Salmonella* sp; 12.5 mg mL^{-1}, *M. luteus*: 50 mg mL^{-1}, *B. subtilis*: 25 mg mL^{-1}, *P. mirabilis*: 25 mg mL^{-1}, *C. albicans*: 3.125 mg mL^{-1}, *A. niger*: 1.563 mg mL^{-1}
	Naufalin *et al.*[29]	*In vitro*	300 mg mL^{-1}	MIC to *S. aureus*: 13 mg mL^{-1} (ethanol extract), 10 mg mL^{-1} (ethyl acetate extract)
	Angin [30]	*In vitro*	Not mentioned	Inhibition zone to *S. typhi*: 1.9 mm, *Shigella* sp.: 1.8 mm
	Susanti *et al.*[34]	*In vitro*	Not mentioned	MIC to *S. aureus*: 33.3 g mL^{-1}, *B. cereus*: 33.3 g mL^{-1}, *C. albicans*: 0.4 g mL^{-1}, *C. neoformans*: 0.05 g mL^{-1}
Anti-oxidant	Abdelwahab *et al.*[11]	*In vitro*	10 mg mL^{-1}	IC_{50}: 995.1 g mL^{-1}
	Anzian *et al.*[12]	*In vitro*	20, 10, 5 and 2.5 mg mL^{-1}	IC_{50}: 9520 g mL^{-1}
	Chan *et al.*[13]	*In vitro*	Not mentioned	IC_{50}: 3.87 g mL^{-1}
	Ghasemzadehk *et al.*[8]	*In vitro*	10, 20, 40, 80 and 160 g mL^{-1}	IC_{50}: 3.45 g mL^{-1}
	Jackie *et al.*[2]	*In vivo*	50, 100, 200 mg kg^{-1} b.wt.	Not mentioned
	Maimulyanti and Prihadi[3]	*In vitro*	10, 20, 30 and 40 g mL^{-1}	MeOH extract, IC_{50}: 21.14 g mL^{-1} EtOAc extract, IC_{50}: 68.24 g mL^{-1}
	Srey *et al.*[4]	*In vitro*	Not mentioned	IC_{50}: 134.27 g mL^{-1}
Anti-tumor	Ghasemzadehk *et al.*[8]	*In vitro*	20, 40, 80, 160, 320 and 640 g mL^{-1}	IC_{50}: 173.1 g mL^{-1} (MCF-7) IC_{50}: 196.2 g mL^{-1} (MDA-MB-231)
	Habsah *et al.*[18]	*In vitro*	10 mg mL^{-1}	IC_{50} (g mL^{-1}) EtOAc extract: 24.4 (CEM-SS), 6.25 (MCF-7) $CHCl_3$ extract: 14.0 (CEM-SS), 26.0 (MCF-7) Hexane extract: 42.5 (CEM-SS), 36.0 (MCF-7) MeOH extract: 46.0 (CEM-SS), 47.0 (MCF-7)
	Krajarng *et al.*[24]	*In vitro*	0, 5, 10, 15, 20 and 25 g mL^{-1}	IC_{50}: 15 g mL^{-1}
	Lestari and Ruswanto[26]	*In vitro*	Not mentioned	IC_{50}: 372.12 g mL^{-1} (n-hexane extract), IC_{50}: 455.26 g mL^{-1} (ethyl acetate extract), IC_{50}: 448.59 g mL^{-1} (methanol extract)
	Mackeen *et al.*[27]	*In vitro*	Not mentioned	CD_{50}: 10 g mL^{-1}
	Mai *et al.*[28]	*In vitro*	50-250 g mL^{-1}	IC_{50}: 170 g mL^{-1}
	Rusanti *et al.*[32]	*In vitro*	Not mentioned	IC_{50}: 19.21 g mL^{-1}
Anti-hyperglycemic	Srey *et al.*[4]	*In vitro*	25 g mL^{-1}	Inhibition (%) to α-glucosidase: 95.34% Inhibition (%) to α-amylase: 45.39%
Anti-hyperuricemic	Dewi *et al.*[5]	*In vivo*	200 mg kg^{-1} b.wt.	% inhibition to uric acid levels: 17.09%
Anti-inflammatory	Srey *et al.*[4]	*In vitro*	1-100 g mL^{-1}	IC_{50}: 19.36 g mL^{-1}
Anti-larvae	Koraag *et al.*[23]	*In vitro*	5, 7.5, 10, 12.5, 15, 17.5 mg mL^{-1}	LC_{50} to Aedes aegypti: 12 mg mL^{-1} (leaves extract) LC_{50} Aedes aegypti: 0.5 mg mL^{-1} (flowers extract)
Skin whitening	Nithitanakool *et al.*[9]	*In vitro* and *In vivo*	Not mentioned	Anti-tyrosinase, IC_{50}: 10.16 mg mL^{-1} Anti-collagenase, IC_{50}: 0.02 mg mL^{-1}
Wound healing	Handayany *et al.*[19]	*In vivo*	50, 70, 90 mg mL^{-1}	Not mentioned

**S. aureus*: *Staphylococcus aureus*, *B. cereus*: *Bacillus cereus*, *M. luteus*: *Micrococcus luteus*, *B. subtilis*: *Bacillus subtilis*, *L. monocytogenes*: *Listeria monocytogenes*, *S. typhimurlum*: *Salmonella typhimurlum*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *B. thuringiensis*: *Bacillus thuringiensis*, *E. coli*: *Escherichia coli*, *P. mirabilis*: *Proteus mirabilis*, *C. albicans*: *Candida albicans*, *A. niger*: *Aspergillus niger*, *C. neoformans*: *Candida neoformans*, MeOH: Methanol, EtOAc: Ethyl acetate

Table 5: Antimicrobial activity (MIC) of *E. elatior* extract

References	Microorganisms	MIC (mg mL^{-1})
Chan *et al.*[6]	*B. cereus*	25.00
Ghasemzadehk *et al.*[8]	*B. subtilis*	0.08
Lachumy *et al.*[7]	*B. thuringiensis*	6.25
Lachumy *et al.*[7]	*E. coli*	12.50
Ghasemzadehk *et al.*[8]	*L. monocytogenes*	0.04
Lachumy *et al.*[7]	*Micococcus* sp	50.00
Chan *et al.*[6]	*M. luteus*	6.30
Ghasemzadehk *et al.*[8]	*P. aeruginosa*	0.06
Lachumy *et al.*[7]	*P. mirabilis*	25.00
Lachumy *et al.*[7]	*Salmonella* sp.	12.50
Ghasemzadehk *et al.*[8]	*S. typhimurlum*	50.00
Chan *et al.*[6]	*S. aureus*	50.00
Lachumy *et al.*[7]	*A. niger*	1.56
Lachumy *et al.*[7]	*C. albicans*	3.12

Table 6: Anti-tumor activity of *E. elatior*

References	Cancer cells	IC_{50} (g mL^{-1})
Mai *et al.*[28]	HT-29	170.00
Ghasemzadehk *et al.*[8]	MCF-7	173.10
	MDA-MB-231	196.20
Mackeen *et al.*[27]	HeLa	10.00
Habsah *et al.*[18]	CEM-SS	4.00
Krajarng *et al.*[24]	B16	15.00
Lestari and Ruswanto[26]	T47D	372.12
Rusanti *et al.*[32]	P-388	19.21

group son the B-ring resulted greater destruction activity against microorganism membrane cell wall due to the more hydroxylation processes[45,47].

Meanwhile, the effect of *E. elatior* as anti-fungal is predicted due to the high level of phenolic content especially by caffeic acid derivates which act on cell wall damage[48], disrupting plasma membrane[49], inhibition of isocitrate lyase enzyme activity[50] and dimorphism inhibition[49].

Caffeoylquinic acid isomers which are esters of caffeic and quinic acids, e.g., chlorogenic acid, are known to affect fungal cell membrane by forming pores and depriving potential electricity of the membrane and leading to the breakdown of membrane permeability barrier, ultimately causing cytoplasmic content leakage by releasing ions and other materials[49]. Chlorogenic acid derivatives will impair fungal cell wall by attacking1,3-β-D-glucan synthase, the essential enzyme in the forming of fungal cell wall[48]. Chlorogenic acid as antifungal can interrupt glyoxylate cycle with the isocitrate lyase enzyme inhibition, which in turn will disturb defense mechanism of fungal in nutrient-limited host niches[50]. Moreover, chlorogenic acid also shows an effect on fungal dimorphism by inhibiting and destructing the forming of hyphae or pseudohyphae[49].

Endophytic microbes isolated from plants against various diseases have been proven in possessing pharmacological activities such as anti-cancer, anti-hyperglycemic, anti-oxidant, anti-inflammation, anti-microbials and anti-viral[51-57]. Moreover, endophytic bacteria isolated from *E. elatior* roots indicated anti-fungal activity against *Culvularia* sp., *Fusarium oxysporum*, *Rigidoporusmicroporus*, *Rhizoctoniasolani* and *Saprolegnia* sp. Eleven isolates of endophytic bacterial were obtained, in which seven of them are Gram-negative while the other four isolates were Gram-positive with diplococcus, streptobacillus and staphylococcus cell arrangements. The anti-fungal activity of endophytic bacterial isolated from *E. elatior* roots was predicted caused by alkaloid, saponin and terpene bioactive compounds[33]. Alkaloid works by disrupting (1,3)-β-glucan synthase, while saponin impairs to sterol in the cell membrane in increasing its permeability and protein denaturing of the cell membrane[58]. The mechanism of action of terpenes, i.e., monoterpenes and sesquiterpenes, as antifungal were reported by disrupting the membrane integrity and also destroying the fungal mitochondria[59,60].

Anti-oxidant activity: *E. elatior* leaves, inflorescences and rhizomes exhibited diverse antioxidant activity level analyzed through ascorbic acid equivalent antioxidant capacity (AEAC) and gallic acid equivalent (GAE) in FRAP determination. Rhizomes were observed possessed the highest activity[11]. The scavenging effect against free radicals of *E. elatior* extract has often been revealed through the ability in reducing violet of DPPH to the yellow of DPPH-H and the ability to reduce ferric (Fe^{3+}) tripyridyltriazine complex to ferrous (Fe^{2+}), forming deep blue colour by FRAP assay determination[12]. The fresh whole plant extract of *E. elatior* proved potential antioxidant activity through DPPH assay[11].The result of DPPH radical scavenging activity of methanol and ethanol extracts showed elevated percentage of DPPH by 76.26 and 63%, respectively[7,8]. Moreover, ethyl acetate fraction showed the lowest IC_{50} with 12.60 g mL^{-1} if compared to other solvents such as aqueous, ethanol, methanol, ethyl acetate, dichloromethane, butanol and hexane[3,4,8].

Moreover, another study by Anzian *et al.*[12] investigated the scavenging activity of three different drying methods (freeze-, oven- and sun-drying)of unopened *E. elatior* inflorescences by DPPH and FRAP assay and revealed that the freeze-drying method exerted the best free radical reduction with 89.24% of DPPH radical scavenging effect and 1973.01 mg/100 grams of the FRAP values and the IC_{50} obtained were 9.52 mg mL^{-1} [12]. The highest anti-oxidant activity of the freeze-drying method is probably due to the reduction of degradative enzyme activity, which leads to the absence of thermal degradation during the drying process. This particular method takes high extraction efficiency due to

the forming of ice crystals within the plant matrix, leads to the rupture of cell structure and furthermore, causes cellular components leakage. High amount of solvent will enter the cells and ultimately give better extraction yield[61].

Further study proved that *E. elatior* flower extract exhibited potent anti-oxidant activity by increasing the antioxidant enzyme levels such as SOD, GPx, GST and total anti-oxidants and also by lowering LPO and PCC proteins as biomarkers of protein oxidation due to oxidative stress[2,20]. It was supported by study investigations in lead acetate toxicity perturbation in inducing oxidative stress within rats serum levels[2] and on a testicular functional damage and spermatogenesis capabilities of rats[20].

The anti-oxidant activity of *E. elatior* revealed the potential effect of reducing free radicals in human physiology systems due to the high level of bioactive compounds such as phenolic and flavonoid[8,11]. The high amount of flavonoids content in *E. elatior* demonstrates various mechanisms in preventing injury caused by free radicals, which including direct scavenging activity against reactive oxygen (ROS), activation of anti-oxidant enzymes[62], inhibition of oxidases[63,64], metal chelating activity[65], reduction of tocopheryl radicals[63,66], increase in uric acid levels[67], increase in anti-oxidant properties of low molecular antioxidants[68], mitigation of oxidative stress caused by nitric oxide[69]. While, anti-oxidant mechanisms of phenolic compounds are based on the ability of donating hydrogen atom or electron to neutralize free radicals[70], chelating metal ions[70], acts as prooxidants[71] and the ability of OH groups in phenolic to react with the peroxyl radical (ROO^-)[72].

Anti-tumor activity: Many studies have revealed the potent anti-tumor activity of *E. elatior* plant extracts against various cancer cells and have minimal effect against normal cells (Table 6). The antitumor activity of the aqueous extracts of *E. elatior* leaves showed potent activity against human breast cancer cell lines MCF-7 and MDA-MB-231 if compared to tamoxifen. Tamoxifen is highly toxic against normal cells, in which the concentration of tamoxifen inducing toxicity was more than 120.4 g mL^{-1}, while the extract was not found to be toxic to normal cells[8]. Meanwhile, the combination of stigmasterol and -sitosterol isolated from *E. elatior* showed the highest potent anti-tumor activity with 85.1% of inhibition rate against Raji cell line[18].

The acetone extract of *E. elatior* leaves indicated potent antiproliferative and apoptotic activity against colorectal carcinoma cells (HT-29) and did not interrupt any proliferation inhibition to the normal cells of Chinese Hamster Ovary (CHO) cells. Moreover, the acetone leaves extracts promoted the HT-29 cells death at the initial stage of apoptosis by PS apoptotic cells translocation from inner to the outer leaflet of cell membrane, while both caspase-3 activation and PS translocation took place at the later stage of apoptosis. The apoptosis activity against HT-29 cells was confirmed by ELISA assay with the extent of apoptosis and necrosis with 2.353-fold and 0.229-fold increases, respectively[28].

A further study by Krajarng *et al.*[24] proved the activity of *E. elatior* extract in inhibiting cancer cell progression on melanoma B16 cells through the caspase-independent pathway and the inhibition of ERK1/2, p38 and Akt signaling pathway, compared to Vero monkey cells[24]. The *E. elatior* extract has shown to induce early onset of apoptosis of cells through nuclear condensation, phosphatidylserin exposure and loss of mitochondrial membrane potential, which was acquired about 14% in the beginning of apoptosis stage at 4 and 8 h and the end stage of apoptosis increased by about 40% at 16 and 24 h, in which the apoptosis process appears when phosphatidylserine is transmitted from the inside to the outside of the cell membrane and will signal to the phagocytes to eat the cell. Based on the study, *E. elatior* extract did not enhance the expression of antiapoptosis and proapoptosis proteins such as of Bcl-2, Bax and caspase 3/7, 8 and 9 after extracts administration. However, Bim protein expression showed a significant improvement level, in which Bim is the proapoptotic protein subgroup of the third Bcl-2 family. To conclude, *E. elatior* extract of 15 μg mL^{-1} can only induce apoptosis through the expression of proapotosis protein of Bim and through the caspase-independent[24]. The mechanism of caspase-independent cell line mortality can be encouraged by factors liberated from mitochondria including endonuclease G (EndoG) and apoptosis-inducing factor (AIF), where either of these factors move to the cell nucleus and cause large-scale chromatin condensation and DNA fragmentation. The discharge of endoG from mitochondria is stimulated by BH3 proteins for instance tBid and Bim and inhibited by Bcl-2[73].

However, the effect of *E. elatior* extract in lowering the protein expression of extracellular signal-regulated kinase (ERK) and Akt has been reported. The expression of p38, ERK1/2, phosphorylated of p38 (P-p38) and phosphorylated of ERK1/2 (P-ERK1/2) decreased after the administration of *E. elatior* extract. Also, the extracts showed an inhibition of B16 melanoma cell through the suppression of Akt, which decreased total Akt activity and phosphorylated Akt (Ser473 and Thr308). ERK signaling can stimulate cell differentiation, proliferation and cell survival, in which c-Jun N-terminal kinase (JNK) and p38 are a stress-activated protein kinases[24]. The inhibition of ERK pathways in melanoma cells with BRAF inhibitors causes the cell cycle to stop and

stimulate cell death by apoptosis[74]. The AKT pathway is a serine/threonine kinase protein that can stimulate cell growth, proliferation and survival. Phosphorylation Akt may inhibit the release of cytochrome c and apoptotic factors that would obstruct apoptosis and cancer cell development[75].

The antiproliferative activity of *E. elatior* may be attributed to the high levels of flavonoids by the ortho-catechol moiety of a C2-C3 double bond and in ring B on flavones and flavanones. As to polymethoxylated-flavones, crucial contribution in providing high activity is given by the C3 hydroxyl and C8 methoxyl groups[76]. The flavonoids inhibition on tumor cells involved cell cycle arrest by interfering checking points regulation of both G1/S and G2/M and inhibiting all CDKs[77-81] and also apoptosis promotion by inhibiting DNA topoisomerase I/II activity[82-84], decreasing ROS[85], regulating the expression of heat shock protein[86], signaling pathways modulation[87], down regulating of NF-kB, activating endonuclease and suppressing Mcl-1 protein[73,86,88,89].

Anti-hyperglycemic activity: By inhibiting either α-glucosidase or α-amylase enzymes, it will further delay carbohydrate absorption and decrease sugar absorption after meals and eventually reduces glucose uptake and blood glucose[89]. *E. elatior* ethanol extract (25 μg mL^{-1}) showed potent inhibition on α-glucosidase and α-amylase compared to acarbose inhibition[4].

Anti-hyperuricemic activity: The anti-hyperuricemic activity of *E. elatior* flower extract in rats had been proven by Dewi *et al.*[5] by determining uric acid level. The flower extract could suppress uric acid in blood serum up to 31.78%, while allopurinol was 45.65%. The potent anti-hyperuricemic activity was related to the high levels of polyphenols, flavonoids and saponin[5]. Flavonoids structure plays important role in inhibiting xanthine oxidase (XO) by controlling the overproduction of uric acid formation[90]. The double bond between C2 and C3 and also the hydroxyl groups at C5 and C7 were potentially exhibited inhibitory activity on XO[64]. The planar flavonols and flavones with a 7-hydroxyl group such as kaempferol, chrysin, quercetin, luteolin, isorhamnetin and myricetin had an elevated inhibition activity on XO by occupying the site of action competitively and by interacting with the enzyme either at a site or other than the active site[90].

Anti-inflammatory activity: The study of anti-inflammatory activity of *E. elatior* plant has not been widely reported yet. The potent anti-inflammatory activity of *E. elatior* once reported by Srey *et al.*[4] which conducted on the *E. elatior* rhizome extract inhibition to wards nitric oxide (NO) production in murine macrophage-like cell-line (RAW264.7). Rhizome extract at the concentration up to 100 g mL^{-1} could suppress the production of NO up to 91% with IC_{50} of 21 g mL^{-1} and compared to indomethacin with 85% of inhibition and 19 g mL^{-1} of the IC_{50}. The anti-inflammatory activity of *E. elatior* plant was caused by the terpenoid aglycone[4]. For instance, several flavonoid and terpenoids groups have been reported to inhibit the expression of various enzymes related to the regulation of inflammation response such as inhibition of prostanoid biosynthesis (lipoxygenase, cyclooxygenase, inducible nitric oxide synthase), inhibition of histamine release, inhibition of phosphodiesterases, inhibition of protein kinases and transcription activation[91]. Water extract of red ginger could inhibit the rate of prostaglandin production in COX-1 and COX-2[92]. Many phytoconstituents, e.g., flavonoids, diterpenoids, chalcones, interact with Arg120 and/or Tyr355 in COX-1 and with Tyr385 and/or Ser530 in COX-2, which are similar to the binding mode of NSAIDs. Nonetheless, based on the selectivity index calculation (cSI), only a few of the flavonoids and diterpenoids are categorized as selective COX-2 inhibitors[93].

Toxicity study: *E. elatior* extract was found to be non-toxic based on the study of Lachumy *et al.*[7] using brine shrimp lethality bioassay (LC_{50} = 2.52 mg mL^{-1}) at 24 h. Thus, *E. elatior* extracts and the pharmaceutical properties contained can be categorized as biologically safe compounds[7].

CONCLUSION AND FUTURE PERSPECTIVES

This review study on *E. elatior*, its phytoconstituents and pharmacological activities have revealed that the plant is potential to be utilized as phytopharmaceuticals. The most prominent pharmacological activities are anti-microbial, anti-oxidant and anti-tumor activities in consistent with the dominated levels of flavonoids and phenols. However, integrated research on the molecular mechanism of anti-inflammatory activity, particularly its inhibitory activity on NOS and modulation on NF-kappaB expression, as well as the level of flavonol synthase in the plant's leaves, are being carried out.

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