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Review

An insight on the immunomodulatory potential of wood oil of *Aquilaria malaccensis* Lam. with an emphasis on related phytomedicine, biomarkers, pharmacology, and toxicity

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ABSTRACT

Critically endangered *Aquilaria malaccensis* Lam. is known for highly expensive agarwood with unique aroma. Agarwood has been used as a phytomedicine in chronic degenerative neurological disorders, paralysis, rheumatism, asthma, and others. Its production is dependent naturally or artificially on interaction of endophytic fungi, and by nailing, drilling, and microbial inoculation respectively. The majorly produced biomarkers of terpenes, fatty acids, alkanes, chromones, and flavonoids exhibited several biological activities in congruence to their ethnomedicinal claims. During the pandemic, several *in-silico*, studies showed the potential of a few sesquiterpene hydrocarbons against covid-19. The review aimed to deliver a comprehensive outline of the immunomodulatory potential of agarwood oil with allied traditional medicinal use, biomarkers, pharmacological evaluation, toxicity, and mechanistic action. The review eventually showed the agarwood oil, extracts, and major biomarkers viz., aromadendrene II, valencene, phytol, octacosane, caryophyllene oxide, β-caryophyllene, hinesol, agarospirol, with immunomodulatory, anti-inflammatory, and allied neural, antidiabetic, antimicrobial activity, toxicity, along with molecular target binding potential against 3CLpro, RDRP, Mpro, PLpro, Spike protein S1 of SARS-CoV2 through *in-vitro, in-vivo, in silico* studies and limited human clinical trials. The expression of *HMGR, ASS, ADXPS, ADXPR, FPS*, and *WRKY* genes of sesquiterpenoid biosynthetic pathways were upregulated for signature aroma and immunomodulatory markers viz., δ-guaiene, dodecane, tetracosane, agarospirol, farnesol, and geranylgeraniol acetate as a defensive response. The review would ignite future research on potential immunomodulatory markers viz., caryophyllene oxide, octacosane, heneicosane, agarospirol, n-hexadecanoic acid, α-eudesmol, α-santalol and inoculum guided *in-vitro* agarwood production restoring the prized aroma, therapeutic efficacy, and wild population.

List of abbreviations: 3CLpro, 3-chymotrypsin-like protease; 5-HT, 5-hydroxytryptamin (serotonin); AACT, Acetyl CoA C-acetyl transferase; AchE, Acetylcholinesterase; ACTH, Adrenocorticotropic hormone; ADH, Alcohol dehydrogenase; ALB, Albumin; ALDH, Aldehyde dehydrogenase; ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate aminotransferase; BALB/c, Bagg albino mouse; Chrnd, Cholinergic receptor nicotinic delta subunit; CMC, Carboxymethylcellulose; CNS, Central nervous system; CORT, Corticosterone; COX-2, Cyclooxygenase 2; CRF, Corticotropin releasing factor; CRFR, Corticotropin-releasing factor receptor; Crhr2, Corticotropin-releasing hormone receptor; CYP2E1, Cytochrome P450 2E1; DAVID, Database for annotation visualization and integrated discovery; DDY, Deutschland Denken and Yoken; DLA, Dalton Lymphoma ascites; DMSO, Dimethyl sulfoxide; EAC, Ehrlich-Lettre ascites carcinoma; EPM, Elevated plus maze; FMLF/CB, N-formyl-L-methionyl-L-leucyl-L-phenylalanine cytochalasin B; GLU, Glucanase; GPT, Glutamic pyruvic transaminase; GRN, Granulocyte; GSH, Glutathione; GST, Glutathione-S-transferase; HBMMC, Human bone marrow mesenchymal cell; HCT 116, Human colon cancer cell; HFFD, High fructose fat diet; HPA, Hypothalamic-pituitary-adrenal axis; HRBC, Human red blood cell; ICR, Institute of Cancer Research; IDX, Insulin, dexamethasone and 3-isobutyl-1-methylxanthine; IL, Interleukin; KEGG, Kyoto encyclopedia of genes and genomes; LDE, Light dark exploration; LDH, Lactate dehydrogenase; LOX, Lipoxygenase; LPS, Lipopolysaccharide; LYM, Lymphocyte; MALDI-TOF-MS, Matrix assisted laser desorption/ionization time of flight mass spectrometry; MAO, Monoamine oxidase; MCF-7, Michigan Cancer Foundation-7; MDA, Malondialdehyde; MEP, Methylerythritol 4-phosphate; MIC, Minimum inhibitory concentration; MON, Monocyte; MTT, (3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide); MYC, Myelocytomatosis; MYB, Myloblastosis; nNOS, Neuronal nitric oxide; NO, Nitric oxide; OF, Open field; Pb$(C_2H_3O_2)_2$, Lead acetate; PBMCs, Peripheral blood mononuclear cell; PI3K, Phosphoinositide 3-kinase; PMA, Phorbol 12 myristate 13-acetate; PPARγ, Peroxisome proliferator-activated receptor gamma; RAW 264.7 cell, Murine macrophage cell line; RBL-2H3, Rat basophilic Leukemia cell line; SCFE, Slipped capital femoral epiphysis; SD, Sprague Dawley rats; SGPT, Serum glutamic pyruvic transaminase; STZ, Streptozotocin; TP, Total protein; TNFα, Tumor necrosis factor alpha; WST, Water-soluble tetrazolium salt; ZoI, Zone of inhibition

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1. Introduction

Uniquely aromatic agarwood is produced by *Aquilaria malaccensis* Lam., of the family *Thymelaeaceae* Juss. The species is known as Gaharu, Agor or Aguru. Agarwood is one of the costliest resinous substances around the globe. It is produced in the heart wood as a response to fungal and other microbial infections in *A. malaccensis* and its allied species including *A. baillonii* Pierre ex Lecomte, *A. beccariana* Tiegh., *A. crassna* Pierre ex Lecomte, *A. filaria* (Oken) Merr., *A. hirta* Ridl., *A. khasiana* Hallier f., *A. microcarpa* Baill., *A. rostrata* Ridl., *A. rugosa* K.-Le-Cong & Kessler, *A. sinensis* (Lour.) Spreng., *A. subintegra* Ding Hou and *A. yunnanensis* S.C. Huang (Lee and Mohamed, 2016; Sangareswari et al., 2016). From the prehistoric ages, agarwood was greatly valued in the international market in ancient Egypt, Greece, Rome, China, and India (Groom, 1981). In the traditional system of medicines, it was referred against mostly degenerative ailments viz., psychoneurosis, epilepsy, rheumatism, inflammation, sexual debility, weakness, bronchitis, and as an immunosuppressant (TKDL, 2001). The current price of per gram Agarwood oil is approximately Rs 32,500.00 (https://m.indiamart.com/prodde). According to the Industry Analysis and Forecast, the global market for Agarwood oil is expected to reach about 0.362 billion US Dollars by 2026 (www.maximizemarketresearch.com). Apart from high-value agarwood, *A. malaccensis* has several allied industrial and environmental applications viz., agar tea from air-dried leaves in SE Asia (Batubara et al., 2016; Adam et al., 2017; Kuo et al. 2020), medicated liquor from agarwood from Malaysia (Asia-Taipei and Asia, 2005), biodiesel and bioenergy (Limhengha et al., 2021; Tamuly, 2021) and as an agent of phytoremediation for absorption of heavy metals such as Cd and Cu (Keeren et al., 2013; Hamzah and Atikah, 2018). For its high demand in perfumery industries, commercial benefits, and in traditional medicines, *A. malaccensis* had been overexploited in the wild and was enlisted as 'critically endangered' (Harvey-Brown, 2018). The micropropagation and mass multiplication techniques were recommended to conserve this endangered elite species (Siah et al., 2016).

The strong perfumery odor of agarwood is markedly induced by terpene derivatives viz., α-agarofuran, β-caryophyllene, caryophyllene oxide, and others, where its demand relies upon its aroma quality (Naef, 2011). Several genes viz., *WRKY, MYC*, and *MYB* exhibited a significant role in the biosynthesis of terpene derivatives (Islam et al., 2020). Moreover, β-caryophyllene, a sesquiterpene hydrocarbon biomarker of agar oil exhibited great potential against covid-19 by strongly inhibiting the protease of the *nCoV* virus (Jahan et al., 2021). Despite its great economic potential and traditional uses, earlier reviews and publications concentrated mainly on phytochemistry and specific pharmacological properties of agarwood without comprehensive information on immunomodulatory activity, and biomarker-guided quality agarwood production and gene expression (Naef, 2011; Ismail et al., 2015; Eissa et al., 2018; Eissa et al., 2020). Therefore, this study aimed to impart an updated overview of the immunomodulatory potential of *A. malaccensis* with an emphasis on allied phytomedicines, key biomarkers, pharmacological evaluation, toxicity, and mechanistic action. Approximately 157 references including the earliest from 1783 on species identity to delve deeper into immunomodulatory potential against SARS-CoV2 were reviewed from several online databases and web portals, published literature, and Ph.D. thesis (Adam, 2017) till April 2022. The search keywords used were viz., *Aquilaria malaccensis* taxonomy, biomarker, immunomodulatory, anti-inflammatory, antidiabetic, neurological, antimicrobial, toxicity, clinical trial, SARS-CoV2, gene expression, agarwood formation, biosynthetic pathway, fungal association, and microbial inoculum. Taxonomic identity and scientific names were verified through http://www.plantsoftheworldonline.org/. PubChem IDs of major biomarkers were compiled and redrawn by ChemDraw (Barman et al., 2021).

2. Botanical note

The genus *Aquilaria* Lam. belongs to the tribe *Aquilarieae* (RBr.) Baill. under the subfamily *Thymelaeoideae* Burnett, family *Thymelaeaceae* (Herber, 2003). Apart from *Aquilaria*, agarwood is also produced by the other genera such as *Phaleria* Jack, *Enkleia* Griff., *Wikstroemia* Spreng., *Gyrinops* Gaertn., *Aetoxylon* (Airy Shaw) Airy Shaw and *Gonystylus* Teijsm. & Binn. (Lamarck and Poiret, 1783; Herber, 2003; Eurlings and Gravendeel, 2005; Lee et al., 2018). In international trade, *Aquilaria* along with *Gyrinops* and *Gonystylus* were classified under Appendix II of CITES (CITES, 1994). As species substitution alters the quality of aroma and therapeutic value of agarwood oil, the botanical differences among the allied species and the genera were thoroughly reviewed viz., *Aquilaria khasiana* Hallier f. differs from *A. malaccensis* in having villous pedicel and tube, ovate-triangular tube lobes, obovate to oblanceolate fruits and ovoid–ellipsoid seeds whereas *A. malaccensis* has glabrous pedicel and tube, ovate-oblong tube lobes, obovate capsular fruits and ovoid–globose seeds (Hou,1964; Eurlings and Gravendeel, 2005; Mir et al., 2017). The differences among *Aquilaria* and allied genera were critically reviewed. *Aquilaria* differs from *Enkleia* being a tree while *Enkleia* is a liana. *Aquilaria* has alternate leaves whereas *Wikstroemia* has opposite leaves. *Aquilaria* has number of stamens (8-12) twice of calyx lobes but *Gyrinops* has equal numbers of stamens (5) and calyx lobes. *Aquilaria* has loculicidal capsule as fruit but *Phaleria* has drupes. *Aquilaria* has 1-2 chambered fruits but *Aetoxylon* has 3 or more chambered fruits. *Aquilaria* has number of petaloid appendages double of calyx lobes but petaloid appendages not doubled in *Gonystylus* (Quisumbing, 1946; Eurlings and Gravendeel, 2005).

Initially *Aquilaria agallocha* Roxb. was treated as a separate species from *A. malaccensis* Hooker (1886) distinguished *Aquilaria agallocha* from *A. malaccensis* Lam. in having 3.8-5 cm oblanceolate-acuminate glabrous to coriaceous fruits compared to ca. 3.8 cm broadly obovoid thick woody fruits of *A. malaccensis*. As the morphology of both the species were conspecific, D. Hou (1960; 1964) reduced *Aquilaria agallocha* as a synonym under *A. malaccensis*. *Aquilaria malaccensis* Lam. is a tree with glabrous elliptic-oblong to lanceolate leaf lamina acuminate at the apex. Inflorescences are umbels at terminal or axillary position. Flowers are green or greenish yellow with a campanulate calyx tube. Nectarial scales or petaloid appendages are present. Stamens are twice in a number of calyx lobes. The ovary is pubescent and stigma is capitate. Fruits are obovoid or obovoid-oblong capsules (Hou, 1960; 1964). It is widely distributed in Bhutan to SE Asia, mostly up to 1000 m (CITES, 2003).

3. Phytomedicine

Different plant parts of *Aquilaria malaccensis* had been used by various tribal communities in Asia. It had been used as a immunosuppressant, in rheumatism, and inflammation in Ayurveda; stomach problem, sexual debility, epilepsy, psychoneurosis, cardiac problem, weakness in Unani; bronchitis and others in Siddha. In folklore, it was mostly reported in the treatment of digestive, respiratory, metabolic, neurological disorders, snake bites, and others by the tribes such as *Bodo-Kachari, Nyishi, Ao naga, Chakma, Khasia, Phom, Chothe, Lotha naga* from North East India and Bangladesh (Changkija, 1994; TKDL, 2001; Jamir et al., 2010; Jamir and Tsurho, 2016; Esha et al., 2012; Uddin and Mukul, 2012; Basumatary et al., 2014; Balkrishna et al., 2021). Even though the distribution of the species was reported from Bangladesh to Malaysia, ethnic use of the species was reported in mouth infection and cancer by tribal communities of Morocco (Bourhia et.al 2019; Merzouki et al. 2000; Table 1).

Table 1
A few phytomedicinal uses of ***Aquilaria malaccensis*** Lam.

Phytogeographical region	Local name	Tribe /Ethnic group/Region	Parts used	Health ailments/other uses	Reference
NE INDIA	Agar, Agaru, Sanchi	Assamese, Assam, India	Bark, leaves, stem, oil	Itchy throat, leprosy, holy scripts	Nath and Saikia (2002); Saikia et al., (2006); Sarma et al., (2015)
	Agar	Bodo-Kachari, Assam, India	Bark	Stomach pain, snake bite, vomiting	Basumatary et al., (2014)
	Thing-rai	Nyishi	-	Constipation, diarrhea, vomiting, snake bite	Balkrishna et al., (2021)
	Tssungza, Agor	Lotha naga, Phom, Nagaland, India	Whole plant, wood, resin	Asthma, diarrhea, dysentery, rheumatism, paralysis	Jamir et al. (2010); Jamir and Tsurho (2016)
	Agor, Machi	Chothe, Thadou (Kuki), Vaiphei, Chiru, Ireng (Rongmei), Meitei, Manipur, India	Bark	Incense stick, perfumery, diarrhea	Sanglakpam et al., (2012); Khan et al., (2015)
	Thingrai	Mizo, Mizoram, India	Resinous wood	Antiasthmatic, antirheumatism, diuretic, leukoderma	Rai and Lalramnghinglova (2010)
	Agar	Tripuri, Tripura, India	Bark, twig	Burial, dead soul purification, rheumatic pain	Majumdar and Datta (2009); Debnath et al., (2016)
	Agor	Laleng (Patra)	-	Sacred plant	Partha (2014)
	Sungza sung	Aonaga	Oil	Stomach disorders	Changkija (1994)
South India	Agaru	Adilabad, Telangana, India	Bark	Coldness	Gurrapu and Mamidala (2016)
	Akil, Karakil	Malayaraya, Kerala	Resinous wood, oil	Dermatological ailment, blood purifier	Sudeesh (2012)
South East Asia	Agar, Akod, Agor	Khasia, Sylhet, Chakma, Madhupur forest Reserve, Garo & Nongaro, Tangail, Bangladesh	Leaves, resin/ resinous oil, wood	Vomiting, joint/body/ rheumatic ache, cough, diarrhea, fever, skin disease, ulcer, jaundice	Rahmatullah et al., (2011); Esha et al., (2012); Uddin and Mukul (2012); Islam et al., (2014)
	Agaru	Lower Khengkha, Bhutan	Wood	Cardiac, neurological disorder	Wangchuk et al., (2017)
	Kagas / Gaharu/ Garu/ Alim	Batak toba, Talang mamak, Orang melayu, Indonesia	Leaves, trunk, bark, sap wood	Morning sickness, joint/ abdominal ache; construction, firewood	Grosvenor et al., (1995); Wiryono et al., (2017); Silalahi et al., (2019); Susandarini et al., (2021)
	Johuk /Gaharu/ Karas	Aborigines, Jahai, the Malay peninsula	Leaves	Asthma, bathing	Nurraihana et al., (2016); Ayuni et al., (2018)
Africa	Ighris/ Aoud Laqmari	Casablanca-Morocco, Ksarlakbir, Morocco, Africa	Bark, trunk	Cancer, mouth infection	Merzouki et al., (2000); Bourhia et al., (2019)

4. Biomarkers

Numerous research and review papers were published on phytochemicals of *Aquilaria malaccensis* (Naef, 2011; Ismail et al., 2015; Peng et al., 2015; Samadi et al. 2017; Wang et al., 2018a; Eissa et al., 2020). Strongly aromatic yellowish agarwood oil was reportedly produced approximately 0.05–0.2% in the infected trees (Tajuddin and Yusoff, 2010; Samadi et al., 2017; Samadi et al., 2020). The approximated yield varies in healthy (0.15%), and infected trees viz., naturally infected (0.8%), and artificially infected (0.4%), respectively. The major biomarkers and content varied with the severity of the infection and nearly 25% of aromadendrene II (**10**), 18% of valencene (**43**), 9% of calarene (**54**), and 9% 1,(5)-6-guaiadiene (**7**) were reported in oil from highly infected trees, followed by 17% t-cadinol (**49**) in moderately infected trees and 39% 1-methyl-1-caprolactone (**100**), 32% 7-(Hydroxymethyl) 2-methoxy xanthone (**148**) and 2% aromadendrene II (**10**) in less infected trees (Benedict, 2009; Bhuiyan et al., 2009; Jayachandran et al., 2014). However, significant biomarkers reported were viz., terpenes (**1-65**), fatty acids and amide (**66-71**), aldehydes (**72-80**), alcohols and phenols (**81-90**), acids and esters (**91-103**), alkane hydrocarbons (**104-118**), cyclic hydrocarbons (**119-123**), flavonoids, flavanols, chromones and xanthones (**124-152**), and others (**153-159**) [Fig. 1**, Table S1**]. The most prevalent terpenes reported were sesquiterpenes (56–93%) comprising oxygenated sesquiterpenes (30-36%) and sesquiterpene hydrocarbons (15-20%), followed by monoterpenes, diterpenoids, triterpenoids, sesquiterpene alcohol, sterols, and alkaloids, including noteworthy other biomarkers viz., caryophyllene oxide **(25)** (11%), β-caryophyllene **(18)** (6–8%), α-eudesmol **(46)** (2–3%) and others (Tajuddin and Yusoff, 2010; Jayachandran et al., 2014; Peng et al., 2015). Major fatty acids reported were saturated fatty acid viz., palmitic acid **(68)** (26–28%), fatty aldehyde like pentadecanal **(74)** (31–32%), monosaturated fatty aldehyde like tetradecanal **(78)** (5–7%), and others. Notable alcohols identified in *A. malaccensis* are viz., cis-3-hexanol **(85)**, 1-octanol **(82)**, guaiacol **(87)**, and others (Samadi et al., 2017; Nasution et al., 2020). Among the acids and esters, notable reported biomarkers were mono and dicarboxylic acids and esters comprising trichloroacetic acid **(91)**, succinic acid **(95)**, benzyl salicyclate **(99)**, glucopyranosyl sinapate **(102)**, and others (Samadi et al., 2017; Eissa et al., 2020; Hashim et al., 2020). Significant alkane hydrocarbons reported were viz., nonacosane (**112**), octacosane (**113**); cyclic hydrocarbons viz., azulene (**119**), and quindoline (**123**) (Bhuiyan et al., 2009; Jayachandran et al., 2014; Samadi et al., 2017). Several flavonoids, flavanols, chromones, and xanthones were commonly reported viz., aquisiflavoside (**126**), luteolin **(134),** 8-methoxy-2-(2 phenylethyl) chromen-4-one (**143**), 2-(2-Phenylethyl) chromone (**144**) (27%), homomangiferin (**149**), and mangiferin (**150**); and as benzophenone, aquilarisinin (**151**) (Eissa et al., 2020; Nasution et al., 2020; Wirjosentono et al., 2020; Kao et al., 2021). In the majority of the publications, the markers were identified by LC-MS, Liquid Chromatography-Q-TOF-MS, SPME-GC-FID-MS, and GC-MS/TLC without being further characterized by NMR (Peng et al., 2015; Eissa et al., 2020; Wirjosentono et al., 2020).

5. Pharmacology

Experimental data of *in vitro, in vivo* studies, and clinical trials of the solvent extracts, essential oil, and biomarkers were critically reviewed for immunomodulatory and majorly allied biological activities known at present. The reviewed studies were compiled and presented with approximate values for easy understanding.

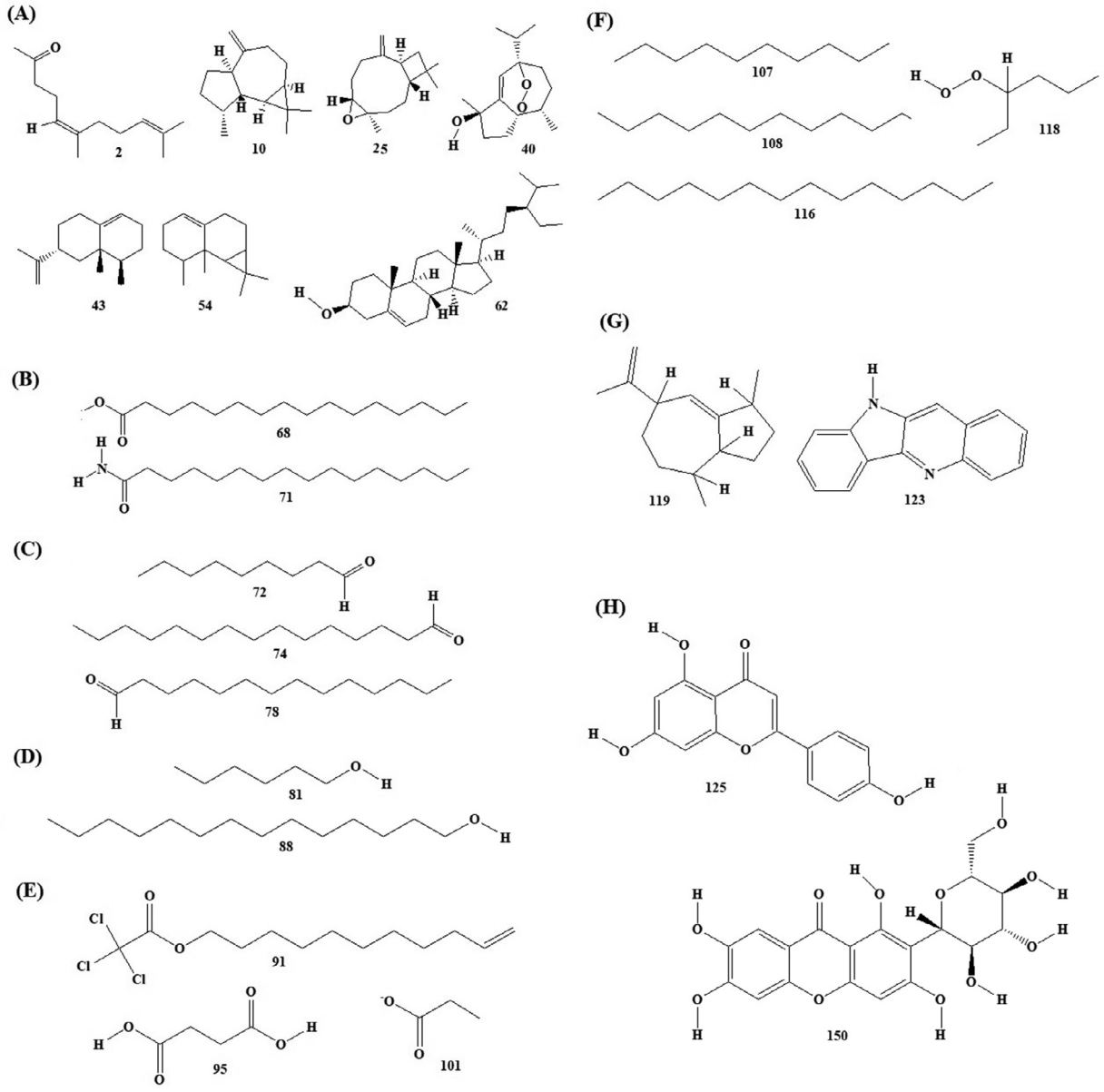

Fig. 1. Some biomarkers of ***Aquilaria malaccensis***: **A.** Terpenes, **B.** Fatty acids and amide, **C.** Aldehydes, **D.** Alcohol and phenols, **E.** Acids and esters, **F.** Alkane hydrocarbon, **G.** Cyclic hydrocarbon, **H.** Flavonoids, flavonols, chromones, xanthones.

5.1. Anti-inflammatory and immunomodulatory activity

In vivo and *in vitro* studies with the best findings of anti-inflammatory and immunomodulatory activity were compiled (Table 2). In 30 days multiple *in vivo* studies among 25 numbers 8–10 weeks old female albino rats of 200–270 g, methanolic bark extract of *Aquilaria malaccensis* decreased the WBC (<4.1), LYM (<4.0), GRN (<0.4), MON (<0.5), heart lipid peroxidation marker MDA (< 1 μmol/mg), and body weight gain (<0.15 g/day) in methanolic extract and HFFD treated group from only HFFD treated group WBC (< 5), LYM (<4.1), GRN (<0.55), MON (<0.7), MDA (< 3 μmol/mg) and body weight gain (< 1.06 g/day) exhibiting immunomodulatory potential. In a similar 15 days study $Pb(C_2H_3O_2)_2$ 100 mg/kg and *Aquilaria* powder 10 g/kg b.w. decreased body weight and relative liver weight of experimental rats from 198 g and 3.2 g to 196 g and 2.6 g which were gained by $Pb(C_2H_3O_2)_2$ treatment compared to control i.e., 291 g and 2.5 g respectively (Derouiche et al., 2019). In another study among 24 male and female Wistar rats of 150–200 g, *A. malaccensis* wood oil at 100 mg/kg exhibited a reduction in carrageenan-induced paw edema after 3 hours <63% than <69% with diclofenac (10 mg/kg) as anti-inflammatory activity (Rahman et al., 2012). *In vitro* studies with bioactive markers from *A. malaccensis* such as 1α,7α-dihydroxy-8oxo-4αH,5αH-guaia-9(10),11(13)-dien-12-oate (**8**), phytol (**55**), n-hexadecanoic acid (**68**), phorbol esters (**58**), essential oil by SCFE inhibited NO synthesis in LPS stimulated RAW 264.7 cells with IC_{50} <19.0 μM, concentration-dependent albumin denaturation <71%, elastase release in FMLF/CB induced human neutrophils with IC_{50} 0.8–2.7 μM, enhanced superoxide in FMLF/CB induced human neutrophils, concentration-dependent protection of HRBC cell membrane in a hypotonic solution than diclofenac and inhibited BSA denaturation by 29–52% (Rahman et al., 2012; Wagh et al., 2017; Eissa et al., 2018; Zainurin et al., 2018; Ma et al., 2021). Most of the *in vivo* experiments lacked the use of the equal ratio of male and female individuals, and *in vitro* studies lacked the use of negative control, standard, and reference exhibiting results without the potential of translational use in human therapeutics.

Table 2
Anti-inflammatory and immunomodulatory activity of ***Aquilaria malaccensis*** Lam.

Study type	Part used	Extract/Compound	Experimental model/set up	Dosages	Control	Activity	Reference
In vivo	Bark	Methanolic [Apigenin **(125)**, epicatechin **(128)**, naringenin **(136)**, quercetin **(137)**, kaempferol **(132)**, rutin **(139)]**	Adult female albino rats (8–10 weeks old), 200–270 g, 25 rats, 5/group	HFFD + MeOH extract (200 mg/kg/d) for 30 days	Normal diet	Decreased body weight gain in methanol extract and HFFD treated group (<0.15 g/day) than only HFFD group (<1.06 g/day) and control (< 0.54 g/day) exhibiting immunomodulatory potential.	Derouiche et al. 2019
In vivo	Bark	Methanolic [Apigenin **(125)**, epicatechin **(128)**, naringenin **(136)**, quercetin **(137)**, kaempferol **(132)**, rutin **(139)]**	Adult female albino rats (8–10 weeks old), 200–270 g, 25 rats, 5/group	HFFD + MeOH extract (200 mg/kg/d) for 30 days	Normal diet	Decreased WBC (<4.1), LYM (<4.0), GRN (<0.4) and MON (<0.5) in methanol extract and HFFD treated group than only HFFD treated group viz., WBC (< 5), LYM (<4.1), GRN (<0.55) and MON (<0.7) exhibiting immunomodulatory potential.	Derouiche et al. 2019
In vivo	Bark	Methanolic [Apigenin **(125)**, epicatechin **(128)**, naringenin **(136)**, quercetin **(137)**, kaempferol **(132)**, rutin **(139)]**	Adult female albino rats (8–10 weeks old), 200–270 g, 25 rats, 5/group	HFFD + MeOH extract (200 mg/kg/d) for 30 days	Normal diet	Decreased heart lipid peroxidation marker MDA in methanol extract and HFFD treated group (< 1 μmol/mg) than only HFFD group (< 3 μmol/mg) exhibiting immunomodulatory potential.	Derouiche et al. 2019
In vivo	Heartwood	*Aquilaria malaccensis* heartwood powder	Wistar female albino rats about 220 g treated with $Pb(C_2H_3O_2)_2$ 100 mg/kg for 70 days, 25 numbers in 15 days study	$Pb(C_2H_3O_2)_2$ 100 mg/kg + *Aquilaria* powder 10 g/kg body weight	Control without treatment	Decreased body weight from 198 g to 196 g gained by Pb $(C_2H_3O_2)_2$ treatment compared to control i.e., 291 g. Decreased relative liver weight from 3.2 g to 2.6 g compared to control 2.5 g.	Samir et al. 2017
In vivo	Heartwood	*Aquilaria malaccensis* heartwood powder	Wistar female albino rats about 220g treated with $Pb(C_2H_3O_2)_2$ 100 mg/kg for 70 days, 25 numbers in 15 days study	$Pb(C_2H_3O_2)_2$ 100 mg/kg + *Aquilaria* powder 10 g/kg body weight	Control without treatment	Decreased MDA 1.3 μmol/mg from 2.26 μmol/mg gained by $Pb(C_2H_3O_2)_2$ treatment compared to control i.e., 1.84 μmol/mg to restore oxidative stress caused by $Pb(C_2H_3O_2)_2$. Increased GSH 0.2 nmol/mg from 0.1 nmol/mg reduced by $Pb(C_2H_3O_2)_2$ treatment similar to control i.e., 0.2 nmol/mg to restore oxidative stress caused by $Pb(C_2H_3O_2)_2$. Increased GST 9.2 nmol/min/mg from 6.3 nmol/min/mg reduced by Pb $(C_2H_3O_2)_2$ treatment compared to control i.e., 14.3 nmol/min/mg to restore oxidative stress caused by Pb $(C_2H_3O_2)_2$. Decreased Catalase 1.3 UI/mg from 17.6 UI/mg gained by $Pb(C_2H_3O_2)_2$ treatment compared to control i.e., 14 UI/mg to restore oxidative stress caused by $Pb(C_2H_3O_2)_2$.	Samir et al. 2017
In vivo	Heartwood	*Aquilaria malaccensis* heartwood powder	Wistar female albino rats about 220g treated with $Pb(C_2H_3O_2)_2$ 100 mg/kg for 70 days, 25 numbers in 15 days study	$Pb(C_2H_3O_2)_2$ 100 mg/kg + *Aquilaria* powder 10 g/kg body weight	Control without treatment	Decreased SGPT 80.5 U/L from 90.5 U/L gained by Pb $(C_2H_3O_2)_2$ treatment compared to control i.e., 89.5 U/L exhibiting to restore liver injury caused by $Pb(C_2H_3O_2)_2$. Liver histopathology of treated animal exhibited to reduce liver damage partially.	Samir et al. 2017
In vivo	Woods	*Aquilaria malaccensis* oil (2.3% w/w)	Wistar male and female rats (150–200 g), Four groups, 6 rats/group	100 mg/kg	Diclofenac (10 mg/Kg)	Reduction in Carrageenan induced paw edema after 3 h <63% than diclofenac <69% as anti-inflammatory activity.	Rahman et al. 2012
In vivo	Heart wood	Ethyl acetate extract	30 numbers of 20–25 g of male albino mice and 170–200 g of	50, 100, 200 mg/kg	2% aqueous tween 80	200 mg/kg ethyl acetate extract reduced acetic acid induced writhing numbers 22 compared to < 19 treated with	Chitre et al. 2007

(*continued*)

Table 2 (*Continued*)

Study type	Part used	Extract/Compound	Experimental model/set up	Dosages	Control	Activity	Reference
			Wistar rats in 5 groups			Diclofenac 10 mg/kg showing analgesic activity. 200 mg/kg ethyl acetate extract reduced formalin induced licking time for paw <32 min. compared to < 73.4 min. treated with Diclofenac 10 mg/kg showing anti-inflammatory activity. 200 mg/kg ethyl acetate extract enhanced tail flicking time compared to Diclofenac treated with showing anti-inflammatory activity. 200 mg/kg ethyl acetate extract reduced carrageenan injected edema compared to Diclofenac treated showing anti-inflammatory activity.	
In vitro	Wood	*n*-hexane /EtOAc1α,7α-dihydroxy-8oxo-4αH,5αH-guaia-9(10),11(13)-dien-12-oate **(8)**	LPS stimulated RAW 264.7 cells by microplate reader		-	Inhibited NO synthesis with IC_{50} <19.0 μM.	Ma et al. 2021
In vitro	Leaves	Leaves supercritical fluid extract	Bovine serum albumin (BSA)	400–16,000 μg/ml	-	Inhibited BSA denaturation by 29–52% as anti-inflammatory activity.	Eissa et al., 2018
In vitro	Leaves	Leaves ethanol extract [Phytol **(55)** 29–34%; n-hexadecanoic acid) **(68)]**	Albumin	400–16,000 μg/ml	-	Exhibited concentration depended inhibition of albumin denaturation <71%.	Zainurin et al. 2018
In vitro	Seeds	Ethanolic extract (27.7 g) (Phorbol esters) **(58)**	Blood of healthy human donor (20–30 years)	10 μM	PMA, P13K inhibitor LY294002	Inhibited elastase release in FMLF/CB inducted human neutrophils with IC_{50} 0.8–2.7 μM by the isolated pure phorbol esters compared to < 3.4 μM of LY294002 exhibiting inflammation modulatory activity.	Wagh et al. 2017
In vitro	Seeds	Ethanolic extract (27.7 g) (Phorbol esters) **(58)**	Blood of healthy human donor (20–30 years)	10 μM	PMA, P13K inhibitor LY294002	Enhanced superoxide in FMLF/CB inducted human neutrophils compared to < 2 μM of LY294002 exhibiting inflammation modulatory activity.	Wagh et al. 2017
In vitro	Seeds	Subfraction 4 of methanolic extract (Aquimavitalin) **(57)**	A23187 and antigen induced degranulation in RBL-2H3 cells, Inhibition of β-hexosaminidase release	10 μg/mL	-	Antiallergic activity by IC_{50} < 0.01 μg/mL (A23187 induced degranulation), < 0.07 μg/mL.	Korinek et al. 2016
In vitro	Woods	*Aquilaria malaccensis* oil (2.3% w/w)	Human red blood cell	100, 250, 500 mg/ml	Diclofenac (50, 100, 200 mg/ml)	Concentration dependant protection of HRBC cell membrane < 40%, <63%, 78% in hypotonic solution than diclofenac <44%, < 64%, < 87% in HRBC membrane stabilization test as anti-inflammatory activity.	Rahman et al. 2012

5.1.1. Immunomodulatory potential against SARS-CoV2

The immunomodulatory potential of *A. malaccensis* against SARS-CoV2 was reviewed through the *in-silico* molecular target binding potential of the reported biomarkers with the targets viz., 3CLpro, ADP ribose phosphatase of NSP3, RNA binding protein of NSP9, RNA-dependent RNA polymerase RDRP, Spike protein S1, Mpro, PLpro and others. Direct studies were very less and the notable *in vitro* and *in-silico* studies on the reported biomarkers of *A. malaccensis* were available in separate publications and the most informative studies were reviewed and compiled (Table 3; Fig. 2). Caryophyllene oxide (**25**) reported 2.8– 8.6% in wood oil, showed a high binding affinity with molecular targets of SARS-CoV2 including 3CLpro (– 6.0 kcal/mol), ADP ribose phosphatase of NSP3 (– 6.3 kcal/mol), RNA binding protein of NSP9 (– 6.3 kcal/mol), and RDRP (– 6.9 kcal/mol), stimulated TNFα and chemotherapeutic agents induced apoptosis and showed anti-invasive effect by suppressing $NF\text{-}_{kB}$ (Tajuddin et al., 2013; Kim et al., 2014; Ahmaed et al., 2017; Duru et al., 2021). Likewise, the RNA-dependent RNA polymerase binding score by octacosane (**113**) was reported higher than the prescribed drug ramdesivir and by heneicosane (**110**) as similar to ramdesivir. Spike protein S1 binding score by heneicosane (**110**) and octacosane (**113**) was higher than umifenovir whereas the main protease enzyme binding score by octacosane (**113**) was comparable to

Table 3
Potential immunomodulatory biomarkers of ***Aquilaria malaccensis*** Lam. against SARS-CoV2.

Study type	Compounds	Result	Reference
In vitro & *In silico*	Caryophyllene oxide **(25)** (2.8–8.6% in wood oil)	High binding affinity with molecular of SARS-CoV2 viz., 3-chymotrypsin-like protease (− 6.0 kcal/mol), ADP ribose phosphatase of NSP3 (− 6.3 kcal/mol), RNA binding protein of NSP9 (− 6.3 kcal/mol), and RNA-dependent RNA polymerase RDRP (− 6.9 kcal/mol). Stimulated TNFα and chemotherapeutic agents induced apoptosis and showed anti-invasive effect by suppressing NF-$_{kB}$.	Tajuddin et al. 2013; Kim et al. 2014; Ahmaed et al. 2017; Duru et al. 2021
In-silico	Octacosane **(113)**, Heneicosane **(110)** (0.3- 20% in wood oil)	RNA-dependent RNA polymerase inhibition binding score by octacosane **(113)** higher than ramdesivir, by heneicosane **(110)** similar to ramdesivir. Spike protein S1 inhibition binding score by heneicosane **(110)**, octacosane **(113)** higher than umifenovir. Main protease enzyme inhibition binding score by octacosane **(113)** comparable to lopinavir.	Bhuiyan et al. 2009; Tajuddin et al. 2013; Wong et al. 2015; Samadi et al. 2017; Senarath et al. 2016; Elwakil et al. 2021
In-silico	α-santalol **(47)** (0.28–3.3% in wood oil)	Inhibited SARS-CoV-2 proteases viz., main protease Mpro < 71%; papaine like protease PLpro < 4.5%.	Faizal et al. 2017; Kao et al. 2018; Strub et al. 2021
In-silico	Agarospirol **(20)** (< 13%), Jinkoh eremol **(51)** (< 12%), Hinesol **(30)** (< 9%) (1.2-12.5%) in wood oil	Agarospirol **(20)**, jinkoh eremol **(51)** exhibited strong binding affinity for immunomodulatory receptor and docking score comparable to diclofenac. Agarospirol **(20)**, jinkoh eremol **(51)**, hinesol **(30)** suppressed release of IL-1β, IL-6,TNF-α in dose dependent manner nearly comparable to diclofenac. Among female Swiss albino mice oil showed dose dependent 12-O-tetradecanoylphorbol-13 acetate induced ear edema reduction in mouse inflammatory model and MDA compared to reference indomethacin and vehicle control.	Norfatirah et al. 2013; Tajuddin et al. 2013, Wong et al. 2015; Yadav et al. 2013
In-vitro	GYF-21 [2-(2-phenyl ethyl) Chromone derivative] (2-(2-phenyl ethyl) Chromone **(144)** 2.07- 26.82% in wood oil	GYF-21 inhibited B cell by inhibiting B cell activating factor through down regulated phosphorylation of NF-$_{kB\ p}$65, STAT3, Akt while upregulated phosphorylation of Erk1/2 influenced by anti-IgM, anti-CD40, IL-4 while strongly inhibited phosphorylation of Erk1/2 and Akt influenced by B cell activating factor in splenocytes of 8-10 weeks aged BALB/c male mice.	Mei et al. 2013; Jong et al. 2014; Guo et al. 2019; Kao et al. 2021

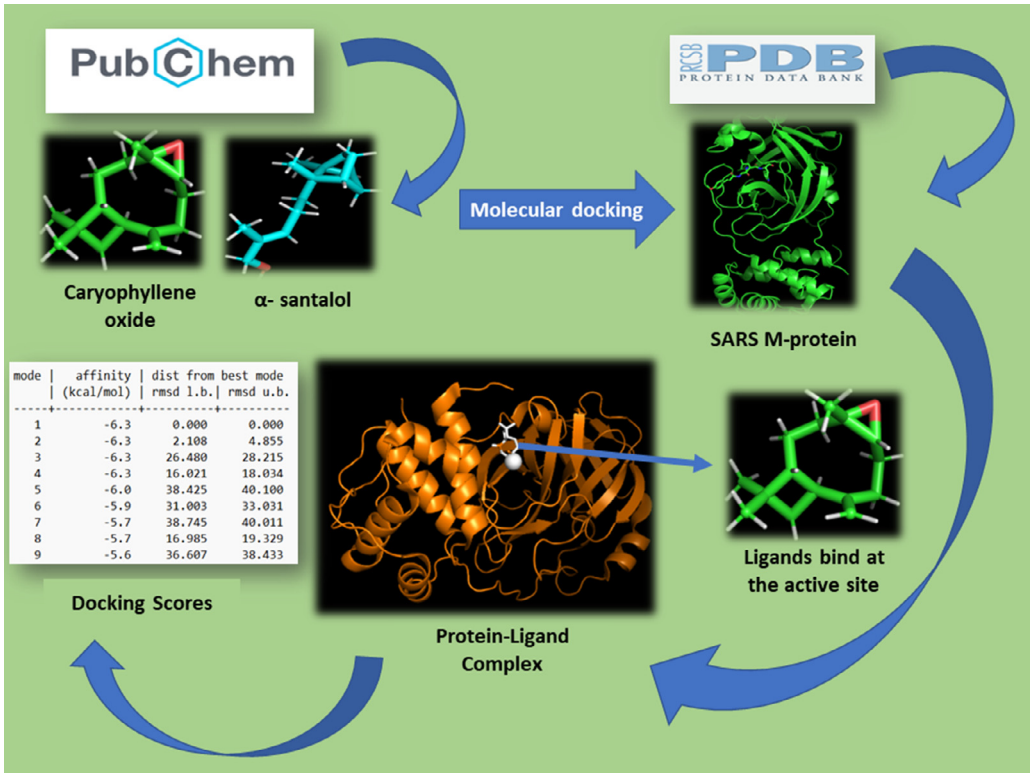

Fig. 2. Molecular docking showing SARS M-protein binding potential of biomarkers of agarwood from ***Aquilaria malaccensis***.

lopinavir (Bhuiyan et al., 2009; Tajuddin et al., 2013; Wong et al., 2015; Senarath et al., 2016; Samadi et al., 2017; Elwakil et al., 2021). Similarly, α-santalol (**47**) reported 0.28–3.3% in wood oil inhibited Mpro (< 71%), PLpro < 4.5%; agarospirol (**20**) (< 13%), and jinkoh-eremol (**51**) (< 12%) exhibited a strong binding affinity for immunomodulatory receptors with docking score comparable to diclofenac. In congruence, agarospirol (**20**), jinkoh-eremol (**51**), and hinesol (**30**) (< 9%) suppressed the release of IL-1β, IL-6, TNF-α in a dose-dependent manner nearly comparable to diclofenac *in vitro*. Among female Swiss albino mice, wood oil showed dose-dependent 12-O-tetradecanoylphorbol -13 acetate induced ear edema reduction and MDA reduction compared to reference indomethacin and vehicle control *in vivo* as anti-inflammatory potential (Norfatirah et al., 2013; Tajuddin et al., 2013; Yadav et al., 2013; Wong et al., 2015). Further, GYF-21, the 2-(2-phenyl ethyl) chromone (**144**) derivative of Chinese agarwood oil inhibited B cell by hindering B cell activating factor through downregulating phosphorylation of NF-$_{kB\ p}$65, STAT3, and Akt. GYF-21 slightly enhanced the phosphorylation of Erk 1/2 induced by anti-IgM, anti-CD40, and IL-4 and strongly suppressed phosphorylation of Erk 1/2 and Akt activated by B cell activating factor in splenocytes of 8-10 weeks aged BALB/c male mice showing immunomodulatory potential on autoimmune diseases of B-cell (Mei et al., 2013; Jong et al., 2014; Guo et al., 2019; Kao et al., 2021).

5.2. Antidiabetic activity

As diabetes is a chronic degenerative ailment leads to deficiency in immunity, the antidiabetic activity of the species was thoroughly studied. Limited numbers of *in vivo* and *in vitro* studies were available for review and the notable studies with the most informative results were compiled (Table 4). In 14 days, *in vivo* study, among diabetic model of 8 weeks old ICR male mice, injected with STZ 100 mg/kg b.w. with fasting sugar > 200 mg/dl, both methanolic and water extracts of leaves of *Aquilaria malaccensis* at 50 mg / kg b.w. brought down blood glucose level to normal range (Fayyadh et al., 2020). In another study of 3-4 months old 30 male mice of 20–35 g, leaf ethanolic extract at 250 mg/kg b.w. lowered blood sugar <188 mg/dl compared to positive control ≤ 218 mg/dl and negative control 276 mg/dl (Musrifani et al., 2020). Air dried leaf methanolic extract inhibited α-glucosidase enzyme by 92% with IC_{50} 84 μg/mL compared to 94% inhibition of Quercetin with IC_{50} < 11 μg/mL and in another study with $IC_{50} \leq 376$ μg/ml while with Acarbose $IC_{50} \leq 824$ μg/ml. Whereas, ethanolic flower extract showed $IC_{50} \leq 701$ μg/mL and dose-dependent inhibition up to 47–92% (Zulkifle et al., 2013; Rajagopal et al., 2016; Nadilah et al., 2019). Similarly, leaf methanolic extract inhibited α-amylase with $IC_{50} \leq 397$ μg/mL compared to IC_{50} of Acarbose 940 μg/mL, whereas, ethanolic extract of microwave dried (50 watts) leaves achieved highest inhibition at 75%, and ethanolic flower extract with dose-dependent inhibition

Table 4
Antidiabetic activity of ***Aquilaria malaccensis*** Lam.

Study type	Plant parts	Extract/Compound	Experimental model	Dosages	Control	Activity of Compound/ Extract.	Reference
In vivo	Leaves	95% methanolic; water	Diabetic model, 8 weeks old ICR male mice (injected with STZ 100 mg/kg b.w.) fasting sugar > 200 mg/dl, 14 days study	50, 100, 150 mg / kg b.w.	-	50 mg /kg b.w. of both extracts brought down blood glucose level to normal range.	Fayyadh et al. 2020
In vivo	Leaves	Ethanolic extract	3–4 months old 30 male mice of 20–35 gms	250, 500, 1000 mg/kg b.w. of ethanolic extract + maltose	+ve control, -ve control	250 mg/kg b.w. of ethanolic extract lowered blood sugar <188 mg/dl compared to positive control ≤ 218 mg/dl and negative control 276 mg/dl.	Musrifani et al. 2020
In vitro	Leaves	Aqueous, ethanolic, methanolic, chloroform, hexane extract	α-glucosidase assay	-	+ve control quercetin	Air dried methanolic extract inhibited α- glucosidase enzyme 92% with IC_{50} 84 μg/mL compared to 94% inhibition of quercetin with IC_{50} < 11 μg/mL.	Nadilah et al. 2019
In vitro	Flowers	Ethanolic extract	α-amylase enzyme	50, 100, 200, 400, 800 mg/ml	-	$IC_{50} \leq 801$ μg/ml, dose dependent inhibition 27–99%.	Rajagopal et al. 2016
In vitro	Flowers	Ethanolic extract	α-glucosidase enzyme	50, 100, 200, 400, 800 mg/ml	-	$IC_{50} \leq 701\mu$g/ml, dose dependent inhibition 47–92%.	Rajagopal et al. 2016
In vitro	Leaves (50, 100 and 500 watt microwave drying)	Ethanolic extract	α-amylase enzyme		-	Achieved 75% as highest inhibition in 50 watt microwave drying.	Yunus et al. 2015
In vivo	Leaves	Methanolic extract	Diabetic model STZ (45 mg/kg b.w.) induced SD male rats 200–280 g, 42 number, 7 days study	200, 400, 600, 800, 1000 μg/mL	Acarbose	Inhibited α-glucosidase with $IC_{50} \leq 376$ μg/ml compared to IC_{50} of acarbose ≤ 824 μg/ml.	Zulkifle et al. 2013
In vivo	Leaves	Methanolic extract	Diabetic model STZ (45 mg/kg b.w.) induced SD male rats 200–280 g, 42 number, 7 days study	200, 400, 600, 800, 1000 μg/mL	Acarbose	Inhibited α-amylase with $IC_{50} \leq 397$ μg/ml compared to IC_{50} of acarbose 940 μg/ml.	Zulkifle et al. 2013

27–99% and $IC_{50} \leq 801$ μg/mL (Zulkifle et al., 2013; Yunus et al., 2015; Rajagopal et al., 2016). However, most of the studies were devoid of both positive and negative control, integrated *in vitro* and *in vivo* studies, and further exhibited a very high concentration of IC_{50} values.

5.3. Neural activity

As CNS and the related systems are greatly intertwined with the immune system and neurological ailments are chronic and degenerative in nature, the effect of agarwood from *A. malaccensis* on neural system was critically studied. Noteworthy *in vivo* and *in-vitro* studies were compiled (Table 5). Ethanolic wood chips of *A. malaccensis* significantly decreased stress-related markers viz., AchE, NO, MDA, COX-2, LOX, MAO, $TNF_{\alpha,}$ and Caspase-3 in an experimental rat brain and liver of SD rats with 100 mg/kg dosage once per week compared to methanol-treated rats with 3 g/kg in one *in vivo* study of 35 days (Hamouda, 2019). Agarwood essential oil comprising sesquiterpenes, aromatic and other known compounds showed dose-dependent (10, 20, 40 mg/kg) efficacy i.e., best at 40 mg/kg in anxiety models viz., (EPM) by increased time, distance, and entry in open arms, (LDE) by increased time, distance in the light compartment, (OF) by increased time, and distance using diazepam 2.5 mg/kg as a reference to overcome anxiety; in antidepressant models viz., tail suspension, forced swimming by decreasing immobility using referral paroxetine (10 mg/Kg) to overcome depression in multiple studies among 84 numbers of ≤20 g male ICR mice. Further, the study showed a dose-dependent decrease in IL-1α, IL-1β, and IL-6, suppression of ACTH and CORT against referral drug diazepam, suppression of mRNA in nNOS, decreased gene expression of CRF, CRFR, gene transcription in cerebral cortex and hippocampus to inhibit hyperactive HPA axis to overcome stress (Wang et al., 2018b).

In another *in vivo* study for 7 days in 6–8 weeks adult male BALB/c mice free of disease showed enhanced 5-HT in serum (551 ± 344 ng/mL to 952 ± 334 ng/mL) after inhalation of agarwood smoke for 45 min/day and upregulated expression of neuroactive genes *Crhr2, Chrnd* and relevant interaction pathway of ligand-receptor. The sedative perfumery smoke of agarwood was evaluated through a gene expression study in the brain cells of mice using the microarray technique. The study revealed a total of 1417 genes comprising 687 upregulated and 730 downregulated genes with fold change ≥ 1.5 or ≤ -1.5 respectively. Fold changes and genes were accessed using DAVID and KEGG pathways. It was found that agarwood smoke affected five emotion-related pathways including dopaminergic synapse, serotonergic synapse, GABAergic synapse, long-term depression, and neuroactive ligand-receptor interaction. Gene expression was evaluated through qPCR using primer genes *Crhr2, Chrnd*, and *Gapdh*. It was found that *Crhr2* and *Chrnd* genes of the neuroactive ligand-receptor pathway were upregulated by 1.14 and 2.27 folds, respectively. As neuroactive ligand-receptor emotion-related pathways involve serotonin and anti-nociceptive activity via T-type voltage-gated calcium channels, the study revealed that *Crhr2* and *Chrnd* genes had been responsible for the expression of the neuroactive ligand-receptor pathway and upregulated serotonin levels in mice brain cell to overcome stress-related diseases (Fig. 3**)**; (Tuem and Atey, 2017; Kao et al. 2021).

In two consecutive multiple *in vivo* studies, benzene extract of agarwood suppressed CNS depressant activity. Biomarkers jinkoheremol **(51)** and agarospirol **(20)** found in fractionated extract exhibited neuroleptic activity by extending hexobarbital initiated sleeping time < 100 and < 98 min respectively compared to < 93 min by the fractionated extract using 200 mg/kg while nitrazepam showed <110 min at 10 mg/kg and vehicle control < 31 min. Both the biomarkers and the extract lowered the rectal temperature compared to control after 30 mins of administration, antinociceptive activity by reducing acetic acid initiated writhing numbers comparable to aminopyrine and almost 3.5–4 times lower than control applying 200 mg/kg. At a lower dose of 25–50 mg/kg, both the markers significantly decreased spontaneous locomotor count numbers 23 and 38 respectively than 200 in control after 50–60 min of administration. Jinkoh-eremol **(51)** decreased methamphetamine, chlorpromazine, and apomorphine (2 mg/kg) initiated spontaneous locomotor count numbers after 30–120 min and increased monoamine oxidase derivative (Okugawa et al., 1993; 1996). However, most of the experiments lacked either isolation of biomarkers, or results with higher doses lacked potential for translational use in human therapeutics.

5.4. Antimicrobial activity

As weak immune system is prone to get microbial infection, antimicrobial activity of *Aquilaria malaccensis* was carefully studied. The review found that significant antimicrobial activity of various solvent extracts of mostly leaves, stem, bark of *Aquilaria malaccensis* was evaluated by inhibition zone (ZoI), and MIC value against different bacterial strains and fungi (**Table S2**). Ethanolic extract from which 6,7 dimethylquinoxaline (**154**) was isolated showed significant ZoI 20 mm against *Staphylococcus aureus* compared to control amoxycillin, 16 mm against *Candida albicans,* and 7 mm against *Trichophyton sp.* compared to ketoconazole (Batubara et al., 2021). Likewise, ethyl acetate extract with 1,7 dihydroxy-3 methoxyanthraquinone (**121**) showed ZoI 12 mm against *Bacillus cereus* and 9 mm against *Vibrio cholerae* using kanamycin as a reference was isolated (Shoeb et al., 2010). Leaf ethanolic extract (1 mg/mL) exhibited significant MIC < 0.004 mg/mL against *Pseudomonas aeruginosa* and < 0.07 mg/mL against *Proteus mirabilis* using amoxicillin as reference (Apridamayanti and Sari, 2019). Most of the experiments were conducted with extracts without isolating the biomarkers and lacked the use of positive and negative controls, used non-polar extracts viz., chloroform, hexane, and lacked MIC values.

5.5. Miscellaneous

As immunity is related to overall wellbeing against any health ailment, several other biological activities exerted by *A. malaccensis* available in published literature were also studied (**Table S3**). Crude aqueous leaf extract with 250 μm particle size of dried leaves exhibited the highest non-competitive inhibition (82%) on pancreatic lipase showing anti-obesity activity (Muhd Rodhi et al., 2020). However, 100 mg/kg/day leaf aqueous extract and 100 mg/kg/day aqueous extract + 200 mg/kg cyclophosphamide significantly enhanced the number of oocytes, fertilization rate, fragmentation degree of cleavage in the embryo, and blastomere structure of cleavage compared to control and cyclophosphamide showing improvement in fertility in multiple *in vivo* study for 63 days among SD rats (Ismail et al., 2019). In another study, leaf ethanolic extract viz., 400 mg/kg b.w. /day, extract + paracetamol 3 mg/kg b.w. lowered hepatotoxicity markers namely AST, ALT, ALP, LDH, bilirubin, cholesterol, ALB, TP, body weight, and liver weight than the paracetamol treated hepatotoxicity group (1% CMC, 1 mL/kg b.w. + paracetamol 3 mg/kg b.w.) (Alam et al., 2017). However, the studies were insufficient to derive a therapeutic window against obesity, reproductive health, and hepatoprotective efficacy.

6. Human clinical trials

Only three human clinical trials were available with direct use of *A. malaccensis* in polyherbal products. A study for 8 months period among 10 males and 5 females of 16–40 years with an ayurvedic polyherbal formulation of *A. malaccensis* at 15 g improved symptoms of pulmonary tuberculosis (Raghuvanshi et al., 2004). Further, another polyherbal drug containing *A. malaccensis* at 6 g improved the skin disorder in a clinical trial conducted among 120 patients for 12 weeks

Table 5
Neural activity of ***Aquilaria malaccensis*** Lam.

Study type	Extract/Part used	Compound	Experimental animal	Dosages	Control	Activity	Reference
In vivo	Agarwood smoke	2-(2-Phenylethyl) Chromone **(144)**	6–8 weeks old male BALB/c mice free of disease	Inhalation 45 min /day for 7 days	-	Enhanced 5-HT in serum, up-regulated *Chr2* and *Chrnd* gene expression and interaction pathways of ligand-receptor.	Kao et al. 2021
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers for 35 days	100 mg/Kg once per week	Untreated rats showed < 0.85 mU/ml AchE in brain	Reduced AchE < 1.5 mU/mL than methanol treated < 4 mU/mL.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers 100 mg/Kg once per week	100 mg/Kg once per week	Untreated rats showed < 3.5 mU/ml NO in brain	Reduced NO < 7 mU/mL than methanol treated ≤ 22 mU/mL.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers	100 mg/kg once per week	Untreated rats showed <1.7 nmol/g MDA in brain	Reduced MDA < 2 nmol/g than methanol treated ≤ 4 nmol/g.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers	100 mg/kg once per week	Untreated rats showed < 0.025 U/mL COX-2 in brain	Reduced COX-2 < 0.035 U/mL than methanol treated < 0.085 U/ml.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers	100 mg/kg once per week	Untreated rats showed < 0.005 μgmol/mg LOX in brain	Reduced LOX < 0.0095 μgmol/mg than methanol treated < 0.0125 μgmol/mg.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers	100 mg/kg once per week	Untreated rats showed < 3.7 μU/ml MAO in brain	Reduced MAO < 5 μU/mL than methanol treated ≤ 13.3 μU/mL.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers	100 mg/kg once per week	Untreated rats showed ≤ 14 pg/mL TNF_{α} in brain	Reduced TNF_{α} ≤ 21 pg/mL than methanol treated ≤ 47 pg/mL.	Hamouda 2019
In vivo	Ethanolic wood chips	Hexadecanamide **(71)**, Octadecanoic acid **(67)** and others	≤110 gm adult male SD rats 40 numbers	100 mg/kg once per week	Untreated rats showed < 0.085 OD for Caspase-3 at 405 nm in brain	Reduced OD of Caspase -3 < 0.095 than methanol treated 0.13.	Hamouda 2019
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known (≤ 20%) compounds	≤20 gm Male ICR mice 84 numbers	10,20,40 mg/kg per day	Diazepam 2.5 mg/kg	Dose dependent increased time, distance, entry in open arms in Elevated plus maze experiment to overcome anxiety.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known (≤ 20%) compounds	≤20 gm male ICR mice 84 numbers	10,20,40 mg/kg per day	Diazepam 2.5 mg/kg	Dose dependent increased time, distance in light compartment in Light dark exploration experiment to overcome anxiety.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%) compounds	≤20 gm male ICR mice 84 numbers	10,20,40 mg/Kg per day	Diazepam 2.5 mg/kg	Dose dependent increased time, distance in central area in Open field experiment to overcome anxiety.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%)	≤20 gm male ICR mice 84 numbers	10,20,40 mg/kg per day	Paroxetine (10 mg/kg)	Decreased dose dependent immobility in Tail suspension experiment to overcome depression.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%)	≤20 gm male ICR mice 84 numbers	10,20,40 mg/kg per day	Paroxetine (10 mg/kg)	Decreased dose dependent immobility in Forced swimming experiment to overcome depression.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%)	≤20 gm male ICR mice 84 numbers	10,20,40 mg/kg per day	Diazepam 2.5 mg/kg	Decreased IL-1α, IL-1β and IL-6 to inhibit hyperactive HPA axis to overcome stress.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%)	≤20 gm male ICR mice 84 numbers	40 mg/kg per day	-	Suppressed mRNA of nNOS in cerebral cortex and hippocampus to inhibit hyperactive HPA axis to overcome stress.	Wang et al. 2018b
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%)	≤20 gm male ICR mice 84 numbers	40 mg/kg per day	-	Decreased gene expression of CRF, CRFR and gene transcription in cerebral cortex and hippocampus	Wang et al. 2018b

(*continued*)

Table 5 (*Continued*)

Study type	Extract/Part used	Compound	Experimental animal	Dosages	Control	Activity	Reference
						to inhibit hyperactive HPA axis to overcome stress.	
In vivo	Essential oil	Sesquiterpenes (≤ 51%), aromatic (≤ 24%), known compounds (≤ 20%)	≤20 gm male ICR mice 84 numbers	10,20,40 mg/kg per day	Diazepam suppressed CORT without effect on ACTH	Dose dependently suppressed ACTH and CORT.	Wang et al. 2018b
In vivo	Benzene extract (Fraction I 0.55 g, 0.155%), Fraction B (1.51 g, 0.41%)	Jinkoh-eremol **(51)** (519 mg,0.228%), Agarospirol **(20)** (216 mg, 0.095%) from Fraction I	Mice	200 mg/kg	Vehicle control	Fraction B extended hexobarbital initiated sleeping time < 93 min, Jinkoh-eremol **(51)** (200 mg/Kg) showed < 100 mins, Agarospirol **(20)** (200 mg/kg) < 98 mins, Nitrazepam (10 mg/kg) <110 min, control < 31 mins showing neuroleptic activity.	Okugawa et al. 1996
In vivo	Benzene extract (Fraction I 0.55 g, 0.155%), Fraction C (1.61 g, 0.44%) of wood	Jinkoh-eremol **(51)** (519 mg,0.228%), Agarospirol **(20)** (216 mg,0.095%) from Fraction I	Mice	200 mg/Kg	Vehicle control	Fraction C lowered rectal temperature after 30 min < 37°C whereas Jinkoh eremol **(51)** < 36 °C, Agarospirol **(20)** <37 °C, control < 38 °C.	Okugawa et al. 1996
In vivo	Benzene extract (Fraction I 0.55g, 0.155%), Fraction C (1.61 g, 0.44%) of wood	Jinkoh-eremol **(51)** (519 mg, 0.228%), Agarospirol **(20)** (216 mg,0.095%) from Fraction I	Mice	200 mg/Kg	Vehicle control	Fraction C decreased acetic acid initiated writhing number <3, Jinkoh-eremol **(51)** (200 mg/Kg) < 4, Agarospirol **(20)** (200 mg/kg) 3, Aminopyrine (100 mg/kg) <2.0, control <15 showing antinociceptic activity.	Okugawa et al. 1996
In vivo	Benzene extract (Fraction I 0.55g, 0.155%), Fraction C (1.61 g, 0.44%) of wood	Jinkoh-eremol **(51)** (519 mg, 0.228%), Agarospirol **(20)** (216 mg, 0.095%) from Fraction I	Mice	200 mg/kg 25 mg/kg	Vehicle control	Fraction C decreased spontaneous locomotor count numbers 63, Jinkoh eremol **(51)** by 58, control 270 after 50–60 min. Jinkoh eremol **(51)** decreased spontaneous locomoter count numbers 23, Agarospirol **(20)** 38, control 200 after 50–60 min. Jinkoh-eremol **(51)** decreased methamphetamine, chlorpromazine, apomorphine (2 mg/kg) initiated spontaneous locomoter count numbers after 30–120 min. showing neuroleptic potential. Monoamine oxidase derivative homovallinic acid was increased after 30 min. of administration of 50 mg/kg Jinkoh-eremol **(51)** and Agarospirol **(20)**.	Okugawa et al. 1996
In vivo	Benzene extract of wood	-	Male DDY mice	1000 mg/kg	-	Suppressed CNS depressant activity by gross behaviour, spontaneous motility, increase in hexobarbiturate initiated sleeping time, lowered rectal temperature, acetic acid initiated reduction of writhing numbers as analgesic activity.	Okugawa et al. 1993
In vitro	Wood	5,6-dihydroxy -2-(2-Phenylethyl) Chromone **(145)** and other chromones		30 μM		Stimulated adiponectin synthesis by PPARγ mediated interaction ≤ 2-fold than IDX (control).	Ahn et al. 2019

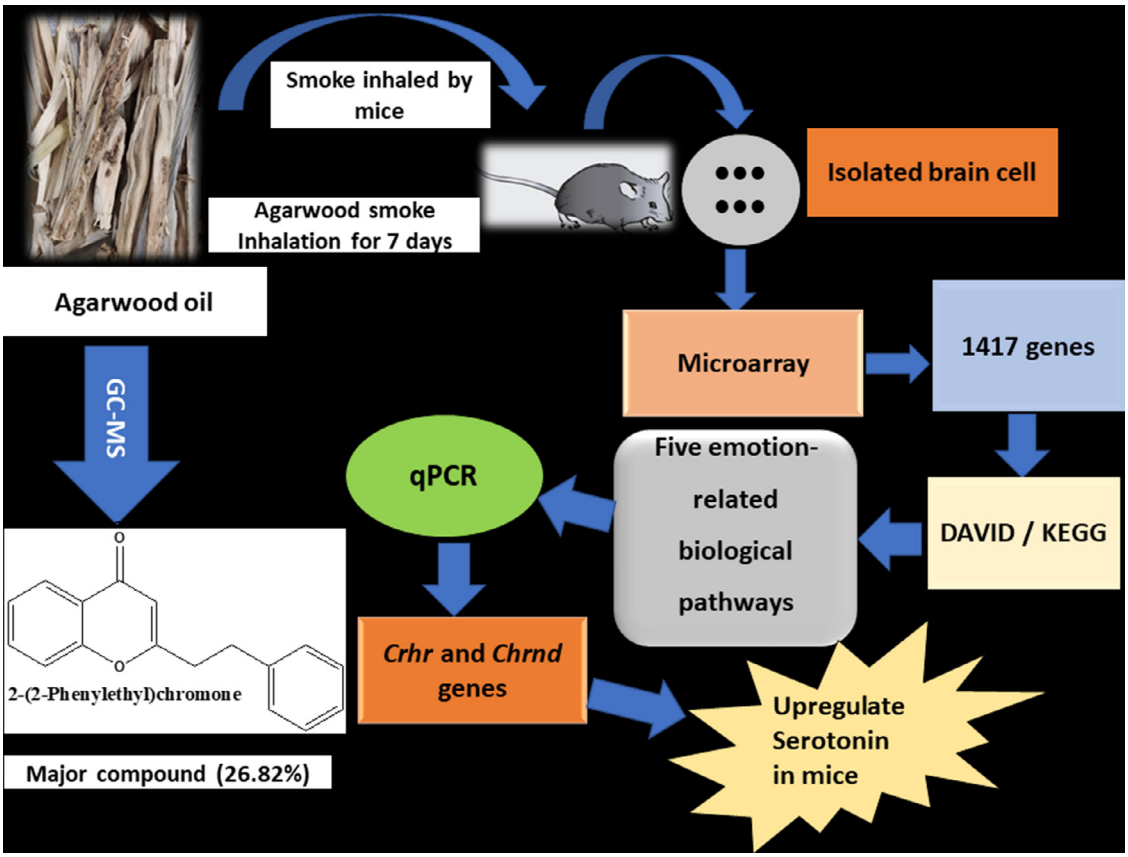

Fig. 3. Gene expression of neuronal activity by biomarkers of agarwood from ***Aquilaria malaccensis***.

(Sharma et al., 2019). Orally administered buagafuran (**65**), isolated from *A. malaccensis*, at 30–70 mg/kg b.w. lowered anxiety, increased plasma counts, and stimulated brain concentration without increasing body weight in an open uncontrolled study comprising 12 healthy males (22–40 years) of 55–70 kg (Yang et al., 2017). All these studies were conducted for a short duration, mostly single blind without the experimental design on safety, pharmacokinetics, drug interaction, and others.

7. Toxicity

Both *in vivo* and *in vitro* studies available on toxicity were reviewed and the most significant results were compiled where the anticancer activity of *A. malaccensis* was also assessed majorly based on cytotoxicity and cell viability (Table 6). Both acute and subacute oral toxicity studies with aqueous leaf extract among healthy ICR mice and SD rats in multiple experiments revealed that 2000 mg/kg b.w./ day for 7–14 days with LD_{50} > 2000 mg/kg showing nontoxic experimental dose for the duration while in ICR mice with increased sperm count < 1.2 10^6/ mL compared to control (saline). However, subacute oral toxicity after 21 days of a repeat dose of 100 mg/kg b.w. and 150 mg/kg b.w. exhibited an increased number of sperms compared to control (saline) in mice but enhanced hepatotoxic markers viz., AST, ALT, alkaline phosphatase, formation of vascular congestion, lymphocytic infiltration in the liver, cytoplasmic vacuolation and pyknotic nuclei in the kidney after 28 days, showing toxic effect in rats (Razak et al., 2018; Musa et al., 2019). In a mixed study, crude ethanolic leaf extract before and after inoculation at 200 mg/kg and 400 mg/kg increased the mean survival period in EAC injected Wistar albino rats against DLA cell line rats i.e., 25–31 days similar to cisplastin treated ≤ 31 days, greater than control EAC mice of 21 days where IC_{50} values against DLA cell line were 72-75 μg/mL and EAC cell line < 80 μg/mL (Hegde et al., 2018). *In vitro* cytotoxicity experiment was mostly conducted by MTT, Trypan Blue, and WST-1 assay on several cancer cell lines. Bark oil extracted by Supercritical Fluid extraction exhibited good cytotoxicity with IC_{50} value < 4 μg/mL and growth inhibition < 99.5% in the most effective fraction on HCT 116 cancer cell whereas methanolic bark extract containing 2-(2-Phenylethyl) Chromone (**144**) and other compounds exhibited moderate cytotoxicity with IC_{50} <14.50 μg/mL on Murine leukemia P-388 cells and resin oil with an IC_{50} value of 44 μg/mL against MCF-7 breast adenocarcinoma cell (Ibrahim et al., 2011; Hashim et al., 2014; Adam, 2017; Gameil et al., 2019; Eissa et al., 2020; Rudiana et al., 2021). Leaf ethanolic extract showed strong cytotoxicity with IC_{50} < 25 mg/mL and LD_{50} 4537 mg/kg against PBMCs cell and both ethanolic and aqueous extracts showed cytotoxicity against Vero cells with CC_{50} < 260 μg/mL and < 1720 μg/mL respectively, compared to CC_{50} of diminazene aceturate < 32 μg/mL (Dyary et al., 2014;Adam et al., 2018). Most of the studies lacked the use of reference drugs and the use of normal or Vero cell lines in assessing cytotoxicity and IC_{50} values were >10 μg/mL, beyond the potential of therapeutical use in human.

8. Agarwood production and gene expression

Agarwood oil naturally produced in *Aquilaria malaccensis* by interaction of endophytic fungi or microbes is dependent on the age of the plantlet and longer duration of time than by nailing, drilling, fungal inoculation and others (Blanchette et al., 2015; Azren et al., 2019; Islam et al., 2020). The microbial diversity associated with the agarwood and the characteristic strong aroma of agar oil were reviewed and the most significant information was compiled (**Table S4**). Artificial infection by mechanical drilling and inoculation of *Fusarium solani* (Mart.) Sacc. exhibited agarwood formation where oil contained

Table 6
Toxicity of ***Aquilaria malaccensis*** Lam.

Study type	Type of toxicity	Extract /Compound	Experimental model	Dosage/assay type	Effect	Reference
In vivo	Acute oral toxicity, Sub-acute oral toxicity	Leaf aqueous extract	12–14 weeks old male ICR mice nearly 34 g	2000 mg/Kg	LD_{50} > 2000 mg/kg in acute oral toxicity showing nontoxic treatment dose and increased sperm count < 1.2 10^6/ mL compared to control (saline). After 21 days of repeat dose of 100 mg/kg b.w. and 150 mg/kg b.w., number of sperms increased compared to control (saline).	Musa et al. 2019
In vivo	Reproductive toxicity	Leaf aqueous extract	8–12 weeks old 48 males SD rats of 150–200 g in 8 groups, 63 days study	100 mg/kg/day aqueous extract	Increased sperm count < 2.37 × 10^7 /mL, motility < 55.5%, viability < 84.2%, abnormal < 13% than 200 mg/kg cyclophosphamide treated < 2.1 × 10^7 /mL, < 41.3%, < 65.5%, abnormal < 28.3%. Decreased abnormal sperm head < 1.4, tail < 11.6 % than 200 mg/kg cyclophosphamide treated < 2.3, < 26.1%.	Razak et al. 2019
In vivo	Sub-acute oral toxicity	Leaf aqueous extract	8–12 weeks old SD rats of 150–200 g Female in acute oral toxicity (8 numbers), 14 days. 20 females and 20 males in subacute oral toxicity, 28 days	2000 mg/kg	No observed change in histopathology. LD_{50} > 2000 mg/kg in acute oral toxicity showing non-toxic treatment dose. Increased hepatotoxicity markers viz., AST, ALT, alkaline phosphatase, globulin, albumin, protein, formation of vascular congestion and lymphocytic infiltration in liver and cytoplasmic vacuolation and pyknotic nuclei in kidney after 28 days showing toxicity.	Razak et al., 2018
In vivo		Leaf ethanolicextract	Wistar albino rats of either sexes (EAC injected)	200 mg/kg, 400 mg/kg, Tumor control (EAC) survival period ≤21days	BF & AF of ethanol extract increased mean survival period in EAC injected albino rats 25–31 days similar to Cisplastin treated ≤ 31 days.	Hegde et al. 2018
In vitro	Cytotoxicity	Methanolic bark extract [2-(2-Phenylethyl) Chromone **(144)** and other compounds]	Murine leukemia P-388 cells	MTT-	IC_{50} <14.50 μg/mL	Rudiana et al. 2021
In vitro	Oral toxicity	Leaf ethanolic extract	Oral epithelial cell	WST-1 assay	10 μg/mL decreased cell viability < 93%.	Eissa et al. 2020
In vitro	Cytotoxicity	Agarwood hydrosol [16-hentriacontanone **(105)**, 1-tricosene **(104)**]	Calu-3 adeno carcinoma lung cancer cell	Trypan blue (dye attachment assay), MTT	Dye attachment assay inhibited < 22.5%, Highest inhibition < 95.2%.	Gameil et al. 2019
In vitro	Cytotoxicity	Leaf ethanolic extract	EAC & DLA cell lines	100 μg/ml extract of leaves before inoculation (BF) & after inoculation (AF)	IC_{50} against DLA cell line 72–75 μg/ml, EAC < 80 μg/ml compared to normal spleen cell with IC_{50} value > 100 μg/ml.	Hegde et al. 2018
In vitro	Cytotoxicity	Leaf methanolic extract	PBMCs cell	MTT	IC_{50} < 25 mg/mL, LD_{50} < 4537.5 mg/kg, resulted comet shaped fragmented DNA.	Adam et al. 2018
In vitro	Cytotoxicity	Methanolic leaf extract	PBMCs cell	MTT	IC_{50} < 25 mg/mL, LD_{50} < 4537.5 mg/kg, resulted comet shaped fragmented DNA.	Adam 2017
In vitro	Cytotoxicity	Resin oil	MCF-7 breast adenocarcinoma cell	-	IC_{50} value 44 μg/ml, ≤ 50% reduction in cell viability at 0.2 mg/ml	Hashim et al. 2014
In vitro	Cytotoxicity	Leaf aqueous extract, Ethanolic extract	Vero cells of monkey	MTT	CC_{50} of ethanolic extract < 260 μg/ml and aqueous extract < 1720 μg/ml compared to control. Diminazene aceturate CC_{50} <32 μg/ml.	Dyary et al. 2014
In vitro	Cytotoxicity	Bark oil by Supercritical Fluid extraction	HCT 116 cancer cell	MTT	Most effective fraction with IC_{50} value < 4 μg/ml and growth inhibition < 99.5%.	Ibrahim et al. 2011

biomarkers viz., aromadendrenepoxide **(24)**, -8-methoxy-2-(2phenylethyl) chromen-4-one **(143)**, benzylacetone **(120),** guaiacol **(87)**, palmitic acid **(68)**, squalene **(61),** tridecanoic acid **(69)**, α-santalol **(47)** and others (Faizal et al., 2017; Nasution et al., 2020). Fungal association was identified through rDNA *ITS* region of the cultured fungi genera viz., *Alternaria, Cladosporium, Curvularia, Fusarium, Phaeoacremonium, Trichoderma* and others (Premalatha and Kalra, 2013). Similarly, *Cunninghamella, Curvularia, Fusarium, Trichoderma, Lasiodiplodia* were inoculated where infected trunk oil contained benzylacetone **(120)**, anisylacetone **(50)**, guaiene **(13)** and palustrol **(39)** (Mohamed et al., 2010; Mohamed et al., 2014). Similarly, *Aspergillus, Bacillus, Trichoderma, Pantoea dispersa, Penicillium*

Table 7
Gene expression of ***Aquilaria malaccensis*** Lam.

Genes/Transcription factor/Enzyme	Experiments	Activity	Reference
TDF 1(δ-selinene Synthase), *TDF-2*(δ–Guaine synthase), *TDF-3* (1-deoxy-D-xylulose-5-phosphate-synthase), *TDF-4*(Farnesyl pyrophosphate synthase), *TDF-5*(Sesquiterpene synthase 4)	RNA was extracted from infected, non-infected and artificially induced wood samples of *Aquilaria malaccensis*. cDNA library was prepared and transcription factors and genes were analysed through qRT-PCR in cDNA-AFLP method.	*TDF-1* involved in oleoresin synthesis, *TDF-5* yielded δ-guaiene **(19)** <75%, *TDF-3* involved in MEP pathway of sesquiterpene backbone synthesis, *TDF-4* was found as branch point enzyme to catalyze terpenoid biosynthesis in agarwood. 11 numbers of differentially expressed transcription derived factors (*DE-TDFs*) were detected in infected or commercially beneficial agarwood as response to defense.	Islam and Banu. (2021)
Putative functional terpene synthase genes	*In-silico* analysis of genomics and transcriptomics data of public domain	Study revealed putative functional terpene synthase genes associated with stress, light and hormones in *Aquilaria malaccensis*.	Das et al. (2021)
Chromone derivatives, sesquiterpenes	Use of Methyl jasmonate (MeJA) *in vitro* detected chromone derivatives, sesquiterpenes, and aqueous crude extract of *Fusarium solani* detected alkanes, fatty acid derivatives and aroma compounds in *in vitro* raised shoots.	MeJA and aqueous crude extract of *Fusarium solani* acted as elicitor for production of compounds of agarwood *in vitro*.	Faizal et al. (2017)
HMGR, ASS, ADXPS, ADXPR, FPS, WRKY, MYC, MYB and others	Agarwood was wounded mechanically, artificially and chemically and total RNA was isolated and gene expression of 25 genes of terpenoid biosynthesis were analysed using semi-quantitative PCR and qRT-PCR from heathy and infected woods.	25 genes of sesquiterpenoid biosynthetic pathway were upregulated to ≤ 41.6 fold in agarwood than healthy wood exhibiting genes of agarwood formation expressing more in naturally grown plant than artificially induced.	Islam et al. (2020)
Malate Synthase and Nicotinamide Adenine Dinucleotide Phosphate quinone oxidoreductase subunit 2B	Detected proteins expressed after wounding by 2-D gel electrophoresis coupled to MALDI-TOF-MS	Revealed wounding effect on protein expression in agarwood formation.	Lee et al. (2018)
HMGR, AACT, GPS, FPS, GGPS, NPPS	Transcriptome libraries was prepared from *in vitro* induced callus tissue of *Aquilaria malaccensis* and qRT-PCR revealed gene expression in healthy, wounded and senescing calli.	Genes of KEGG pathways for terpenoids biosynthesis were expressed in calli revealing effect of wounding alike senescence.	Siah et al. (2016)
Farnesyl diphosphate synthase, δ-guaiene synthase, Type 1 Isopentenyl diphosphate isomerase, acetoacetyl-CoA ligase genes	Farnesyl diphosphate synthase, δ-guaiene synthase, Type 1 Isopentenyl diphosphate isomerase, acetoacetyl-CoA ligase genes were co-expressed in δ-guaiene in mevalonate pathway engineered *E. coli*	Fragrant δ-guaiene **(19)** synthesis was increased 30–42 μg/mL in the culture in addition of mevalonolactone.	Kurosaki et al. (2016)
Genes viz., *WRKY*, β-1-3-glucanase, actin and ubiquitin cDNAs	Total RNA was extracted from mechanically wounded agarwood tree at 4 hour intervals, 24 hour for 30 days and gene expression was analysed by qRT-PCR.	*WRKY* expression was recorded 2 times after mechanical wounding of 6 hour (6 fold), 30 days (9 fold) while *GLU* strongly expressed at 16 hour (22 fold) exhibiting wound induced *WRKY*, phenylalanine ammonia lyase and β-1-3-glucanase expression for agarwood formation.	Wong et al. (2013)
PAL (Phenyl alanine ammonia-lyase) gene	RNA was extracted from 2 year old wounded seedling and gene fragment were amplified through PCR, cloned in pGEM-T easy vector and were analyzed by BLAST with Genebank database.	Cloned gene fragment showed 92% similarity with *PAL* exhibiting stress/wound induced phenylpropanoid synthesis in agarwood.	Wong and Mohamed. (2009)

polonicum were used for highest production of marker agarospirol (**20**) (Chhipa and Kaushik, 2017). However, *Fusarium sp.* inoculum in tissue culture raised calli showed markers viz., dodecane (**108**), tetracosane (**115**) and spiro [4.5] dec-7-ene, 1, 8-dimethyl-4-(1-methylethenyl)-, [1S-(1α, 4β, 5α)]- (**155**) for aroma, farnesol (**129**), geranylgeraniol acetate (**130**) as precursor of terpenoid and agarospirol (**20**) and 8-eudesmol (**48**) for sesquiterpenes (Sen et al., 2017). Gene expression for the biomarkers for aroma and other secondary metabolites and biosynthetic pathways were reviewed and the most significant findings were furnished. Nearly 25 genes of sesquiterpenoid biosynthetic pathway viz., *HMGR, ASS, ADXPS, ADXPR, FPS, WRKY, MYC, MYB*, and others were upregulated ≤ 41.6 fold in agarwood than healthy wood but the genes for sesquiterpenes synthesis were expressed more in naturally infected tree than manually inoculated tree. Further, *TDF-1* (δ-selinene synthase) of oleoresin, *TDF-5* (sesquiterpene synthase 4) of δ-guaiene (**19**) (<75%), *TDF-3* (1-deoxy-D-xylulose-5-phosphate-synthase) of sesquiterpene backbone, *TDF-4* (Farnesyl pyrophosphate synthase) of terpenoid biosynthesis were expressed along with 11 numbers of differentially expressed transcription derived factors (*DE-TDFs*) in infected or commercially or therapeutically beneficial agarwood as response to defense (Islam et al., 2020; Islam and Banu, 2021). Cloned gene fragment of wounded plant showed 92% similarity with *PAL* exhibiting stress or wound induced phenylpropanoid synthesis. Moreover, *WRKY* was expressed 2 – 9-fold after mechanical wounding of 6 h to 30 days and *GLU* 22-fold at 16 h exhibiting wound induced phenylalanine ammonia lyase, *WRKY* and β-1-3-glucanase expression in agarwood formation (Wong and Mohamed, 2009; Wong et al., 2013). Wounding expressed proteins viz., Malate Synthase and Nicotinamide Adenine Dinucleotide Phosphate quinone oxidoreductase subunit 2B, *SesTPS1* and *GuaiS1* genes in sesquiterpene synthetic pathway in agarwood in *Aquilaria malaccensis, A. sinensis,* and *A. crassna* (Azzarina et al., 2016; Lee et al., 2018). Further, genes of KEGG pathways for terpenoids biosynthesis were expressed in *in vitro* raised calli revealing effect of wounding alike senescence (Siah et al., 2016). Also, fragrant δ-guaiene synthesis in agarwood was increased 30–42 μg/mL in the culture of engineered *E. coli* with the addition of mevalonolactone (Kurosaki et al., 2016). *In-silico* analysis of genomics

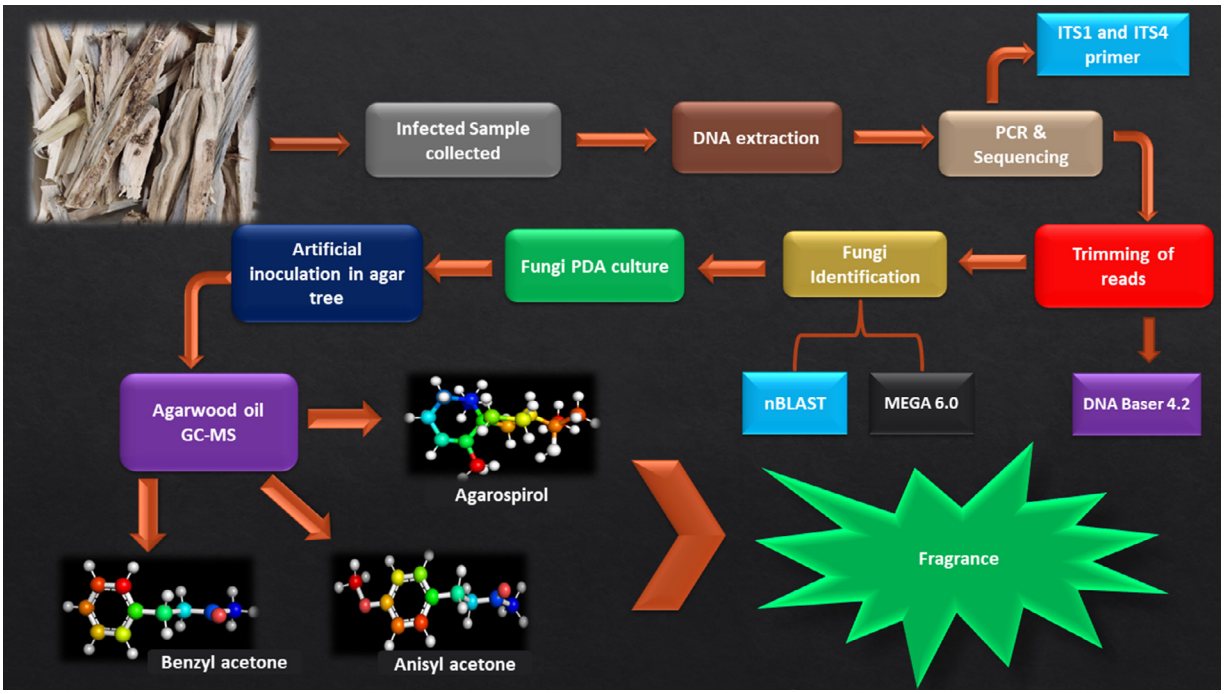

Fig. 4. Fungal association in agarwood formation from ***Aquilaria malaccensis*** with signature biomarkers with potential of immunomodulatory activity.

and transcriptomics data revealed that putative functional terpene synthase genes were associated with stress, light, and hormones in *Aquilaria malaccensis* (Das et al., 2021) [Table 7; Fig. 4]. A thorough investigation is awaited for targeted gene expression in engineered vectors to establish commercial agarwood production.

9. Conclusion and future prospects

The current review found the phytomedicinal uses of agarwood in congruence with immunomodulatory and anti-SARS CoV2 activity by pharmacological evaluation viz., use as anti-histaminic or immunosuppressant agent, use in asthma, cold, itchy throat, blood purification, weakness, neurological disorders, rheumatism, diabetes, cancer, leprosy, diarrhea, and others. Based on the abundance and quality of aroma, the review found the following biomarkers as signature markers in agarwood of *A. malaccensis* viz., aromadendrene II (**10**), valencene (**43**), calarene (**54**), t-cadinol (**49**), caryophyllene oxide **(25)**, β-caryophyllene **(18)**, α-eudesmol (**46**), dodecane (**108**), tetracosane (**115**), δ-guaiene (**19**) and others. The pharmacological evaluation showed immunomodulatory, anti-inflammatory activity exerted by the biomarkers viz., 1α,7α-dihydroxy-8oxo-4αH,5αH-guaia-9 (10),11(13)-dien-12-oate (**8**), phytol (**55**), n-hexadecanoic acid (**68**), and phorbol esters (**58**), whereas biomarkers with *in-silico* potential against SARS-Cov2 were viz., caryophyllene oxide (**25**), octacosane (**113**), heneicosane (**110**), α-santalol (**47**), agarospirol (**20**), and jinkoh-eremol (**51**), hinesol (**30**) and others. Caryophyllene oxide (**25**) showed *in-silico* high binding affinity with 3CLpro, ADP ribose phosphatase of NSP3, RNA binding protein of NSP9, and RDRP of SARS CoV2. Caryophyllene oxide also stimulated TNFα, chemotherapeutic agents induced apoptosis and anti-invasive effect by suppressing NF-$_{kB}$ *in vitro*. Markers like, agarospirol (**20**), and jinkoh-eremol (**51**), showed high docking scores and suppressed the release of IL-1β, IL-6, and TNF-α comparable to anti-inflammatory drug *in vitro*. Thus, agarospirol (**20**) exhibited neuroleptic, antinociceptic activity *in vivo* and anti-inflammatory potential both *in silico* and *in vitro*. Moreover, RDRP, Spike protein S1, and main protease enzyme binding score by octacosane (**113**), and heneicosane (**110**) were comparable to standard drugs.

The following significant biological activity of *A. malaccensis* in respect to immunity found in the review were viz., methanolic and water extracts of leaves at 50 mg / kg b.w. brought down blood glucose level to normal range in diabetic mice model. The neuroleptic activity exhibited by biomarkers Jinkoh-eremol **(51)** and agarospirol **(20)** whereas the anxiolytic effect was exhibited by buagafuran (**65**) in the human clinical trial. The wood ethanolic extract showed ZoI 20 mm against *Staphylococcus aureus* while the wood oil fraction exhibited cytotoxicity with IC_{50} value < 4 μg/mL against the HCT 116 cell line. However, *in vitro, in vivo* experiments lacked standard guidelines on herbal products research viz., used nonpolar solvents, lacked MIC, devoid of the bioactive markers, positive controls, short study duration, lacked cytotoxicity assay in normal cell line which required to be supplemented for their translational use in human therapeutics addressing efficacy, safety, tolerability, bioavailabity, drug interaction, toxicity, adverse effect and others (Izzo et al., 2016; Izzo et al., 2020; Andrew and Izzo, 2017).

The review found the associated fungi in agarwood formation viz., *Alternaria, Cladosporium, Curvularia, Fusarium, Phaeoacremonium, Trichoderma,* and others. *Fusarium sp.* inoculum raised calli showed the presence of markers viz., dodecane (**108**), tetracosane (**115**), and spiro [4.5] dec-7-ene, 1, 8-dimethyl-4-(1-methylethenyl)-, [1S-(1α, 4β, 5α)]- (**155**), farnesol (**129**), geranylgeraniol acetate (**130**), agarospirol (**20**), 8-eudesmol (**48**) for aroma, terpenoids, and sesquiterpenes. Several genes *WRKY, PAL, GLU* were expressed during the formation of agarwood as a response to fungal infection, mechanical damage, stress as a defensive mechanism viz., defense responsive transcription-derived factors of oleoresin, sesquiterpene backbone, and terpenoid biosynthesis viz., for aroma δ-guaiene (**19**), dodecane (**108**), tetracosane (**115**), for terpenoids and sesquiterpenes agarospirol (**20**), 8-eudesmol (**48**), farnesol (**129**), and geranylgeraniol acetate (**130**). The genes of sesquiterpenoid biosynthetic pathway were upregulated in agarwood compared to healthy wood. But the genes for sesquiterpene synthesis for aroma were expressed more in the naturally infected tree than an artificially inoculated tree. Cloned gene fragment of the wounded plant showed wound-induced phenylalanine ammonia lyase, *WRKY*, and β-1-3-glucanase expression whereas, genes of KEGG pathways for terpenoid biosynthesis exhibited the effect alike senescence. The synthesis of aroma marker

δ-guaiene, was increased in culture of engineered *E. coli* by adding mevalonolactone. Biomarker of Chinese agarwood inhibited B cell activating factor through downregulating phosphorylation of NF-$_{kB}$ $_{p}$65, STAT3, and Akt via Erk 1/2 and Akt pathway showing potential in autoimmune diseases.

The futuristic scope lies on pathway-guided targeted gene expression in engineered vectors to establish commercial agarwood production maintaining the quality aroma and therapeutic effect by retaining the effective biomarkers.

Authors' contribution

Prasanna Sarmah: Retrieving references, redraw biomarkers using software, preparation of figures, tables, writing -original draft (major part); Bikas Das: retrieving references, preparation of tables, writing -original draft (part); Jadumoni Saikia: redraw biomarkers using software, preparation of figures, tables, writing -original draft (part), review; Parthapratim Konwar: retrieving references, review - (part); Kalpataru Dutta Mudoi, Siddhartha Proteem Saikia: review - (part); Dipanwita Banik: Conceptualization, methodology, supervision, tables, figures, writing – review, editing, and final draft.

Declaration of Competing Interest

There is no conflict of interests among the authors.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.sajb.2022.10.020.

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