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Research article

Potential and mechanisms of indigenous Indonesian medicinal plants in treating sexual dysfunction: A systematic review and pharmacological network overview

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ABSTRACT

The epidemiology of Erectile Dysfunction (ED) continues to exhibit an increasing trend annually. The use of synthetic drugs in treating ED often leads to undesirable side effects and has limited efficacy. In Indonesia, several indigenous plants have been empirically utilized for ED remediation. This study aims to identify the latest scientific evidence on the potential of native Indonesian medicinal plants for ED treatment and elucidate the underlying molecular mechanisms using a systematic review and Pharmacological Network approach. There are 12 potential plants most commonly used by ethnic groups in Indonesia to treat erectile dysfunction (ED) as reviewed in this study. A systematic review search was conducted across three databases (PubMed, Scopus, and Springer) without limiting the publication years. Article screening was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. Determination of compound target genes was carried out using GeneCards, while disease target genes were analyzed using DisGeNET. Network topology was explored with Cytoscape 3.10, and the construction of Protein-Protein Interaction Networks was realized using STRING version 12.0. GO and KEGG analyses were subsequently conducted with SRplot. The systematic review findings indicated that 12 articles met the predefined inclusion criteria. The pharmacology network analysis demonstrated that the compounds present in *Eurycoma longifolia*, specifically stigmasterol, eurycomanone, and eurycomalactone, target 13 genes associated with erectile dysfunction (ED), which include BCL2, AKT1, SOAT1, PCSK9, ACHE, BDNF-AS, TMX2-CTNND1, GSK3B, LINC01672, TP53, H19, HIF1A, and IL1B. These target genes are connected to the biological mechanisms underlying steroid hormone biosynthesis, which is essential for the formation of testosterone. Therefore, *Eurycoma longifolia* demonstrates significant potential for development as a promising phytopharmaceutical candidate in the treatment of sexual dysfunction.

1. Introduction

Sexual dysfunction is medically defined as a disturbance in one or more aspects of the sexual response cycle, which includes desire, arousal, orgasm, and pain, or as pain associated with sexual intercourse. It is characterized by difficulties in the ability to respond sexually or experience pleasure during sexual activity, causing significant distress and negatively impacting sexual and overall

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satisfaction for both men and women [1,2]. Erectile dysfunction (ED), also referred to as male impotence, is characterized by a man's inability to achieve and sustain an erection sufficient for a mutually satisfying sexual experience with his partner. ED is a significant component of male sexual dysfunction, often serving as a model for understanding sexual health problems due to its multifaceted nature involving physical, psychological, and social dimensions [3]. ED not only impacts one's sexual life but can also lead to infertility, reduced overall well-being, and even premature aging [4]. Globally, the prevalence of ED varies, ranging from 3 % to 76.5 % [5]. It can be attributed to a wide range of factors, including psychological aspects such as anxiety, depression, stress, fear of intimacy, and nerve-related disorders. Furthermore, ED can stem from physiological factors like stroke, brain disorders, trauma, neurodegenerative conditions such as Alzheimer's and Parkinson's, chronic diseases such as diabetes and hypertension, vascular issues, atherosclerosis, phimosis, Peyronie's disease, lifestyle factors such as chronic alcohol consumption and smoking, age-related hormonal changes, as well as systemic diseases affecting vital organs like the heart, liver, kidneys, lungs, and cancer [6,7]. Previous studies have demonstrated a potential correlation between prostate disease, kidney disease, renal function, and an increased risk of erectile dysfunction [8].

The molecular mechanism underlying erectile dysfunction (ED) involves various complex processes, particularly disruptions in the nitric oxide (NO) and cyclic GMP (cGMP) pathways. The NO-cGMP pathway is central to normal erectile function. Nitric oxide (NO), produced by nitric oxide synthase (NOS), is released from nerves and endothelial cells in response to sexual stimulation. NO activates guanylate cyclase in smooth muscle cells, increasing cyclic guanosine monophosphate (cGMP) levels. This leads to Smooth muscle relaxation in the corpora cavernosa, Increased blood flow into penile tissues, and compression of venous outflow, sustaining an erection. However, in individuals with ED, NO production is impaired due to endothelial damage or disrupted neural signaling. Additionally, excessive activity of phosphodiesterase-5 (PDE-5) enzymes degrades cGMP, further hindering the erection process [9–11].

Oxidative stress, characterized by excessive production of ROS, damages endothelial cells and reduces NO bioavailability. This impairs vasodilation and contributes to ED [12]. Chronic conditions such as diabetes, hypertension, and increases levels of pro-inflammatory cytokines like TNF-α and IL-6. These cytokines further damage erectile tissue and promote fibrosis of penile tissues, reducing their elasticity and impairing erectile function. This is particularly relevant in conditions like Peyronie's disease or long-standing diabetes [11,12].

Currently, the primary oral treatment for ED involves phosphodiesterase type-5 (PDE-5) inhibitors like sildenafil, vardenafil, and tadalafil. These medications work by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP), a crucial second messenger, in the smooth muscle cells of the penis [13]. Sildenafil citrate, for instance, has demonstrated its ability to positively influence the penile hemodynamics [14]. Nevertheless, it's worth noting that these ED drugs have their limitations, including suboptimal effectiveness, undesirable side effects, and contraindications for individuals with specific medical conditions [15].

The exploration of natural substances with potential aphrodisiac or erectile dysfunction (ED) treatment properties offers a promising avenue for addressing the side effects and efficacy limitations associated with ED drugs [16]. Indonesia, rich in cultural heritage and herbal plant diversity, particularly possesses a treasure trove of potential remedies for ED. Indonesian medicinal plants refer to various types of plants with medicinal properties that naturally grow and thrive in Indonesia. Their utilization has been developed through exploration based on local knowledge, particularly ethnomedicine and community traditions. Previous ethnomedicine studies have reported the use of 204 plant species from 78 families to address erectile dysfunction (ED). The five most commonly utilized plant families are Zingiberaceae, Euphorbiaceae, Arecaceae, Fabaceae, and Rubiaceae. The most frequently used plant species include *Imperata cylindrica* (used by 19 ethnic groups), *Zingiber officinale Roscoe* (17 ethnic groups), *Areca catechu* L. (14 ethnic groups), *Eurycoma longifolia Jack.* (10 ethnic groups), *Piper nigrum* L. (9 ethnic groups), *Pimpinella pruatjan* (5 ethnic groups), *Panax ginseng* (4 ethnic groups), *Kaempferia galanga* (4 ethnic groups), *Talinum paniculatum* (4 ethnic groups), *Luvunga sarmentosa* (4 ethnic groups), *Piper retrofractum* (3 ethnic groups), and *Mimosa pudica* (3 ethnic groups) [17,18]. However, no systematic review has yet been reported regarding the potential of these native Indonesian medicinal plants for addressing ED.

Surprisingly, there have been no reported reviews or systematic reviews focused on native Indonesian medicinal plants with the potential to alleviate ED. Furthermore, the molecular mechanisms and potential gene targets associated with these plant compounds, which could hold the key to ED treatment, remain largely uncharted territory. Therefore, this review takes on the challenge of employing a pharmacological network approach to predict the molecular mechanisms, identify gene targets, and illuminate pathways that play pivotal roles in the treatment of ED.

In the context of addressing sexual dysfunction, pharmacological network analysis stands as a vital tool for uncovering the mechanisms of action and the impact of specific compounds on the biological processes that govern sexual function. This approach is firmly rooted in the realm of protein-protein interactions, shedding light on how these compounds interact with various biological components that intricately regulate sexual responses.

The overarching objective of this research is to meticulously sift through the findings of studies concerning native Indonesian medicinal plants with ED-treatment potential. Subsequently, we aim to elucidate the state-of-the-art utilization of bioactive compounds and their mechanisms in the realm of ED treatment, all through the lens of a comprehensive pharmacological network approach.

2. Methods

2.1. Systematic review

2.1.1. Data sources and search strategy

We performed and reported this systematic review in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) checklist. Studies were systematically identified using electronic databases (PubMed, Scopus, Springer Link) until June 30, 2023. The plants were selected based on previous studies on the exploration of local ethnomedicine knowledge and community-based medicinal plants in Indonesia across 34 provinces and 405 ethnic groups. Among the 204 plant species identified as having potential for addressing erectile dysfunction (ED), 12 medicinal plants were most frequently used by ethnic groups in Indonesia for ED treatment: *Imperata cylindrica* (used by 19 ethnic groups), *Zingiber officinale Roscoe* (17 ethnic groups), *Areca catechu* L. (14 ethnic groups), *Eurycoma longifolia Jack.* (10 ethnic groups), *Piper nigrum* L. (9 ethnic groups), *Pimpinella pruatjan* (5 ethnic groups), *Panax ginseng* (4 ethnic groups), *Kaempferia galanga* (4 ethnic groups), *Talinum paniculatum* (4 ethnic groups), *Luvunga sarmentosa* (4 ethnic groups), *Piper retrofractum* (3 ethnic groups), and *Mimosa pudica* (3 ethnic groups) [17,18]. Therefore, the literature search utilized the following phrases:

'*Eurycoma longifolia*,' *'Imperata cylindrica*,' *'Zingiber officinale*,' *'Areca catechu*,' *'Piper nigrum*,' *'Panax ginseng*,' *'Pimpinella pruatjan*,' *'Kaempferia galanga*,' *'Piper retrofractum*,' *'Mimosa pudica*,' *'Lavanga sarmentosa*,' *'Talinum paniculatum*,' in conjunction with '*aphrodisiac*' and *'Erectile Dysfunction* (ED),' while excluding articles falling under the categories of 'Toxicity,' 'Review,' and 'Systematic Review.' Subsequently, from these 12 potential plants, a selection was made of those with strong scientific evidence regarding their potential to address erectile dysfunction (ED) and containing chemical compounds known to play a role in inhibiting the molecular mechanisms of ED. No date restrictions were applied; however, only English-language articles were eligible for inclusion. Additionally, bibliographies of relevant studies or systematic reviews identified by the search strategy will be screened for further studies. In cases where the data required for analysis was not reported, we contacted the corresponding authors of those studies to request the necessary data.

2.1.2. Study selection and eligibility criteria

All recorded articles from electronic searches will be imported into reference management software for further review. Titles and abstracts of all articles found in the initial search will be reviewed independently by two researchers. Sequential group discussions were held to ensure a consensus on the operational definition of variables and the process of data extraction. Any issues or questions that arose during data extraction were further discussed among all authors. Disagreements regarding full-text eligibility will be resolved through discussion with a third reviewer. To determine article eligibility, we will apply the population, intervention, comparator, outcome (PICO) framework as showed in Table 1.

The articles were screened based on the predefined inclusion criteria. The full texts of these selected articles were then thoroughly assessed to determine their eligibility. The evaluation results from both authors were amalgamated. Critical appraisal of the included studies was performed using the Joanna Briggs Institute Critical Appraisal Tool, tailored to cohort studies, cross-sectional studies, and quasi-experimental research. In the event of any uncertainties or differences of opinion, discussion forums were promptly initiated. Data extracted from the included articles were meticulously recorded and organized in a tabular format [19].

2.2. Pharmacology network

2.2.1. Collection and screening of target proteins

To identify target genes associated with erectile dysfunction (ED) in this study, the DisGeNET database (https://www.disgenet.org/) was used.

In the DisGeNET database, 256 genes associated with ED (disease code C0242350) were identified. Subsequently, the target genes of compounds found in *Eurycoma longifolia* were searched using the GeneCards database (https://www.genecards.org/). The target gene search for 11 compounds, namely Eurycomanone, 13α,21-Dihydroeurycomanone, Stigmasterol, Trans-coniferyl aldehyde, Scopoletin, Eurycomalactone, 6α-Hydroxy-eurycomalactone, Eurycomanone, Eurycomanol, Eurycomanol-2-O-β-D-glucopyranoside, and 9-Hydroxycanthin-6-one, identified three compounds with target genes in the database: Eurycomanone, Stigmasterol, and Eurycomalactone. These three compounds were found to target a total of 88 genes. Next, a Venn diagram analysis (https://bioinfogp.cnb.csic.es/tools/venny/) was performed to determine the overlap between ED-associated target genes (256 target genes) and compound-

Table 1
PICOS criteria for inclusion of studies.

Parameter	Inclusion criteria
Population	Humans and animal models
Intervention	All types of extracts or other preparations from traditional Indonesian medicinal plants, such as infusions, decoctions, and pounding, exhibit effects in treating erectile dysfunction.
Comparator	Comparative drugs for erectile dysfunction treatments, like sildenafil, under the same conditions.
Outcome	Therapeutic effects on erectile dysfunction in animal models or humans.
Study Design	All types of experimental laboratory studies

associated target genes (88 target genes).

The topology of the compound-gene target-disease network was then constructed using Cytoscape version 3.10 [20].

2.2.2. Construction of protein-protein interaction (PPI) network and enrichment analysis

Target genes found at the intersection of active substances and diseases were selected for further analysis using the STRING platform version 12.0 (https://string-db.org/). The Protein-Protein Interaction (PPI) network was constructed using shared target proteins with a minimum required interaction score of 0.400. The analysis of the PPI network was employed to investigate biological activity by examining functional gene ontology (GO) annotations and the enrichment of protein pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG), along with their roles in signal transduction. Furthermore, the analysis results were processed using SRplot (http://www.bioinformatics.com.cn/srplot) [21].

3. Results

3.1. Results of systematic review

3.1.1. Indonesian Medicinal Plants with potential as remedies for ED

Article screening was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (see Fig. 1). Following a database search, 248 articles were initially collected and subsequently filtered based on their titles. This process involved the removal of 50 duplicate articles. An evaluation of the remaining 198 articles was undertaken, focusing on their titles and abstracts, which led to the exclusion of 150 articles that did not meet the research objectives. Of the 48 articles that contained full texts, a further assessment was conducted to evaluate their relevance, resulting in the elimination of 36 articles. Ultimately, 12 articles were included in this study.

3.1.2. Traditional used, part used, Dosage Form, and Compound Class

In customary plant species practices used in traditional treatments for sexual dysfunction within Indonesian communities, it was found that herbs (36 %) were the most frequently utilized, followed by rhizomes (15.38 %), shrubs (15.38 %), climbers (7.6 %), and grasses (7.69 %) (Table 2; Fig. 2). These findings align with prior research reports indicating that plants with herbaceous life forms are commonly employed in traditional treatments worldwide due to their wide distribution and ease of collection [41].

Plant parts often employed in the preparation of herbal remedies for the treatment of sexual dysfunction in Indonesia were roots (45.45 %), followed by rhizomes (25.0 %), seeds (16.67 %), herbs (8.33 %), and fruits (8.33 %). This observation is consistent with earlier studies that reported roots as the most frequently used plant part by traditional healers in Indonesia for treating sexual dysfunction. This preference for roots may stem from traditional healers' belief that the greatest treatment potency resides within the

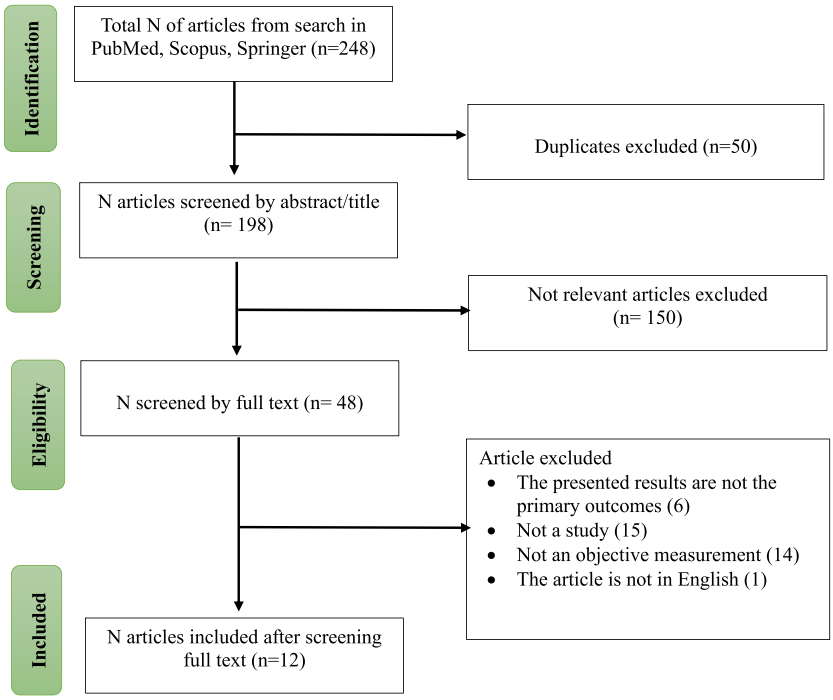

Fig. 1. Preferred reporting Items for systematic reviews and Meta-analyses flowchart.

Table 2
Native Indonesian Medicinal Plants with Efficacy as Remedies for ED, Traditional used, Parts Used, Mode of Administration, Toxicity, and Scientific Validation.

Name of the plant	family	Traditional used	Part(s) used	Mode of administration	Toxicity	Scientific validation
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	Root powder of *E. longifolia* increases sexual performance due to an increase in testosterone levels in animal models of impotence [22]
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	800 mg/kg butanol, methanol, water, and chloroform fractions of *E. longifolia* significantly increase ($p < 0.05$) the laevator ani muscle in animal models [23]
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	Water extract of *E. longifolia* and its isolates can improve sexual dysfunction by inhibiting Rho kinase II [24]
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	The isolate 9-Hydroxycanthin-6-one is believed to be the active component contributing to the aphrodisiac effect of *E. longifolia* by inhibiting the tone of the corpus cavernosum and/or seminal vesicles [24]
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	Water extract of *E. longifolia* results in a dose-dependent improvement in sexual performance in animal models [23]
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	Water extract of *Eurycoma longifolia* increases libido in male rats with sexual experience [25]
Eurycoma longifolia	Simaroubaceae	Tree	Roots	Infusion	No Toxicity [22]	Water extract of *E. longifolia* is useful as a supplement in managing late-onset hypogonadism (LOH) symptoms and hypogonadism in patients [26]
Imperata cylindrica	Poaceae	Grass	Rhizome	Decoction	No toxicity [27]	No records
Zingiber officinale	Zingiberaceae	Rhizomes	Rhizome	Decoction	No toxicity [28,29]	The extract of Zingiber officinale significantly increases sperm motility and sperm count in the epididymis and vas deferens without causing toxic effects on sperm [29]
Areca catechu	Arecaceae	Tree	Fruits	Decoction	No Toxicity [30]	No records
Piper nigrum	piperaceae	Woody Climber	Seed	Pounding	No Toxicity [31]	No records
Panax ginseng	Araliacea	Herb	Roots	Infusion	No Toxicity [32]	Male volunteers consuming *Panax ginseng* infusion showed a significant improvement in sexual experience with no reported side effects [32]
Panax ginseng	Araliacea	Herb	Roots	Infusion	No Toxicity [33]	*Panax ginseng* significantly improves erectile dysfunction in male patients
Pimpinela pruatjan	Araliaceae	Herb	Roots	Decoction	No Toxicity [34]	Extract of *Pimpinela pruatjan* can increase the expression of nNOS in nonadrenergic noncholinergic nerve fibers (NANC) in the corpus cavernosum of the penis. This increased nNOS expression leads to smooth muscle relaxation, which is associated with penile erection [35]
Kaempferia galanga	Zingiberaceae	Rhizomes	Rhizome	Pounding	No Toxicity [36]	No records
Piper retrofractum	Piperaceae	Shurb	seed	Infusion	No Toxicity [37]	No records
Mimosa pudica	Fabaceae	Herb	herb	Infusion	No Toxicity [38]	*Mimosa pudica* has the potential to protect and restore testicular tissue in rats treated with cadmium [39]
Lavanga sarmentosa	Rutaceae	Shurb	roots	Decoction	No records	No records
Talinum paniculatum	Portulacaceae	Herb	Roots	Decoction	No Toxicity [40]	No records

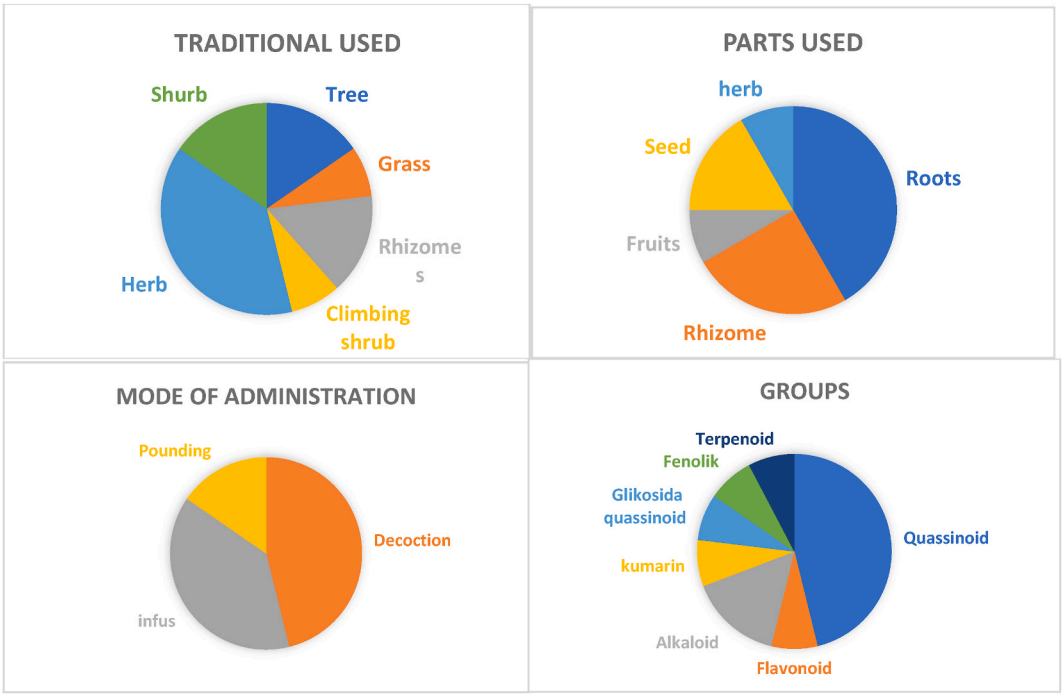

Fig. 2. Traditional used, Parts Used, Dosage Form, and Compound Class in Indonesian Medicinal Plants with Treatment Effects on ED.

roots compared to other plant parts. The effectiveness of roots in treating sexual dysfunction may also be attributed to the fact that roots are the plant parts richest in metabolites [42,43].

Regarding the technique of preparing herbal remedies for aphrodisiacs and sexual dysfunction, decoction is the most commonly used method (46.15 %), followed by infusion (38.6 %), and pounding (15.38 %) (Table 1, Fig. 3). Decoction involves the process of boiling plant materials in hot water until their original volume reduces to approximately one-quarter and is reported as the most widely used herbal preparation method across many cultures [44,45]. Unlike decoction, infusion does not require plant materials to be boiled in hot water, thereby preserving volatile compounds and medicinal constituents in the plant material better than decoction,

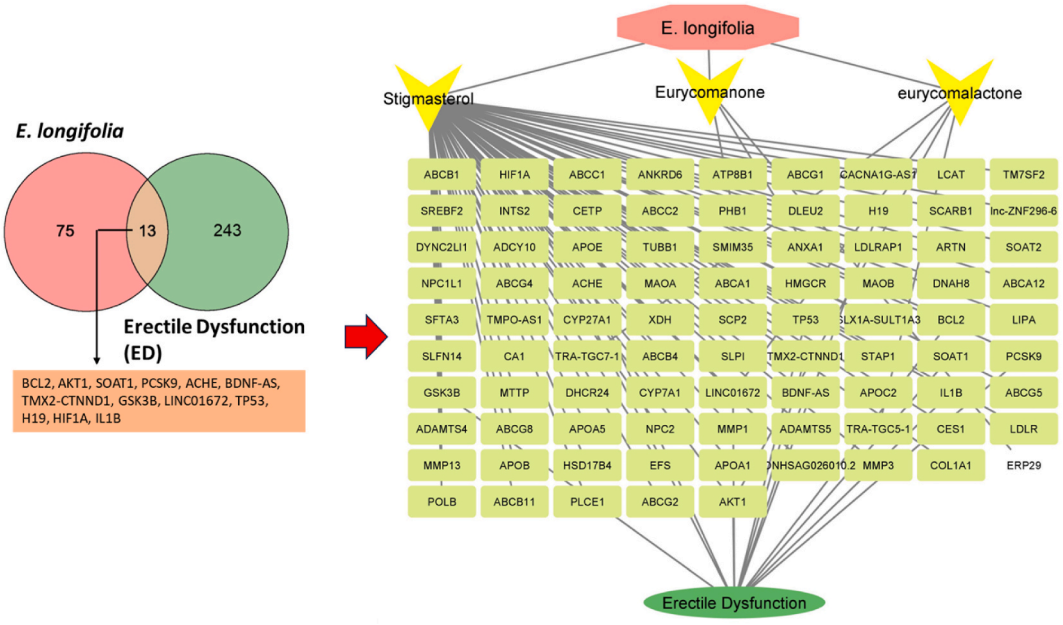

Fig. 3. Venn diagram and Cytoscape of *E. longifolia* compounds (stigmasterol, eurycomanone, Eurycomalacton).

where some volatile components can be lost during heating. In Indonesia, pounding has been reported as one of the most common methods for preparing herbal concoctions, where pounded plant material is mixed with warm water and extracted; the resulting mixture is known as 'Jamu' [46,47].

3.1.3. Compounds and pharmacological activities

In the search for articles regarding scientific evidence related to species empirically used for the treatment of sexual dysfunction (Table 3). This study found that couassinoid compounds were the most frequently reported compounds known for their aphrodisiac effects and as remedies for sexual dysfunction, followed by alkaloid compounds and flavonoids. For further details, refer to the aligned Table 3 and Fig. 2.

In the systematic review conducted on 12 native Indonesian medicinal plants, it was determined that two of these plants are known to contain compounds and exhibit pharmacological activities that can serve as remedies for sexual dysfunction. These two medicinal plants are *Eurycoma longifolia* and Panax ginseng. As shown in Table 2, *Eurycoma longifolia* is noteworthy for its multi-component compounds and multi-target activities associated with ED. Therefore, in order to comprehend the interactions between these components and the molecular mechanisms contributing to the treatment of ED, *Eurycoma longifolia* was selected for this study. Our pharmacological network approach aimed to provide a holistic analysis of how various compounds work synergistically to produce an effect in the treatment of ED.

3.2. Network pharmacology

3.2.1. Gene targets of compounds in E. longifolia for ED treatment

From the pharmacological network analysis results in determining compound target genes, it was found that 11 compounds in *Eurycoma longifolia* have 88 potential gene targets. Data exploration using DisGeNET to identify ED disease target genes revealed 256 genes associated with ED. Through Venn diagram analysis, it was determined that there are 13 overlapping gene targets between the active compound targets and ED disease genes (Fig. 3). These thirteen gene targets include BCL2, AKT1, SOAT1, PCSK9, ACHE, BDNF-AS, TMX2-CTNND1, GSK3B, LINC01672, TP53, H19, HIF1A, and IL1B.

In pharmacological networks, the topology of compound networks pertains to the relationships between compounds (nodes) and their interactions (edges) in regulating the activities of target genes. Fig. 3 illustrates that there are 3 compounds with 86 protein targets (nodes) and 468 interactions (edges) within the network. In this network topology, each node represents a protein, while each edge represents interactions between these proteins. These interactions may involve compound binding to target genes, regulation of gene expression, or other interactions associated with biological regulation.

3.2.2. Protein-protein interaction

In Fig. 4a, the protein-protein interactions of potential target genes in *Eurycoma longifolia* compounds for the treatment of erectile dysfunction have been visualized. This study has found that these protein-protein interactions are associated with biological processes such as GO:0042632 Cholesterol homeostasis, GO:0010876 Lipid localization, GO:0015850 Hydroxy organic compound transport, GO:0055088 Lipid homeostasis, GO:0006869 Lipid transport, GO:0030301 Cholesterol transport, GO:0015918 Sterol transport, GO:0008202 Steroid metabolic process, GO:0016125 Sterol metabolic process, and GO:0008203 Cholesterol metabolic process (Fig. 4b). In addition to the information obtained from the Gene Ontology (GO), this study also explains that these protein interactions are linked to specific biochemical pathways identified in the KEGG database. These pathways, such as hsa04979 Cholesterol metabolism and hsa00100 Steroid biosynthesis, potentially regulate changes in cholesterol and steroid compound production [42]. These findings provide insights into how *Eurycoma longifolia* compounds potentially influence relevant biological regulations associated with ED through complex protein-protein interactions and impact key biochemical pathways.

Table 3
Active compounds in plants with aphrodisiac and Erectile Dysfunction treatment properties, along with their molecular mechanisms.

Name	Chemical Compounds Isolated	group	Pharmacological Effects	References
Eurycoma longifolia	Eurycomanone	quassinoid	Increased testosterone production	[42]
	13α,21-Dihydroeurycomanone	quassinoid	Improved spermatogenesis	
	stigmasterol	Flavonoid	Rho-Kinase II Inhibitory	[48]
	trans-coniferyl aldehid	Alkaloid	Rho-Kinase II Inhibitory	
	scopoletin	Coumarin	Rho-Kinase II Inhibitory	
	eurycomalactone	quassinoid	Rho-Kinase II Inhibitory	
	6α-hidroksieurycomalactone	quassinoid	Rho-Kinase II Inhibitory	
	eurycomanone	quassinoid	Rho-Kinase II Inhibitory	
	eurycomanol	quassinoid	Rho-Kinase II Inhibitory	
	eurycomanol-2-O-β-D-glukopiranosida	glicosida quassinoid	Rho-Kinase II Inhibitory	
	9-hydroxycanthin-6-one	Alkaloid	Inhibits muscle tone of corpus cavernosum and/or seminal vesicles (SV)	[24]
Panax ginseng	ginsenosides	Terpenoid	Increases nitric oxide synthase (NOS) activity and facilitates blood flow to the corpora cavernosa of the penis	[33]
	ginsenosides	Terpenoid	Stimulates the hypothalamic-pituitary-adrenal axis, resulting in increased levels of corticotropin and corticosteroids in plasma	[33]

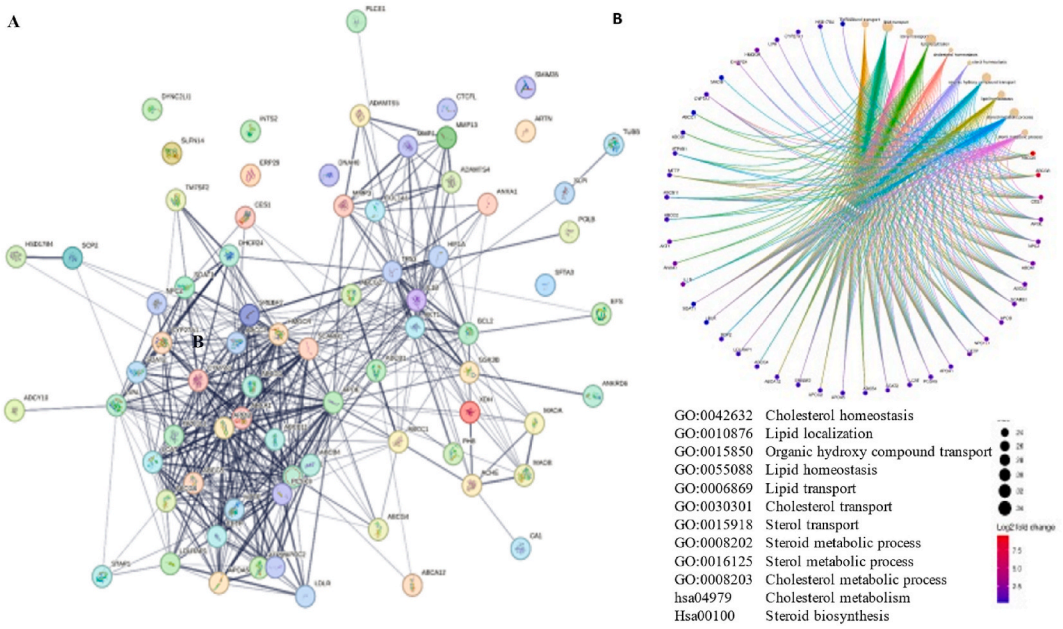

Fig. 4. Protein-Protein Interactions (PPI) of Compounds within *Eurycoma longifolia* for the biological process of ED treatment. The involved compounds are stigmasterol, Eurycomanone, and Eurycomalacton. A) PPI on all gene targets of *Eurycoma longifolia* compounds shows 86 protein targets (nodes) and 468 interactions (edges). B) Potential pathways of compounds in ED treatment, number of involved gene targets, and interaction significance.

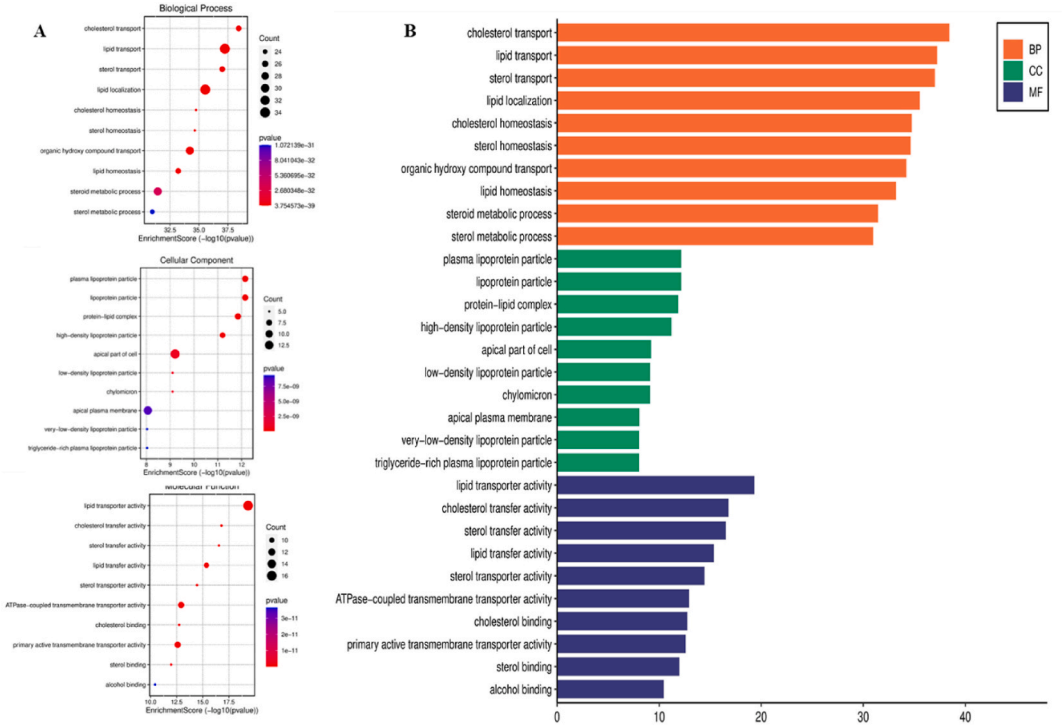

Fig. 5. Enrichment Analysis of Gene Ontology and KEGG Pathway; A) Enrichment bubble diagram indicates the involvement of 32 genes in the biological process of steroid metabolic process. B) Enrichment GO bar diagram for Biological Processes, Cellular Components, and Molecular Functions.

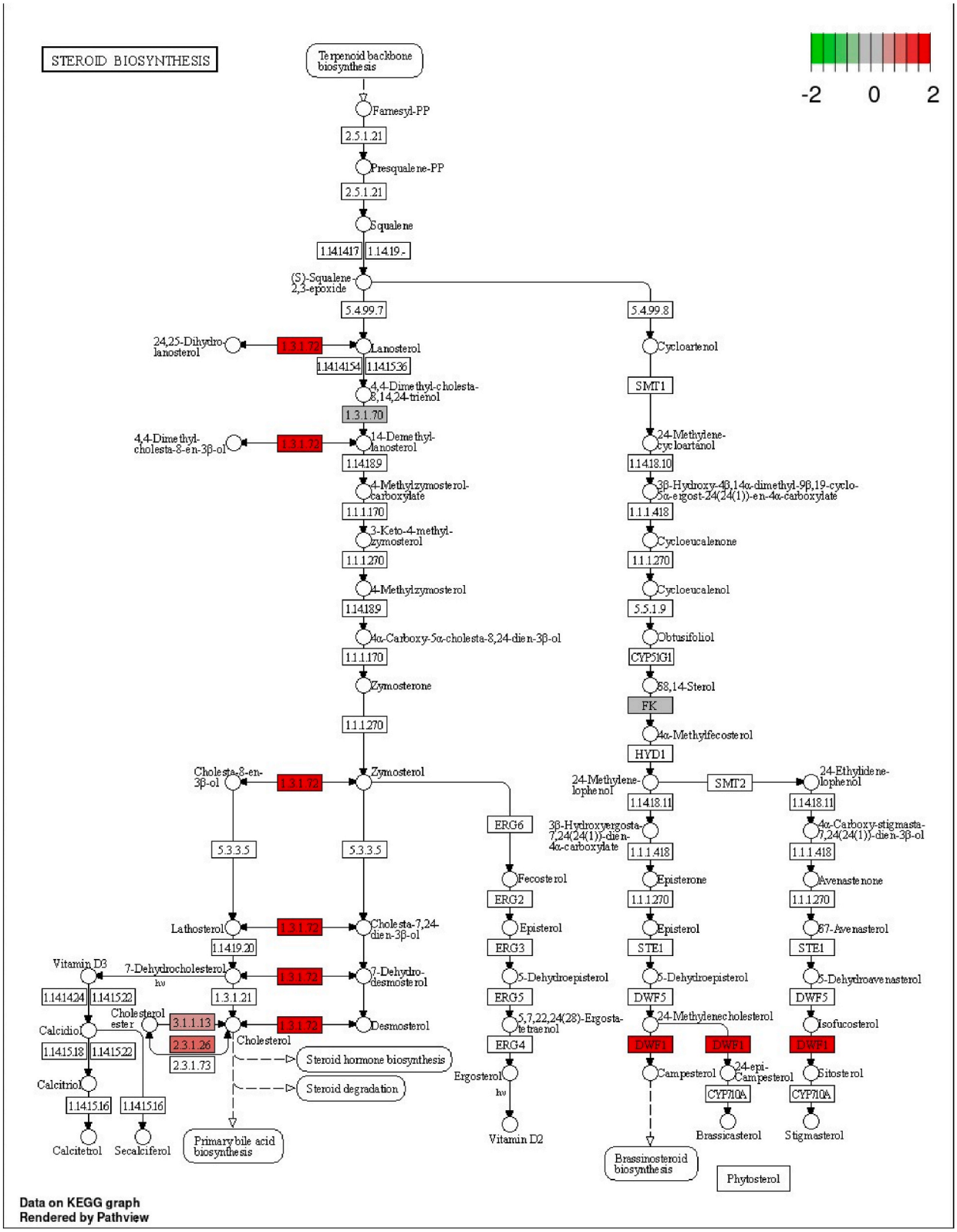

Fig. 6. KEGG hsa00100 Steroid Biosynthesis. This pathway is closely associated with the biosynthesis of steroid hormones that produce steroid hormones such as testosterone.

3.2.3. Enrichment Analysis of Gene Ontology and KEGG pathway

In the gene ontology enrichment analysis, it was discovered that compounds in *Eurycoma longifolia* influence biological processes related to ED (Fig. 5a), including the steroid metabolic process involving 30 potential gene targets. Additionally, the most frequent interactions were observed in lipid transport and lipid localization, each involving 34 potential gene targets. On the other hand, sterol transport also demonstrated significant interactions, involving 26 gene targets. In terms of cellular components, the largest number of interactions were identified in the apical part of the cell, followed by plasma lipoprotein particle and protein lipid complex. Regarding molecular function enrichment, the largest protein target was lipid transporter activity, followed by cholesterol transport activity and sterol transport activity (Fig. 5b).

In this study, it was discovered that compounds found in *E. longifolia*, namely stigmasterol, eurycomanone, and eurycomalcton, interact with the KEGG hsa00100 pathway, which is related to steroid biosynthesis (Fig. 6). This steroid biosynthesis pathway plays a crucial role in the formation of testosterone hormone. This biosynthesis process involves a series of steps, starting from cholesterol transport activity to the eventual production of steroid hormones including testosterone.

4. Discussion

Eurycoma longifolia, also known as Tongkat Ali or Pasak Bumi, is a plant belonging to the Simaroubaceae family. This plant has a long history in traditional medicine in Southeast Asia, especially in Indonesia, where its roots are often used as a herbal tonic [49,50]. In our research, it has been revealed that three compounds from *Eurycoma longifolia* play a significant role in the treatment of ED. These compounds are stigmasterol, Eurycomanone, and Eurycomalacton. These three compounds have 13 target genes associated with ED. The thirteen target genes include BCL2, AKT1, SOAT1, PCSK9, ACHE, BDNF-AS, TMX2-CTNND1, GSK3B, LINC01672, TP53, H19, HIF1A, and IL1B. In the Protein-Protein Interaction (PPI) analysis, 10 biological processes significantly influencing ED were identified, including GO:0042632 Cholesterol homeostasis, GO:0030301 Cholesterol transport, GO:0015918 Sterol transport, GO:0008202 Steroid metabolic process, GO:0016125 Sterol metabolic process, and GO:0008203 Cholesterol metabolic process. These biological processes, when viewed from the perspective of the steroid biosynthesis pathway and the steroid hormone associated with testosterone synthesis, are related to spermatogenesis, which may be linked to the treatment of ED (Fig. 6). Steroid biosynthesis involves a series of chemical reactions that lead to the formation of various steroid hormones, including sexual hormones like testosterone [51]. This process requires precursors such as cholesterol and sterols, which play a role in the regulation of sexual and reproductive functions [52]. Testosterone synthesis, being a primary male sexual hormone, plays a key role in erectile function and reproduction [26]. Deviations in the testosterone synthesis pathway or the availability of necessary precursors for this synthesis can contribute to ED.

Previous studies have reported that the compound Eurycomanone in *Eurycoma longifolia* has the potential to increase testosterone hormone levels [53]. Furthermore, it has been observed that the root extract of *Eurycoma longifolia* and eurycomanone significantly enhances testosterone production in tested rats. This increase is believed to occur through mechanisms related to reproductive hormone regulation [22].

Our findings demonstrate the involvement of the Eurycomanone compound in the steroid biosynthesis pathway, which is an essential pathway associated with the production of steroid hormones, including testosterone (Fig. 6). The general increase in testosterone hormone production is linked to elevated spermatogenesis, the process of sperm formation and development in the testes. Testosterone hormone plays a crucial role in regulating various stages of spermatogenesis, including spermatogonium cell proliferation, spermatid cell differentiation, and mature sperm development [54,55].

It has also been reported that the group of quassinoid compounds, specifically 13α,21-Dihydroeurycomanone, has the potential to enhance spermatogenesis. Eurycomanone and 13α,21-Dihydroeurycomanone compounds are believed to exhibit synergistic effects, as studies on plant fractions have shown greater effects compared to their isolated forms. A possible mechanism explaining the relationship between increased testosterone production and enhanced spermatogenesis involves the elevation of LH hormone that stimulates testosterone production. Testosterone has the ability to regulate genetic expression in spermatogenic cells. By increasing testosterone levels, the quassinoid compound group can influence the genetic regulatory pathways involved in the spermatogenesis process, leading to increased proliferation and development of spermatogonium cells, ultimately resulting in heightened sperm production [56,57].

On the other hand, *Eurycoma longifolia* has also been found to contain compounds such as stigmasterol, trans-coniferyl aldehyde, scopoletin, eurycomalactone, 6α-hydroxyeurycomalactone, eurycomanone, and eurycomanol. These compounds have been reported to inhibit the enzyme Rho-Kinase II. Rho-Kinase II (ROCK-II) is an enzyme involved in regulating cellular function and structural changes in blood vessels. In the context of erectile dysfunction, ROCK-II plays a crucial role in regulating smooth muscle contraction in the penile blood vessels and influencing the blood flow necessary to achieve and maintain an erection [40].

In conditions of erectile dysfunction, increased ROCK-II activity can lead to heightened smooth muscle contraction, inhibition of NO signaling, and abnormal blood vessel remodeling. This disrupts adequate blood flow to the penis, which is essential for a satisfactory erection. Inhibiting ROCK-II has been proposed as a therapeutic strategy to manage erectile dysfunction by reducing smooth muscle contraction and facilitating blood vessel relaxation, thereby enhancing blood flow to the penis [58,59].

The potent activity of *Eurycoma longifolia in* addressing sexual dysfunction is also believed to be associated with its potential as an antioxidant and anti-inflammatory agent. Erectile dysfunction is often associated with oxidative stress, which leads to endothelial dysfunction and impaired nitric oxide (NO) signaling—both essential for achieving and maintaining an erection. ROS can react with NO to form peroxynitrite, which diminishes the availability of NO necessary for vasodilation [60]. ROS also can lead to neuronal damage, reducing the signaling capacity of neuronal nitric oxide synthase (nNOS), which is essential for NO production in response to sexual stimulation [61]. Reduction of NO bioavailability will promoting vascular dysfunction, a key mechanism in the onset of ED [12,

62]. Antioxidants help mitigate these effects by Neutralizing Free Radicals, Enhancing NO Bioavailability, and Reducing Inflammation: Antioxidants can inhibit pro-inflammatory cytokines, further protecting against endothelial damage [63].

Eurycomalactone (EL), the primary compound in Eurycoma longifolia, is a potent inhibitor of NF-κB [64]. Both EL and its ethanolic extract may be advantageous for treating sexual dysfunction, which is associated with inflammatory signaling [65]. Increased levels of aldosterone can cause severe erectile dysfunction (ED) by raising inflammatory cytokines and activating NF-κB in the penile corpus cavernosum [66,67]. The activation of NF-κB and persistent inflammation in the testes might relate to age-related increases in COX-2 and proinflammatory cytokines, leading to testicular dysfunction [68,69].

Furthermore, a compound known as 9-hydroxycanthin-6-one found in *Eurycoma longifolia* has been associated with potential for treating erectile dysfunction. The reported potential mechanism of this compound involves inhibiting the tone of corpus cavernosum and/or seminal vesicles (SV) [24]. This inhibition is suspected to occur due to the compound's inhibition of the enzyme phosphodiesterase type 5 (PDE5). PDE5 is responsible for breaking down cyclic guanosine monophosphate (cGMP) molecules, which are needed for smooth muscle relaxation in the corpus cavernosum and SV. By inhibiting PDE5, this compound can maintain higher levels of cGMP, facilitating smooth muscle relaxation and increasing blood flow to the penis [5,13,70].

5. Limitation

In this review, it is important to note that not all herbal plants that have been empirically proven effective in traditional communities have also been scientifically validated. Among the 12 plants studied, 7 articles were found to lack sufficient scientific evidence. This observation highlights that only 2 plants have been reported to contain active compounds contributing to the mechanisms of sexual dysfunction treatment, namely *Eurycoma longifolia* and *Panax ginseng*. It is worth mentioning that the molecular mechanism predictions in this study are currently based solely on bioinformatics. Further validation through in vitro and in vivo studies is necessary to confirm these findings.

6. Conclusion

This systematic review reveals that out of 12 articles related to the treatment of erectile dysfunction (ED), *Eurycoma longifolia* and *Panax ginseng* are the medicinal plants most supported by scientific evidence. Through a pharmacological network approach, we discovered that three compounds in *Eurycoma longifolia*, namely stigmasterol, eurycomanone, and eurycomalactone, are associated with 13 target genes related to ED, which include BCL2, AKT1, SOAT1, PCSK9, ACHE, BDNF-AS, TMX2-CTNND1, GSK3B, LINC01672, TP53, H19, HIF1A, and IL1B. These target genes are involved in the biological processes of steroid hormone biosynthesis, such as GO:0030301 Cholesterol transport, GO:0015918 Sterol transport, GO:0008202 Steroid metabolic process, GO:0016125 Sterol metabolic process, and the KEGG steroid biosynthesis pathway hsa00100. This steroid biosynthesis pathway plays a crucial role in testosterone hormone formation for erectile and reproductive processes. Therefore, we recommend further development of *Eurycoma longifolia* as a phytopharmaceutical candidate for the treatment of sexual dysfunction.

CRediT authorship contribution statement

Sukardiman: Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization, Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Roihatul Mutiah:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rosita Handayani:** Writing – review & editing, Visualization, Resources, Project administration, Methodology, Formal analysis, Data curation.

Data availability statement

All data obtained or analyzed in this study are available in the published article and supplementary files, accessible at https://doi.org/10.6084/m9.figshare.28330532.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sukardiman reports financial support and administrative support were provided by Universitas Airlangga. Roihatul Mutiah reports a relationship with Maulana Malik Ibrahim Islamic State University Malang that includes: speaking and lecture fees. Roihatul Mutiah has patent pending to Roihatul Mutiah. The authors declared no conflict of interest If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviation

BCL2 B-cell lymphoma 2
AKT1 AKT serine/threonine kinase 1
SOAT1 Sterol O-acyltransferase 1
PCSK9 Proprotein convertase subtilisin/kexin type 9
ACHE Acetylcholinesterase
BDNF-AS Brain-Derived Neurotrophic Factor Antisense
TMX2-CTNND1 Thioredoxin-Related Transmembrane Protein 2-Catenin Delta 1
GSK3B Glycogen Synthase Kinase 3 Beta
LINCO1672 A specific microRNA (miRNA) or gene identifier
TP53 Tumor Protein 53 (p53)
H19 An imprinted non-coding RNA gene
HIF1A Hypoxia-Inducible Factor 1 Alpha
IL1B Interleukin 1 Beta

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42501.

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