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NETWORK PHARMACOLOGY ANALYSIS OF BIOACTIVE COMPOUNDS OF RED BETEL STEM AS AN ANTI-INFLAMMATORY AGENT

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ABSTRACT

Inflammation is a mechanism in the body's defense system that occurs through the release of proinflammatory mediators. However, inflammation must be controlled because it triggers the excessive production of inflammatory mediators, causing tissue damage and disease progression. Various types of first-line anti-inflammatory therapy drugs have the potential for adverse side effects such as anemia, hypertension, and immunosuppression; therefore, alternative anti-inflammatory agents that are considered safe and effective are needed. The red betel stem (*Piper crocatum* Ruiz and Pav.) contains secondary metabolites such as sesquiterpenes, aldehydes, phytosterols, and sterols, which are recognized as anti-inflammatory agents. This study aimed to investigate the anti-inflammatory potential of the red betel plant using pharmacological network analysis. The test compounds were secondary metabolites successfully detected in the red betel stem, including caryophyllene, octadecadienal, stigmasterol, and sitosterol. Proteins related to anti-inflammatory activity were obtained from GeneCards, proteins interacting with the test compounds were predicted using SwissTargetPrediction, and the results of the intersection of both types of proteins were further analyzed using STRING with Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment methods. GO and KEGG enrichment analyses showed involvement of NF-κB, IL-17, PI3K/AKT, and TNF signaling pathways, with 16 key genes related to anti-inflammatory activity targets. The main target proteins of caryophyllene and stigmasterol were HSP90AA1 and STAT3, respectively, whereas octadecadienal and sitosterol showed NFKB1 as the main target protein. These results provide scientific data supporting the use of these secondary metabolites as anti-inflammatory agents.
Keywords: Anti-inflammatory, red betel stem, network pharmacology, in silico

INTRODUCTION

Inflammation is a biological defense mechanism against injury, infection, and oxidative stress, and is characterized by the release of pro-inflammatory mediators. While acute inflammation serves a protective role, chronic inflammation contributes to the pathogenesis of degenerative, autoimmune, cardiovascular, and neuropsychiatric disorders (Gonfa et al., 2023). Uncontrolled inflammation can trigger the excessive production of inflammatory mediators, including inducible Nitric Oxide (NO) synthase, cyclooxygenase (COX-2), interleukin-6 (IL-6), IL-1β, and Tumor Necrosis Factor-α (TNF-α), which may lead to tissue damage and disease progression (Ko et al., 2017). The first-line therapy for inflammation involves the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), including both COX-2 selective and non-selective inhibitors of COX-1 and COX-2, as well as corticosteroids. NSAIDs exert their effects by inhibiting COX enzymes, which play a key role in the synthesis of pro-inflammatory prostaglandins. Unlike corticosteroids, which work by suppressing the expression of pro-inflammatory genes through inhibition of the NF-κB

pathway and the production of inflammatory cytokines. Despite their effectiveness, both are associated with potential side effects. COX-2 selective NSAIDs have been assosiated with adverse effect such as small bowel bleeding and iron deficiency anemia, especially when combined with Proton Pump Inhibitors (PPIs) (Tai & McAlindon, 2021), while non-selective NSAIDs with long half-lives, such as naproxen and piroxicam, are at risk of causing hypertension, gastrointestinal bleeding, and heart failure if used long-term at maximum doses (Wibowo et al., 2021). Corticosteroids have side effects such as hyperglycemia, hypertension, osteoporosis, psychiatric disorders, and immunosuppression, which increases the risk of infection, as well as the potential for gastrointestinal bleeding when used together with NSAIDs. In addition, corticosteroids can cause changes in physical appearance, such as moon face and muscle atrophy (Qutob et al., 2023).

These limitations highlight the urgent need for the development of novel anti-inflammatory agents with improved efficacy and safety profiles, from either synthetic or natural sources. Phytochemicals with known anti-inflammatory properties include sesquiterpenes, aldehydes, phytosterols, and sterols. These compounds are found in red betel stems (*Piper crocatum* Ruiz dan Pav). Recent research identified nine secondary metabolites in the n-hexane extract of red betel stem using gas chromatography-mass spectrometry. Among these compounds, those with established anti-inflammatory activities include caryophyllene, octadecadienal, stigmasterol, and sitosterol (Irawan et al., 2024). These findings suggest that red betel stems contain a diverse array of phytochemicals with anti-inflammatory potential. Caryophyllene has been reported to enhance the levels of IL-10 and Glutathione Peroxidase (GPx), while simultaneously reducing the levels of pro-inflammatory mediators, such as TNF-α, interfeton-γ (IFN-γ), IL-1β, and IL-6 (Gushiken et al., 2022). Phytosterols, including stigmasterol and sitosterol, suppress cell phagocytosis, nitric oxide production, TNF-α release, and the expression and activity of pro-inflammatory mediators, such as COX-2 and iNOS (Yuan et al., 2019). Octadecadienal, an aldehyde compound, has been reported to inhibit proinflammatory mediators of cytokine production and inflammation-related signaling in macrophages (Kang et al., 2018).

The use of red betel extracts has resulted in anti-inflammatory, antioxidant, anticancer, and hepatoprotective effects (Lister et al., 2020; Zulharini et al., 2018). However, its mechanism of action and specific molecular targets are not well understood. Therefore, a network pharmacology approach using in silico methods is essential to elucidate the mechanism of action of the active compounds and to enhance the efficiency and productivity of drug discovery (Wang et al., 2022). Network pharmacology simultaneously analyzes multiple bioactive compounds and their corresponding biological targets, reflecting the multi-component and multi-target nature of herbal medicines (Li et al., 2023). This approach has been effective in identifying potential molecular mechanisms and critical protein targets involved in the regulation of inflammation by creating compound-target-disease interaction networks and performing enrichment analyses of related signaling pathways (Joshi et al., 2024).

RESEARCH METHOD

Instrument and Material

All computational analyses were performed using an Asus A416JA laptop. The SMILES codes of the active compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/), and their targets were predicted using TargetNet (http://targetnet.scbdd.com/), PharmMapper (http://lilab-ecust.cn/pharmmapper/), and Super-

PRED (https://prediction.charite.de/). The active compounds analyzed in this study were caryophyllene (PubChem CID: 5281515), octadecadienal (CID: 53639280), stigmastanol (CID: 5280794), and sitosterol (CID: 3080497).

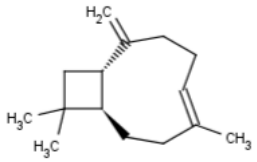
Research Procedure

We used NCBI (https://www.ncbi.nlm.nih.gov/) and GeneCards (https://www.genecards.org/) to identify genes associated with anti-inflammatory activity. Gene targets were selected for *Homo sapiens* with a prediction probability >0,6. Genes in the UniProtKB AC ID format were converted to the UniProtKB format using UniProt (https://www.uniprot.org/), and duplicate gene entries were removed. Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/) was used to determine the overlap between the target compounds and anti-inflammatory agents. Genes were mapped with Protein-Protein Interaction (PPI) using STRING (https://cn.string-db.org/) with *Homo sapiens* and an interaction score 0,6. The topological network was constructed using Cytoscape 3.10.3 with the CytoCNA plugin and Degree Centrality (DC), Betweenness Centrality (BC), and Closeness Centrality (CC) parameters. KEGG pathway and GO analysis were performed using DAVID (https://david.ncifcrf.gov/) with official gene symbol, gene list, and Homo sapiens settings. Terms were selected based on $p < 0.05$ and the highest number of genes. The top five ranked pathways were visualized using microinformatics (https://www.bioinformatics.com.cn/) (Ningrum et al., 2023; Siregar et al., 2025; Wang et al., 2022).

RESULTS AND DISCUSSION

Network pharmacology analysis, including protein-protein enrichment analysis (PPI), Gene Ontology (GO), and Kyoto Encyclopedia of Genes and Genomes (KEGG), can be used to identify and confirm the main bioactive compounds and core targets in a plant that has the potential for certain biological activities, such as the identification and confirmation of hawthorn leaves with potential anti-inflammatory activity. In this study, network pharmacology analysis of bioactive compounds in the stems of the red betel plant was conducted to assess their potential anti-inflammatory activity. The bioactive compounds described were successfully detected through GC-MS analysis of n-hexane extracts of the stems of the red betel plant, including caryophyllene, octadecadienal, stigmasterol, and sitosterol. The structures of the compounds are shown in **Figure 1** (Irawan et al., 2024). Based on the literature, these bioactive compounds have the potential to be used as anti-inflammatory agents (Irawan et al., 2024). Network pharmacology analysis will reveal the mechanism of action of the bioactive compounds and the main potential targets involved in anti-inflammatory activity.

Caryophyllene



Octadecadienal

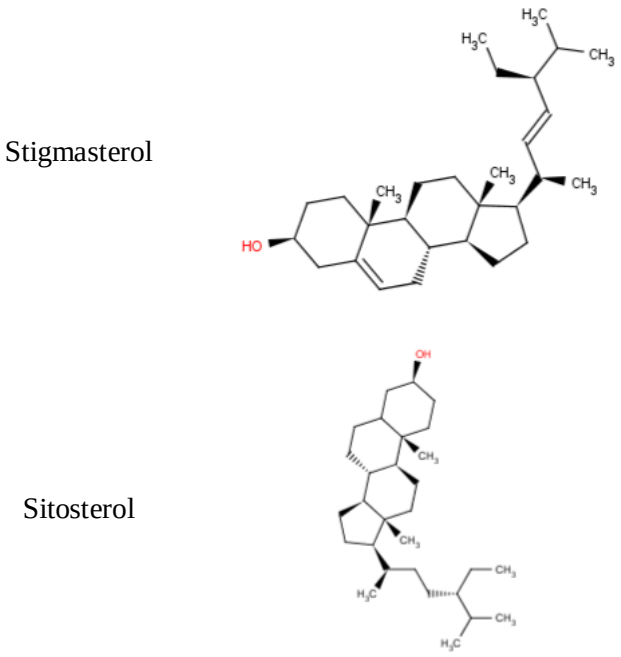
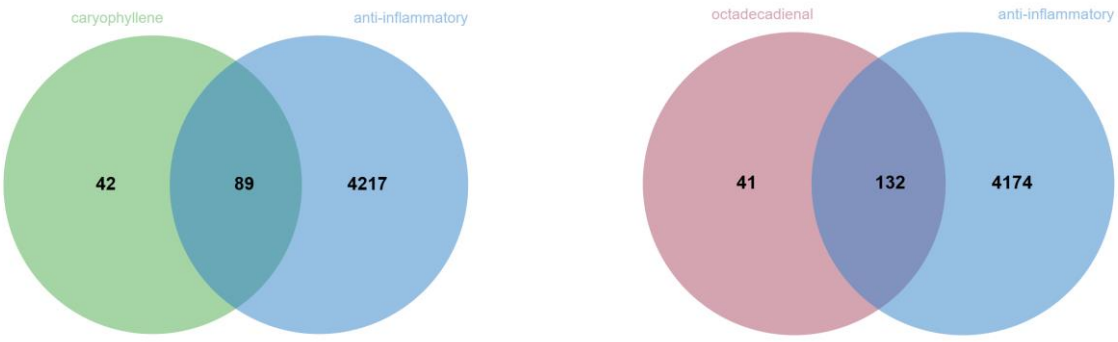


Figure 1. Caryophyllene, octadecadienal, stigmasterol, and sitosterol chemical structure.

In the initial phase, proteins that interact with caryophyllene, octadecadienal, stigmasterol, and sitosterol, as well as proteins involved in anti-inflammatory activity were explored. The interactions of these inflammation-related proteins with bioactive compounds were predicted. The obtained target proteins were then subjected to Protein-Protein Interaction (PPI) analysis using STRING to provide an overview of the interaction network between the target proteins (**Figure 3**).

The search for anti-inflammatory proteins yielded 4,306 protein data points. Caryophyllene is known to have 42 target proteins. Based on the Venn diagram, 89 of the 4,217 anti-inflammatory proteins were predicted to interact with the compound (**Figure 2**). Octadecadienal, which has 41 target proteins, was predicted to interact with 132 of the 4,174 anti-inflammatory proteins (**Figure 2**). Similarly, stigmasterol, known to have 56 target proteins, was predicted to interact with 97 of the 4,209 anti-inflammatory proteins (**Figure 2**). Sitosterol, known to have 39 target proteins, was predicted to interact with 172 proteins among 4134 proteins related to anti-inflammation (**Figure 2**).



Caryophyllene **Octadecadienal**

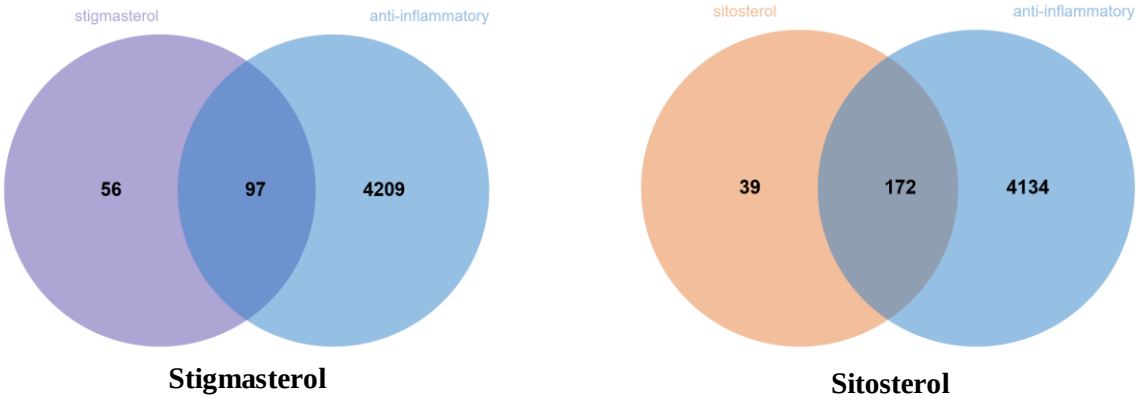


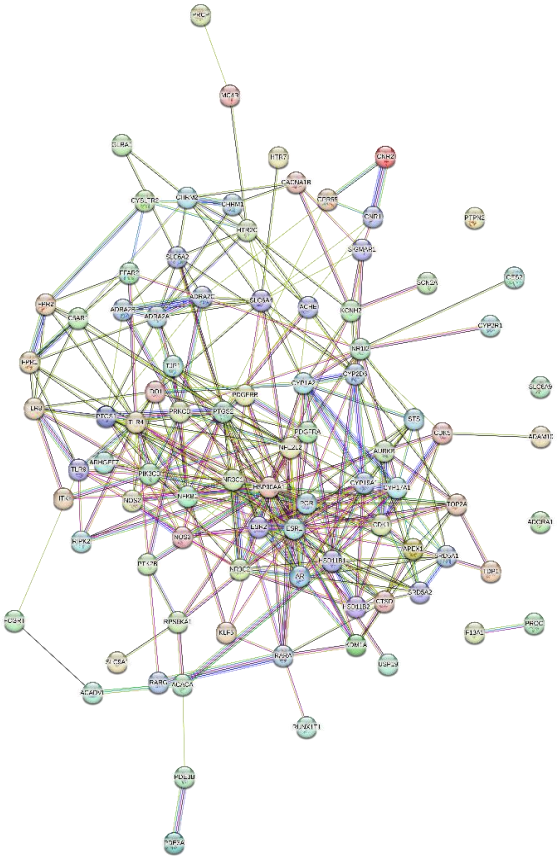
Figure 2. Venn diagram of proteins predicted to interact with bioactive compounds of red betel plant (left) and proteins related to anti-inflammatory activity (right).

Network topology analysis revealed the primary target proteins of each secondary metabolite (**Figure 4 and Table I**). The data revealed key gene hubs involved in anti-inflammatory activity, including HSP90AA1, HSP90AB1, PTGS2, PTGS1, NFKB1, TLR4, NR3C1, EGFR, STAT3, PPARG, PGR, MTOR, PIK3CA, SRC, MAPK1, and MAPK8. These proteins are therapeutic targets for existing anti-inflammatory drugs and are associated with the signaling of inflammatory regulation. Target proteins PTGS2 and PTGS1 are involved in the NF-κB signaling pathway and prostanoid biosynthesis, and their inhibition represents the primary mechanism of action of non-steroidal anti-inflammatory drugs (NSAIDs). The NR3C1 target protein is a glucocorticoid receptor involved in the glucocorticoid receptor pathway, which is also the primary target of glucocorticoid compounds used in anti-inflammatory therapy. The target proteins PPARG and PGR are involved in the PPAR signaling pathway. Activation of the PPAR receptor results in the inhibition of core elements of the inflammatory response by disrupting NF-κB activation and function (Korbecki et al., 2019). Thus, the identification of PTGS1, PTGS2, and NR3C1 in the network validates the biological relevance of the metabolite compounds, as these proteins are well-established therapeutic targets of approved anti-inflammatory drugs.

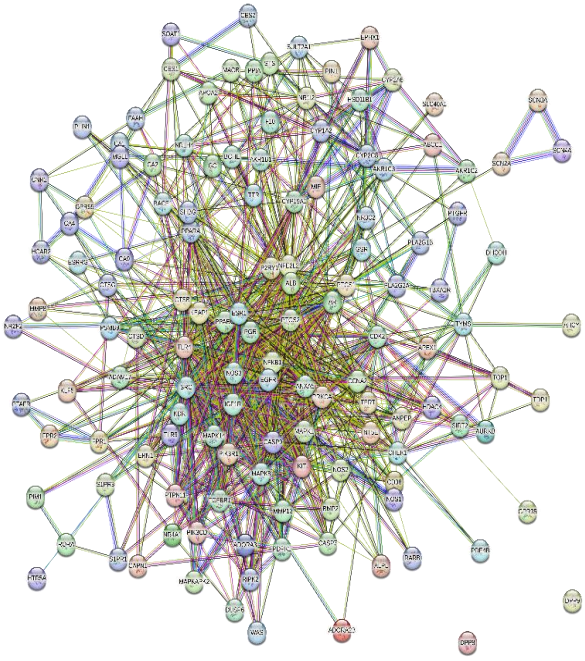
Other hub proteins, although not direct targets of NSAIDs or corticosteroids, play crucial roles in inflammatory signaling. The target protein NFKB1 is associated with the regulation of pro-inflammatory gene expression, including cytokines and chemokines, and is indirectly suppressed by both NSAIDs and corticosteroids (Korbecki et al., 2019). Target proteins TLR4, HSP90AA1, and HSP90AB1 are also involved in the NF-κB signaling pathway and immunomodulatory effects in preclinical studies, which is a key pathway in both acute and chronic inflammatory reactions. The target protein STAT3 is involved in the Jak-STAT signaling pathway, which regulates inflammatory cytokines and immune responses, particularly in inflammation-related cancer therapy (Yu et al., 2016). The target proteins mTOR and PIK3CA are associated with the PI3K-AKT-mTOR signaling pathway. PI3K receptors play a role in regulate certain innate immune responses, and AKT contributes to immune regulation by reducing inhibitory signals and promoting the reactivation of immune cells. MAPK1 and MAPK8, members of the MAPK family, are key regulators of pro-inflammatory gene expression, apoptosis, and cellular stress responses. In addition, EGFR and SRC proteins participate in inflammatory signaling, particularly through the MAPK and PI3K pathways, and their inhibition can modulate and attenuate inflammatory pathways. The involvement of these additional proteins indicates that the metabolite compounds of red betel

may act through multi-target modulation beyond the classical prostaglandin and glucocorticoid pathways. This multi-target activity could be advantageous in persistent inflammation; however, further experimental validation is required.

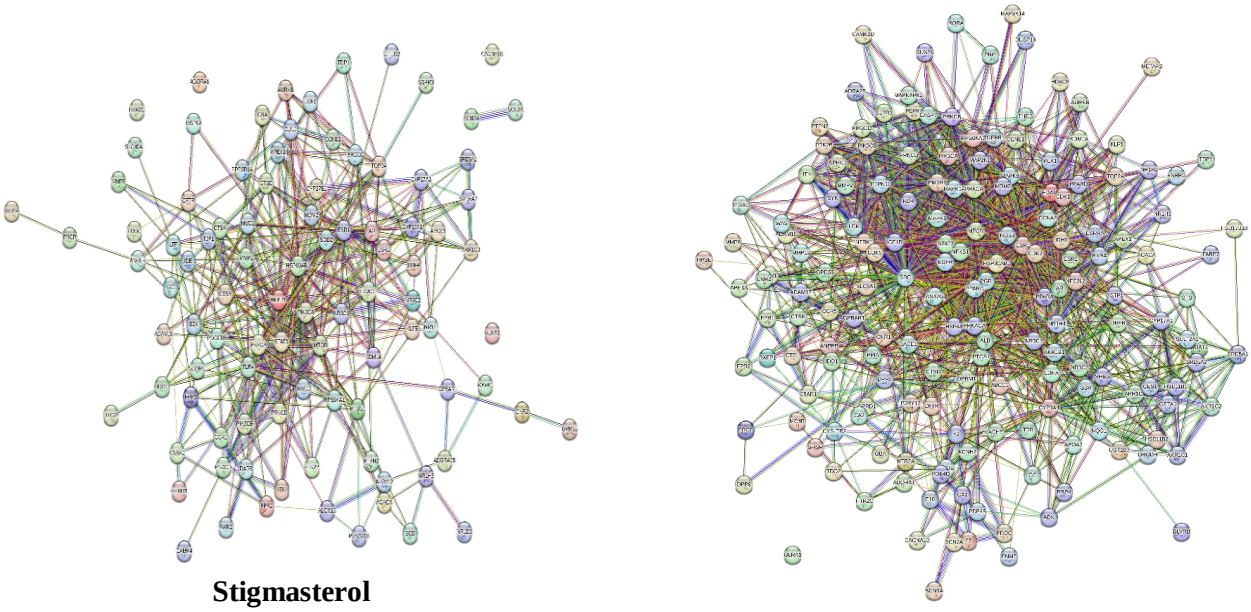
Hub network analysis was performed based on degree (DC), betweenness (BC), and closeness (CC) centralities. The analysis revealed that the central target proteins for caryophyllene and stigmasterol were HSP90AA1 and STAT3, respectively. Octadecadienal and sitosterol exhibited the same central target protein, NFKB1. A previous study showed that red betel leaf extract exhibits anti-inflammatory activity by reducing TNF-α levels, the percentage of necrotic cells, and cell death (Lister et al., 2020). In another study, it was found that secondary metabolite compounds of the flavonoid group found in red betel plant leaves were able to show anti-inflammatory activity, especially in rheumatoid arthritis, through the regulation of the transcription factor nuclear factor kappa B (NF-kB) for TNF-α expression against inflammation.



Caryophyllene

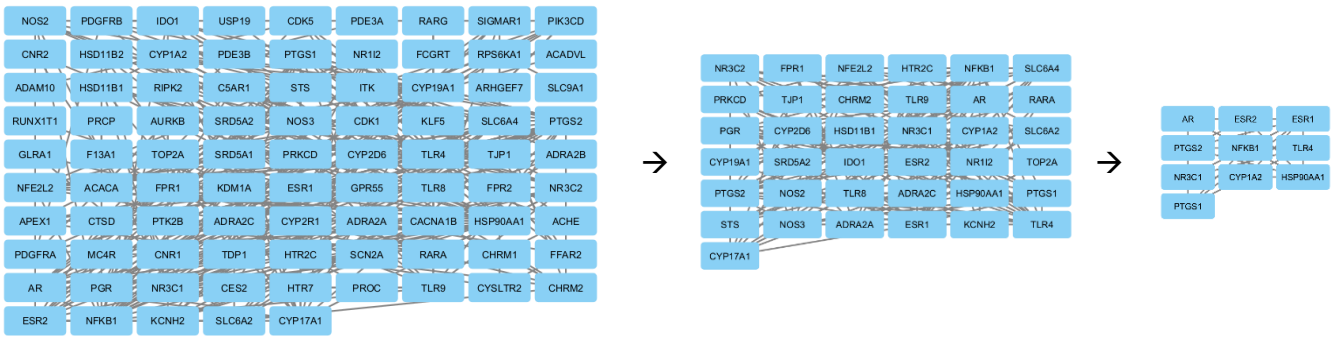


Octadecadienal

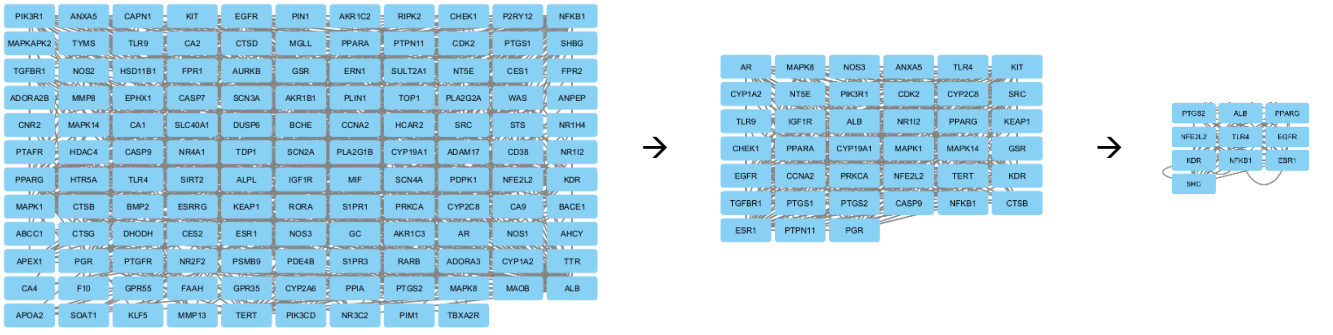


Stigmasterol **Sitosterol**

Figure 3. Protein-Protein Interaction Analysis



Caryophyllene



Octadecadienal

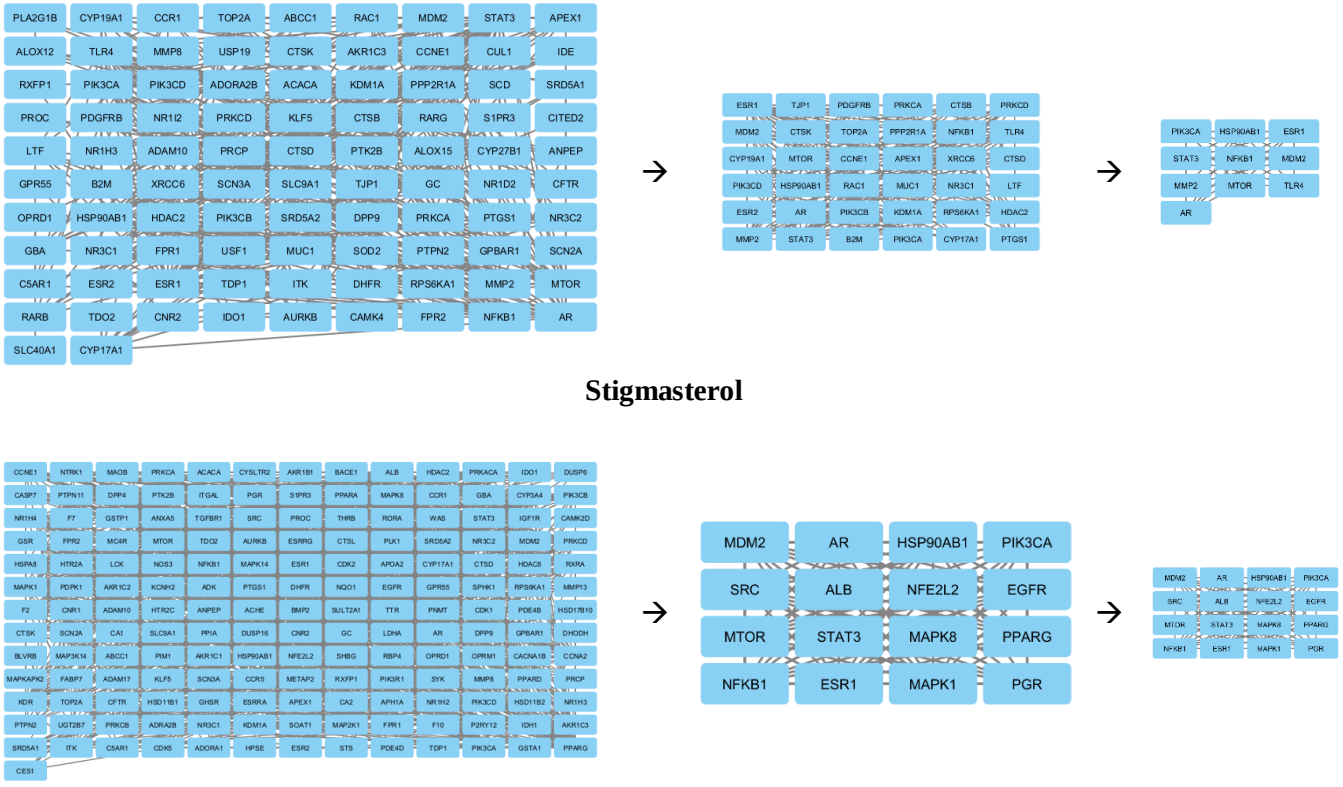


Figure 4. Core target screening based on the network topology of Caryophyllene, Octadecadienal, Stigmasterol, and Sitosterol.

Table I. Main protein targets of bioactive compounds from Cytoscape analysis.

Caryophyllene	10	ESR1, HSP90AA1, PTGS2, NFKB1, TLR4, NR3C1, AR, ESR2, PTGS1, CYP1A2
Octadecadienal	10	ALB, EGFR, NFKB1, ESR1, PPARG, PTGS2, SRC, TLR4, KDR, NFE2L2
Stigmasterol	10	ESR1, STAT3, HSP90AB1, NFKB1, MTOR, PIK3CA, TLR4, MDM2, AR, MMP2
Sitosterol	16	NFKB1, STAT3, EGFR, ESR1, MTOR, SRC, ALB, PPARG, PGR, HSP90AB1, MAPK1, PIK3CA, MDM2, MAPK8, AR, NFE2L2

To further understand the biological mechanisms involving gene function and the biological pathways of the red betel plant's bioactive compounds, GO and KEGG enrichment analyses were performed (**Figure 5** and **6**). Based on the results of the Gene Ontology Enrichment analysis of caryophyllene, the selected genes were involved in the biological processes of cellular response to lipopolysaccharides, positive regulation of DNA-templated transcription, and the cyclooxygenase pathway, with the cellular components mostly localized to the cytoplasm, intracellular membrane-bound organelles, and nucleoplasm. The molecular function was found to be DNA-binding transcription factor activity and RNA polymerase II-specific, indicating a role in regulating gene expression. KEGG enrichment analysis indicated a link between the NF-kappa B and IL-17 signaling pathways. Interleukin 17 (IL17) interacts with the type I cell surface receptor IL-17R, which activates several IL-17 signaling cascades,

leading to chemokine induction. The results of the Gene Ontology Enrichment Analysis of octadecatienal indicated the involvement of selected genes in the biological processes of positive regulation of the canonical Wnt signaling pathway, the innate immune response, and positive regulation of DNA-templated transcription, with the cellular components mostly located in the nucleus, cytoplasm, and perinuclear region of the cytoplasm. Molecular Function was found to be in DNA binding and transcription factor activity, which also indicates a role in regulating gene expression. KEGG Enrichment analysis revealed a link with the PI3K/AKT signaling pathway. Several pathways are involved in the anti-inflammatory mechanism, including the NF-κB, MAPK, and PI3K/AKT pathways. Some of these pathways have primary targets, including AKT1, TNF-α, COX-2, NFKB1, and RELA. The active compounds with inhibitory activity include flavonoids, phenolic acids, and terpenoids. The results of Gene Ontology Enrichment Analysis of stigmasterol indicated its involvement in the biological process of positive regulation of gene expression, negative regulation of apoptotic processes, and signal transduction, with the cellular components mostly located in the cytosol and nucleus. The Molecular Function was found to be transcription activator activity and protein binding, indicating its role as a transcription factor. KEGG Enrichment showed a relationship with several diseases related to infection or the immune system, such as Epstein-Barr virus infection, diabetic cardiomyopathy, viral carcinogenesis, and human immunodeficiency virus 1. The results of Gene Ontology Enrichment Analysis of sitosterol showed that the selected genes are involved in the biological process of regulation of transcription by RNA polymerase II and inflammatory responses, with the cellular components mostly located in the perinuclear region of the cytoplasm, and RNA polymerase II, which supports the data that the target is in the main transcription complex. The Molecular Function was found to be protein kinase activity and protein serine kinase activity, which indicates that the target is involved in a signaling pathway involving kinase enzymes. KEGG Enrichment showed a relationship with the TNF signaling pathway. The TNF signaling pathway has two types of receptors: TNFR-1, which is expressed in many places in the body, and TNFR-2, which is expressed more in immune cells. The main receptor that mediates the cellular effects of TNF is TNFR-1, which can induce cell death by apoptosis.

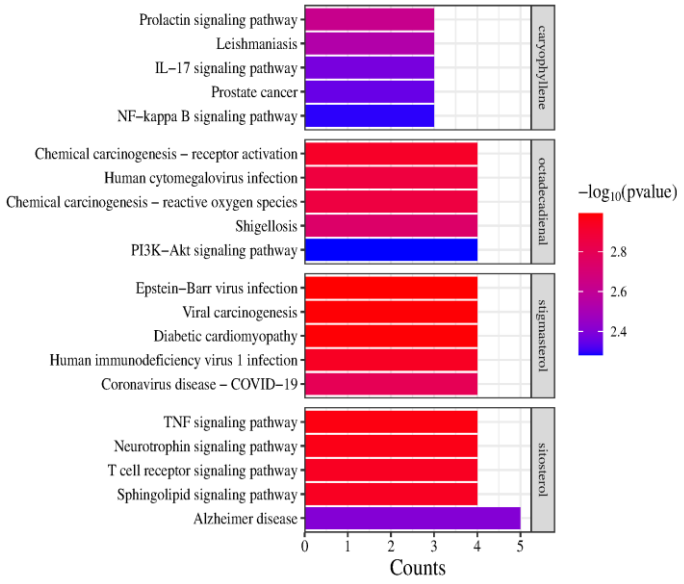


Figure 5. KEGG Chart

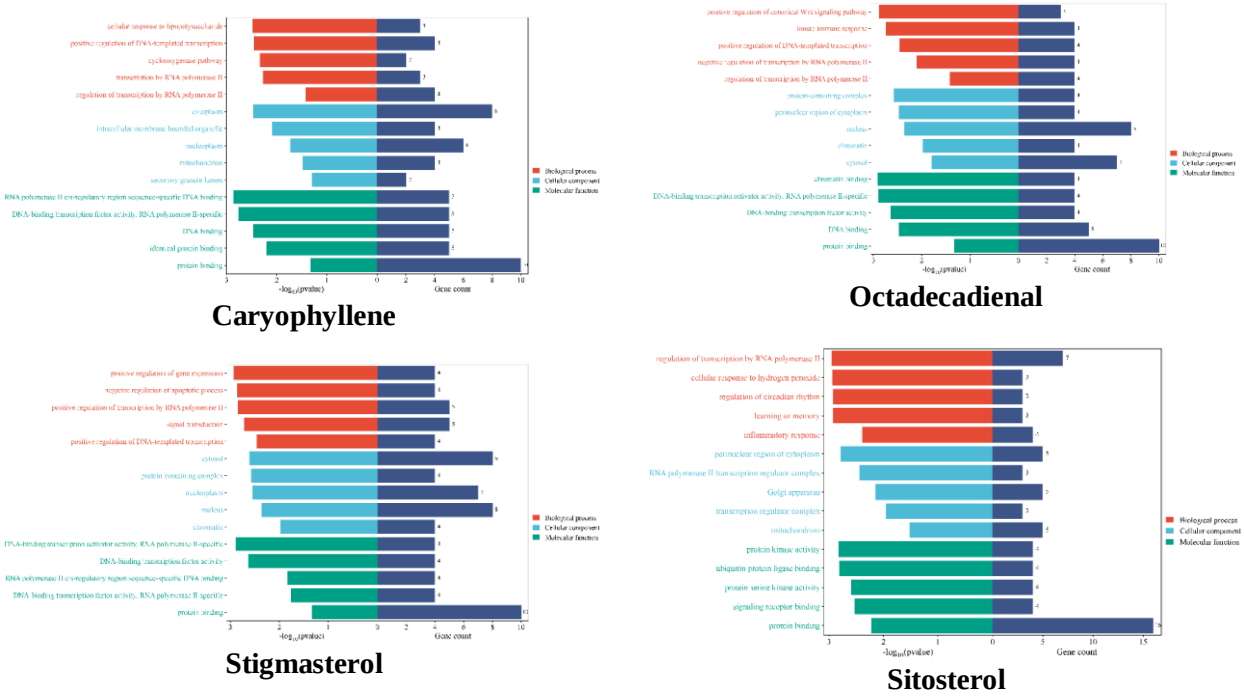


Figure 6. GO function analysis of bioactive compounds in red betel stem.

This study demonstrates that the bioactive compounds of red betel plants have the potential to act as anti-inflammatory agents through various biological mechanisms and signaling pathways related to inflammation regulation. These results can be used as a basis for developing natural compound-based drugs as more effective and safer alternatives. Further research on isolated bioactive compounds can be conducted both in vitro and in vivo to provide scientific evidence for new drug discovery.

CONCLUSION

Secondary metabolites detected in red betel stems through GC-MS analysis, such as caryophyllene, octadecadienal, stigmasterol, and sitosterol, have demonstrated potential anti-inflammatory activity. Network pharmacology analysis revealed that these bioactive compounds modulate biological pathways involved in inflammation regulation, such as NF-κB, IL-17, PI3K/AKT, and TNF signaling pathways. This analysis also identified 16 key genes as potential targets for anti-inflammatory therapy, with the central target proteins of caryophyllene and stigmasterol being HSP90AA1 and STAT3, respectively, while octadecadienal and sitosterol showed NFKB1 as the central protein. Furthermore, the involvement of protein targets of well-established anti-inflammatory drugs, along with additional hubs related to inflammation regulation, suggests that red betel constituents possess potential as multi-target therapeutic agents, particularly in conditions of persistent inflammation. These findings support the need for further research, both through molecular docking studies between the compounds and identified targets and in vitro or in vivo studies of isolated compounds.

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