Jurnal Pharmacia Mandala Waluya Vol.5 No.4
ISSN : 2829-6850
https://jurnal-pharmaconmw.com/jpmw/index.php/jpmw
DOI : https://doi.org/10.54883/jpmw.v5i4.740

Local Herbs To Overcome Cigarette Addiction : An In Silico Study Of Pometia Pinnata As A Nicotine Receptor (nAChR) Inhibitor

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ABSTRAK

Penggunaan tembakau masih menjadi permasalahan kesehatan masyarakat yang serius di Indonesia, dengan prevalensi perokok dewasa mencapai 34,5%. Upaya penanggulangan kecanduan nikotin memerlukan pendekatan baru yang efektif dan aman mengingat terapi farmakologis yang tersedia, seperti vareniklin dan bupropion, masih memiliki keterbatasan akibat efek samping yang ditimbulkan. Salah satu alternatif yang berpotensi dikembangkan adalah pemanfaatan sumber daya alam Indonesia, khususnya tanaman endemik matoa (Pometia pinnata) yang kaya akan senyawa bioaktif. Penelitian ini bertujuan untuk memprediksi struktur tiga dimensi reseptor nicotinic acetylcholine receptor (nAChR) serta mengevaluasi interaksi ligan secara in silico guna mengidentifikasi senyawa aktif dengan afinitas tinggi sebagai kandidat terapi kecanduan nikotin. Metode penelitian meliputi seleksi senyawa aktif dari P. pinnata, analisis bioaktivitas dan ADMET, validasi protein menggunakan PDBsum, pemodelan struktur tiga dimensi dengan AlphaFold2, molecular docking menggunakan AutoDock Vina, serta visualisasi interaksi melalui Discovery Studio dan ClusPro. Senyawa yang diuji meliputi Proanthocyanidin A2, Apigenin 7-O-diglukuronida, Taraxerone, dan Stigmasta-5,22-dien-3-β-ol. Hasil *molecular docking* menunjukkan bahwa Proanthocyanidin A2 memiliki afinitas pengikatan tertinggi terhadap reseptor nAChR α4β2 dengan nilai Vina score sebesar −10,5 kkal/mol melalui pembentukan interaksi ikatan hidrogen, π-anion, dan π-alkil. Sementara itu, Apigenin 7-O-diglukuronida, Taraxerone, dan Stigmasta-5,22-dien-3-β-ol masing-masing menunjukkan nilai afinitas sebesar −9,8; −9,1; dan −9,0 kkal/mol. Berdasarkan hasil tersebut, Proanthocyanidin A2 menunjukkan profil interaksi dan afinitas pengikatan terbaik. Keempat senyawa yang diuji juga memiliki afinitas yang lebih baik dibandingkan vareniklin, sehingga berpotensi dikembangkan sebagai kandidat terapi kecanduan nikotin, meskipun masih diperlukan penelitian farmakologis lebih lanjut untuk mengonfirmasi efektivitas dan keamanannya.

Kata kunci: Kecanduan nikotin; *Pometia pinnata*; *Molecular Docking*; Antagonis Reseptor Asetilkolin Nikotinik (nAChR)

Local Herbs To Overcome Cigarette Addiction : An In Silico Study Of Pometia Pinnata As A Nicotine Receptor (nAChR) Inhibitor

ABSTRACT

Tobacco use is a major public health issue in Indonesia, with 34.5% of adults being smokers. To combat this, new, effective, and safe approaches are needed. Despite existing pharmacological therapies, such as varenicline and bupropion, their effectiveness is limited due to side effects. Indonesian natural resources, particularly endemic plants like matoa fruit, have been chosen for their bioactive compounds, which could be used as an innovative solution to reduce nicotine dependence. This study aims to predict the 3D structure of nAChR receptors and evaluate ligand interactions in silico to identify high-affinity active compounds for nicotine addiction treatment. The in silico study involved compound selection from Pometia pinnata, bioactivity and ADMET analysis, protein validation (PDBsum), 3D modeling (AlphaFold2), docking (AutoDock Vina), and interaction visualization (Discovery Studio, ClusPro). The selected ligands come from natural ingredients such as Proanthocyanidin A2, Apigenin 7-O-diglucuronide, Taraxerone, stigmasta-5,22-dien-3-β-ol. Four compounds were docked to nAChR α4β2. Proanthocyanidin A2 showed the strongest binding (Vina score -10.5 kcal/mol) via hydrogen, π-anion, and π-alkyl interactions. Apigenin 7-Odiglucuronide (-9.8), Taraxerone (-9.1), and Stigmasta-5,22-dien-3-β-ol (-9.0) showed lower affinity. Proanthocyanidin A2 shows the best binding affinity and interaction profile. All four compounds had better affinity than Varenicline and could be potential candidates for nicotine addiction therapy, pending further pharmacological evaluation.

Keywords: Cigarette addiction; *Pometia pinnata*; Molecular Docking; nAChR antagonists

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Info Artikel :
Submitted : 05 Juni 2026
Revised : 25 Agustus 2026
Accepted : 29 Agustus 2026
Published : 31 Agustus 2026

INTRODUCTION

Tobacco use remains a significant public health issue in Indonesia. Data from 2021 indicated that the national survey on tobacco use among adults in Indonesia successfully mapped trends in tobacco consumption and various tobacco control indicators comprehensively, using methods aligned with global standards. Approximately 34.5% of adults, or around 70.2 million people, were identified as tobacco users, with a substantially higher prevalence among males (65.5%) compared to females (3.3%).

The use of electronic cigarettes has also increased sharply over the past decade, rising from 0.3% in 2011 to 3% in 2021. In response, stricter tobacco control policies have been implemented, including increases in tobacco excise taxes, comprehensive bans on tobacco advertising and promotion, and more effective enforcement of smoke-free areas (World Health Organization. Country Office for Indonesia, 2023). However, the low effectiveness of tobacco control policies and the persistently high smoking prevalence indicate that conventional approaches have not been sufficient to reduce smoking rates in Indonesia. This highlights the need for new strategies that specifically target the physiological mechanisms underlying nicotine addiction.

Smoking addiction is primarily caused by the body's response to the pharmacological action of nicotine. Nicotine acts on nicotinic acetylcholine receptors (nAChRs) in the brain, particularly the α4β2 and α7 subunits, triggering dopamine release and producing pleasurable effects that reinforce addictive behavior (Eric J. Nestler et al., 2001; Rosenthal et al., 2011). Although nearly half of smokers attempt to quit each year, only approximately six percent succeed (Centers for Disease Control and Prevention (CDC), 2011). Several therapeutic approaches, such as varenicline, bupropion, and nicotine replacement therapy, have been developed; however, these interventions still present limitations in terms of effectiveness and side effects (PDQ Screening and Prevention Editorial Board, 2002). Furthermore, exposure to cigarette smoke among passive smokers, which affects up to 97% of the population, further emphasizes the urgent need for more targeted therapeutic approaches.

In this context, Indonesia, as a megabiodiversity country, holds great potential to address this challenge. One promising endemic plant is matoa fruit (*Pometia pinnata*), a native plant from Papua known as a rich natural source of antioxidants. Traditionally used in herbal medicine, matoa contains various bioactive compounds, including tannins, saponins, and flavonoids, which contribute to its antioxidant potential (Andriani et al., 2020). Through in silico studies using molecular docking methods, compounds found in matoa fruit may potentially be developed as natural therapeutic agents that directly target the biological pathways involved in nicotine addiction. By scientifically exploring Indonesia's rich natural resources, innovative and sustainable solutions may be developed to address major public health challenges.

METHODS

Data Collection

The initial stage of this study involved data collection based on phytochemical studies and the reported pharmacological activities of 20 bioactive compounds from matoa (*Pometia pinnata*). Previous studies have identified various bioactive constituents from *P. pinnata*, including flavonoids, phenolic compounds, tannins, steroids, and saponins,

as well as individual compounds such as apigenin 7-O-diglucuronide and proanthocyanidin A2. From these 20 compounds, four compounds were selected for further analysis based on their reported biological activities and potential relevance to the central nervous system and nicotinic acetylcholine receptors (nAChRs). This selection was intended to focus the subsequent *in silico* analysis on compounds considered most relevant to the proposed mechanism of nicotine addiction.

The compounds used in the *in silico* analysis were obtained from the PubChem database, with the following PubChem IDs: proanthocyanidin A2 (CID 124025), apigenin 7-O-diglucuronide (CID 126843388), taraxerone (CID 92785), and withanolide (CID 53477765). These compounds were selected as potential agents capable of modulating the central nervous system and inhibiting nAChRs, which are key targets involved in nicotine addiction (Picciotto et al., 2012). The control drug used in this study was varenicline (CID 170361). The target protein was the nicotinic acetylcholine receptor obtained from the Protein Data Bank (PDB ID: 6PV7).

Analysis of Bioactive Compounds and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity)

The bioactivity of the compounds was predicted using the Way2Drug web server, accessible at Way2Drug PASS Online. The chemical Simplified Molecular Input Line Entry System (SMILES) notation for each compound was obtained from the PubChem database according to their respective PubChem IDs. The selected data were based on compounds meeting the criterion of Pa > 0.7. The ADMET profile includes absorption, distribution, metabolism, excretion, and toxicity properties of drugs. In silico ADMET profiling is highly useful for predicting the pharmacological and toxicological properties of compounds, particularly during the early stages of drug discovery. These computational models focus on improving ADMET predictions, which are essential for drug optimization and reducing late-stage drug development failures. By utilizing predictive models, such failures can minimized, thereby saving significant time and financial resources.

The pharmacokinetic analysis in this study was performed using the pkCSM-Web pharmacokinetics tool, accessible at pkCSM-Web. pkCSM-Web introduces an innovative approach for predicting and optimizing ADME/Tox properties of small molecules. This method relies on the integration of graph-based signatures and experimental data.

Protein Evaluation

To assess the quality of the protein model, geometric and stereochemical criteria were applied. The PDBsum tool, accessible at PDBsum, was used for this evaluation. With a focus on stereochemical accuracy and predictive model reliability, PDBsum plays an important role in validating PDB structures. The evaluation primarily relied on Ramachandran plot analysis, which examines the torsion angles Ø (phi) and Ψ (psi) within amino acid residues of the protein. The results are presented as percentages and classify regions into core, additionally allowed, generously allowed, and disallowed regions, thereby providing a comprehensive measure of protein structural quality.

Molecular Modeling and Docking

Computational techniques have long been used to predict three-dimensional (3D)

structures in the absence of experimental data. One of the most significant deep-learning algorithms in biomedicine, AlphaFold, has substantially transformed structural biology. AlphaFold 2 accepts protein sequence data and template structures as input. The target sequence was obtained from the NCBI database, and Google Colab was used for 3D structure prediction based on the sequence through ColabFold AlphaFold2 Notebook.

All ligands were prepared using Open Babel software, including energy minimization and file format conversion from .sdf to .pdbqt. The docking process was carried out using AutoDock Vina included in the PyRx 0.8 package. AutoDock Vina was selected because of its ability to provide more accurate binding poses compared to AutoDock. It should be noted that docking parameters varied for each protein. For docking analysis between Proanthocyanidin A2 and nAChR, the dimensions of the Vina search box were set to X (144), Y (152), and Z (166), with the box center coordinates at X (31), Y (30), and Z (32).

Docking between belimumab and all proteins was performed using ClusPro 2.0, and the selected binding energy was based on van der Waals and electrostatic energy calculations. Visualization of protein–compound docking interactions was conducted using Discovery Studio Client 2021, while protein–protein interactions were analyzed using PDBsum.

RESULTS AND DISCUSSION

RESULTS

1. Bioactivity and ADMET Analysis of *Pometia pinnata* Compounds

The ADMET parameter results, as presented in Appendix 1, provide an overview of the pharmacokinetic activities of the compounds. The absorption profiles of the analyzed compounds showed significant variation. Proanthocyanidin A2 exhibited low water solubility and an estimated intestinal absorption of approximately 69%, although it has the potential to be effluxed by P-glycoprotein. Apigenin 7-O-diglucuronide, despite having similar water solubility, was predicted not to be absorbed through the gastrointestinal tract; however, it may inhibit P-glycoprotein, potentially enhancing absorption.

Taraxerone demonstrated lower solubility but showed excellent intestinal absorption (95.6%), suggesting effectiveness despite poor solubility. Stigmasta-5,22-dien-3-β-ol exhibited a similarly high absorption rate (94.97%) and may also inhibit P-glycoprotein. Overall, compounds with high absorption profiles, such as Taraxerone and Stigmasta-5,22-dien-3-β-ol, appear more promising for smoking addiction therapy, although formulation modifications may be required to improve the bioavailability of the other compounds.

Based on the distribution parameter results, the four compounds—Proanthocyanidin A2, Apigenin 7-O-diglucuronide, Taraxerone, and Stigmasta-5,22-dien-3-β-ol—demonstrated varying capacities for distribution and central nervous system (CNS) penetration. Proanthocyanidin A2 and Apigenin showed low volume of distribution values and logPS values below -1.7, indicating limited blood–brain barrier (BBB) penetration and a low likelihood of acting directly in the brain as anti-addiction agents. In contrast, Taraxerone and Stigmasta-5,22-dien-3-β-ol exhibited positive logPS values, suggesting greater potential for CNS penetration, although predictive models still indicated

limited significant CNS permeability.

Therefore, Taraxerone and Stigmasta appear more promising for further investigation as candidate compounds capable of modulating the neurobiological pathways involved in nicotine addiction. The predicted metabolism data demonstrated distinct profiles of the four compounds (Proanthocyanidin A2, Apigenin 7-O-diglucuronide, Taraxerone, and Stigmasta-5,22-dien-3-β-ol) toward cytochrome P450 (CYP) enzymes, which play a major role in drug metabolism. Proanthocyanidin A2 and Apigenin 7-O-diglucuronide were not identified as substrates or inhibitors of any tested CYP enzymes (CYP2D6, CYP3A4, CYP1A2, CYP2C19, and CYP2C9), suggesting a low risk of drug interactions and indicating that they are likely metabolized through non-CYP pathways. On the other hand, Taraxerone and Stigmasta-5,22-dien-3-β-ol were identified as substrates of CYP3A4, indicating that they are likely metabolized through this hepatic pathway.

Nevertheless, all four compounds were not predicted to inhibit major CYP enzymes, including CYP3A4 and CYP2D6, suggesting a low potential to interfere with the metabolism of co-administered drugs. In the context of smoking addiction therapy development, these findings indicate that Proanthocyanidin A2 and Apigenin may be safer regarding metabolic interactions, whereas Taraxerone and Stigmasta should be considered more cautiously because of their involvement with the CYP3A4 pathway, particularly when used concurrently with drugs metabolized by the same enzyme, such as bupropion or varenicline.

2. Molecular Modeling, Evaluation, and Docking Analysis

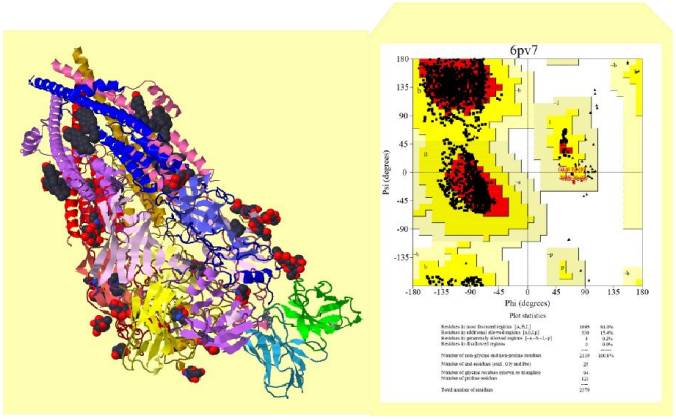
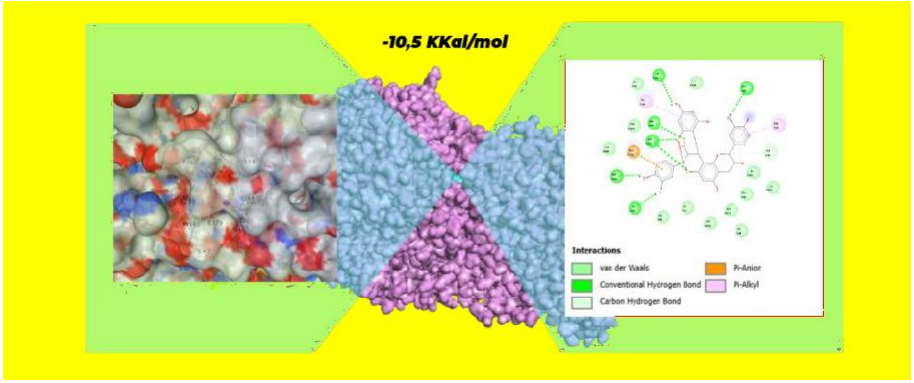


Figure 1. Protein model and evaluation of nAChR.



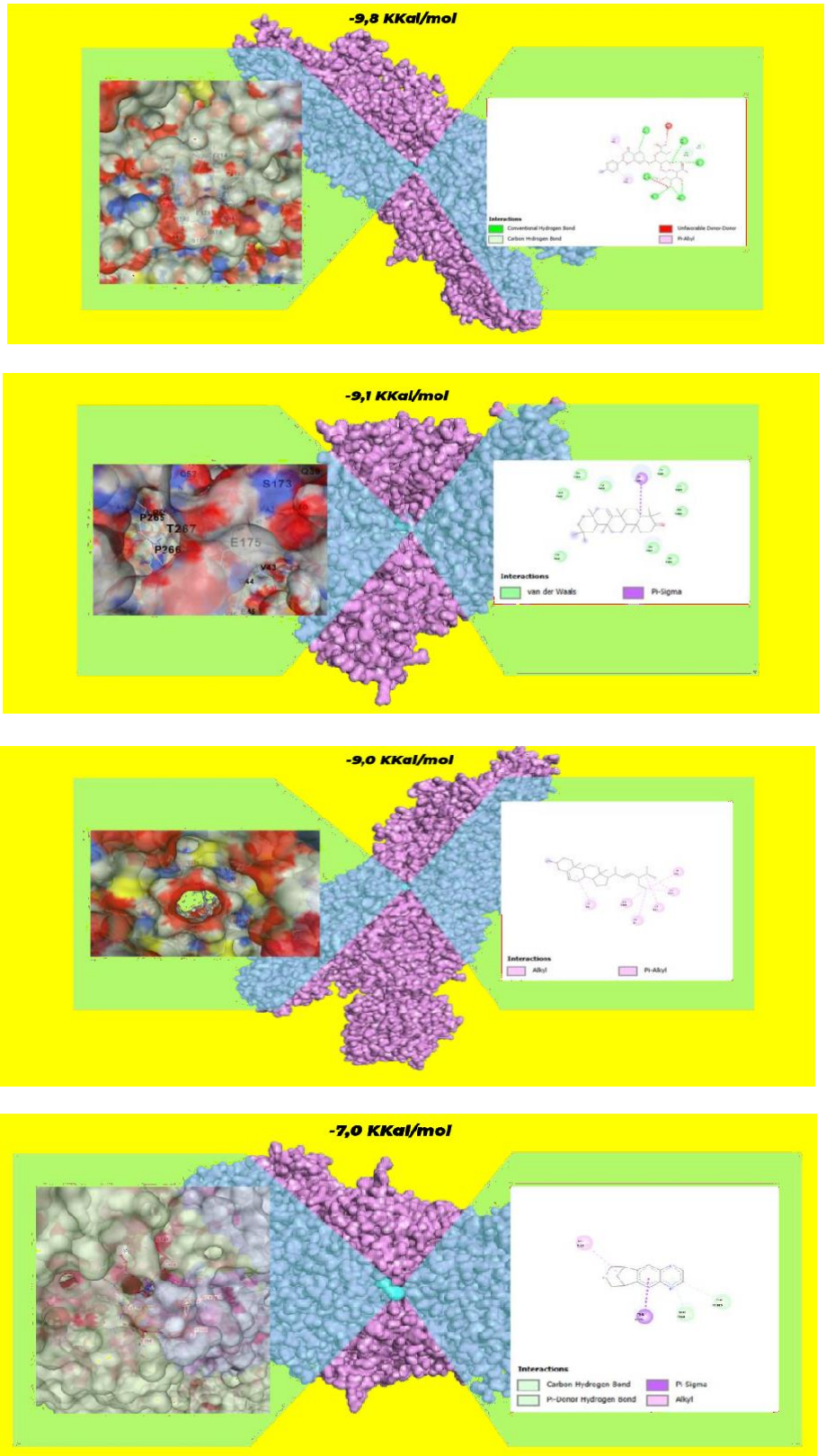


Figure 2. Hasil docking molekul Proanthocyanidin A2 + nAChR (A), Apigenin 7-O-diglucuronide + nAChR(B), Taraxerone + nAChR(C), stigmasta-5,22-dien-3-β-ol + nAChR (D), dan Vareniclin + nAChR (E).

DISCUSSION

1. Bioactivity and ADMET Analysis of *Pometia pinnata* Compounds

The bioactivity of *Pometia pinnata* compounds reflects their potential to inhibit dopamine release associated with nicotinic acetylcholine receptors (nAChRs), thereby effectively suppressing nicotine receptor activity, which is an important characteristic in smoking addiction. Furthermore, these compounds exhibit nicotinic inhibitory properties that play a crucial role in reducing addictive effects within the central nervous system. Proanthocyanidin has demonstrated potential in inhibiting α7-nAChR receptor activity, which is involved in suppressing the proliferative effects of nicotine on lung cancer cells (Alsharairi, 2021).

Apigenin exhibits anti-inflammatory effects in periodontal ligament cells induced by nicotine and lipopolysaccharides (LPS) by reducing inflammatory mediators through the heme oxygenase-1 (HO-1) pathway. Although not directly related to addiction mechanisms, apigenin may protect tissues from smoking-induced damage (Jeong et al., 2009). According to previous research by Deng et al. (2024), taraxerone has protective potential against smoking-related effects through activation of SIRT1 and inhibition of pro-inflammatory M1 macrophages, mechanisms relevant to reducing pulmonary inflammation caused by chronic nicotine exposure.

This finding presents both a challenge and a novel research opportunity regarding the role of taraxerone on nAChRs in smoking addiction. Stigmasterol acts by inhibiting acetylcholinesterase (AChE), an enzyme responsible for degrading the neurotransmitter acetylcholine. This inhibition increases acetylcholine levels in the synapse, thereby enhancing cholinergic signaling (Gade et al., 2017).

The analysis of specific ADMET pharmacokinetic parameters provides a comprehensive overview of the potential activities of Proanthocyanidin A2, Apigenin 7-O-diglucuronide, Taraxerone, and Stigmasta-5,22-dien-3-β-ol. Based on the integration of ADMET parameters (Absorption, Distribution, Metabolism, Excretion, and Toxicity), the four compounds exhibited diverse profiles regarding their potential development as smoking addiction therapies.

Taraxerone and Stigmasta-5,22-dien-3-β-ol demonstrated high absorption rates (95.6% and 94.97%, respectively) and positive logPS values, indicating greater potential to penetrate the blood–brain barrier and influence α7-nAChR receptors, which play an important role in nicotine addiction mechanisms. Both compounds were also identified as CYP3A4 substrates, indicating active hepatic metabolism, although attention should be given to their mild cardiotoxicity potential (hERG II inhibition) and environmental toxicity (Minnow toxicity log mM values of -1.381 and -1.675).

Meanwhile, Apigenin 7-O-diglucuronide and Proanthocyanidin A2 demonstrated superior systemic safety, as they were neither substrates nor inhibitors of major CYP enzymes and did not exhibit significant toxicity. However, their limited brain distribution (logPS < -1.7) and poor blood–brain barrier penetration reduce their potential to directly modulate α7-nAChR receptors. Nevertheless, compounds such as apigenin and Proanthocyanidin A2 may possess indirect modulatory potential through PPAR-γ activation, anti-inflammatory activity, and neuroprotective

effects, which are relevant during withdrawal phases or in restoring reward system function (Alsharairi, 2022; Deng et al., 2024). Therefore, Taraxerone and Stigmasta appear promising for further investigation as nicotinic receptor-targeting compounds, whereas Apigenin and Proanthocyanidin A2 may serve better as supportive agents for repairing neurobiological damage associated with addiction.

2. Molecular Modeling, Evaluation, and Docking Analysis

The method used in this study was molecular docking, an in silico structure-based technique aimed at identifying ligand or drug candidates suitable for the nAChR (nicotinic acetylcholine receptor) target associated with smoking addiction. Molecular docking enables prediction of molecular interactions between ligands and targets, discovery of novel bioactive compounds, and understanding of Structure–Activity Relationships (SAR), even without prior information regarding the chemical structures of other target modulators.

This technique offers the advantage of illustrating how ligands interact directly with receptor targets. The present study aimed to identify several ligand candidates capable of interacting more strongly with nAChRs than reference ligands and possessing the potential to be developed into innovative therapies for nicotine addiction (Putra et al., 2024).

This enthusiasm has become particularly evident since the emergence of AlphaFold in 2020, which marked a major breakthrough in predicting three-dimensional protein structures with remarkable accuracy. AlphaFold is a deep learning-based protein structure prediction system developed by DeepMind. By utilizing neural networks, AlphaFold can predict protein three-dimensional structures from amino acid sequences with accuracy comparable to experimental methods. This innovation has revolutionized structural biology by accelerating the understanding of protein functions and interactions (Jumper et al., 2021).

Based on quality assessment, the model was determined to be reliable according to Ramachandran plot criteria. The homology model of the nicotinic acetylcholine receptor (nAChR α4β2) demonstrated high structural quality, with 88.4% of residues located within favored or allowed regions and 0.0% of residues located in disallowed regions. To support the inhibitory potential against nAChR receptors, several bioactivity indicators may also serve as references in evaluating the effectiveness of compounds derived from *Pometia pinnata*.

Activity as an α7-nAChR antagonist is considered the primary indicator because it directly contributes to inhibition of dopamine release associated with addiction. In addition, compounds exhibiting nicotinic receptor antagonist activity may inhibit various nAChR subtypes such as α4β2 and α7. Additional indicators, including neuromuscular blocking agent and ganglionic blocker activities, suggest inhibitory potential toward peripheral nAChRs and the autonomic nervous system, which may indirectly strengthen nicotine addiction reduction effects.

Docking results with nAChR demonstrated favorable interactions of Proanthocyanidin A2, Apigenin 7-O-diglucuronide, Taraxerone, and Stigmasta-5,22-dien-3-β-ol with the nAChR protein. Proanthocyanidin A2 showed the strongest

predicted affinity, with a Vina score of −10.5 kcal/mol at pocket C3.

Its interaction with the binding pocket involved conventional hydrogen bonding, π-anion, π-alkyl, and van der Waals interactions with residues surrounding the binding site. Residues observed around this region, including Arg209, Trp180, Glu179, Tyr214, Lys262, and Ser265, may contribute to ligand positioning and stabilization through their polar, aromatic, and hydrophobic properties. These interactions support the potential of Proanthocyanidin A2 as an nAChR modulator.

Apigenin 7-O-diglucuronide showed a Vina score of −9.8 kcal/mol at pocket C3 and interacted with residues surrounding the binding region through conventional hydrogen bonding and π-alkyl interactions. An unfavorable donor–donor interaction was also observed, which may influence the orientation of the ligand within the binding pocket. However, the presence of other favorable interactions may contribute to maintaining the ligand within the binding site.

Stigmasta-5,22-dien-3-β-ol showed a Vina score of −9.0 kcal/mol at pocket C2 and predominantly interacted through alkyl and π-alkyl contacts, indicating that hydrophobic interactions contributed to its positioning within the binding pocket. In comparison, Taraxerone showed a slightly more favorable Vina score of −9.1 kcal/mol at pocket C3 and formed a π–sigma interaction with Phe C:253, accompanied by van der Waals contacts with surrounding residues.

The involvement of Phe C:253 suggests that aromatic interactions may contribute to the stabilization of Taraxerone within the binding site. Overall, Proanthocyanidin A2 exhibited the most favorable docking score among the four tested compounds (−10.5 kcal/mol), followed by Apigenin 7-O-diglucuronide (−9.8 kcal/mol), Taraxerone (−9.1 kcal/mol), and Stigmasta-5,22-dien-3-β-ol (−9.0 kcal/mol). The involvement of polar and aromatic residues in the binding pocket, together with hydrogen-bonding, π-related, and hydrophobic interactions, may contribute to the predicted ligand–nAChR binding. These findings suggest that Proanthocyanidin A2 has the most favorable predicted interaction with nAChR among the tested compounds and may therefore warrant further investigation as a potential nAChR modulator in the context of nicotine addiction.

CONCLUSION

Through bioactivity, ADMET, and molecular docking analyses, the active compounds derived from *Pometia pinnata* demonstrated significant potential for the development of therapeutic agents against nicotine addiction. Proanthocyanidin A2 exhibited the highest affinity toward the nAChR receptor (Vina score: -10.5 kcal/mol), indicating its strong potential as a primary nicotinic receptor inhibitor candidate. Taraxerone and Stigmasta-5,22-dien-3-β-ol showed favorable pharmacokinetic characteristics, including good brain penetration ability and strong interactions with receptor binding pockets.

Meanwhile, Apigenin 7-O-diglucuronide and Proanthocyanidin A2 provided additional benefits as supportive agents due to their anti-inflammatory properties and neuroprotective effects. These findings strengthen the potential of these four compounds, either as single therapeutic agents or as part of combination strategies, for more effective management of disorders associated with nicotine addiction.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Faculty of Military Pharmacy, Republic of Indonesia Defense University for providing the facilities and support for this research. Special thanks are extended to Marsma TNI (Purn) Dr. apt. Yuli Subiakto, M.Si for their valuable insights, critical evaluations, and financial support, which significantly enhanced the quality of this manuscript.

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