

A COMPUTATIONAL APPROACH TO UNCOVERING THE ANTIBACTERIAL AND ANTI-INFLAMMATORY POTENTIAL OF PEPTIDES FROM *Piper betle* L. LEAVES

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ABSTRACT

Background: *Piper betle* L. leaf contains bioactive compounds with potential benefits for oral health. Although its extracts and secondary metabolites have been extensively studied, peptides derived from *Piper betle* L. leaf proteins remain underexplored as antibacterial and anti-inflammatory agents. **Purpose:** This study aimed to identify and predict the antibacterial, anti-inflammatory, and toxicity profiles of theoretical peptides generated from a betel leaf protein sequence using a computational approach. **Methods:** A 561-amino-acid sesquiterpene synthase sequence attributed to *Piper betle* L. was retrieved from the UniProt database. In silico proteolysis was performed using trypsin, pepsin, and chymotrypsin to generate theoretical peptide fragments of 8–20 amino acids. These peptides represent putative digestion products derived computationally from the selected precursor protein and were not experimentally identified or quantified in *Piper betle* leaf tissue. Their physicochemical properties were assessed based on molecular weight, hydrophobicity, hydrophobicity, hydrophilicity, charge, and isoelectric point. Antibacterial, anti-inflammatory, and toxicity potentials were predicted using AntiBP3, AIPpred, and ToxinPred3, respectively. **Results:** In silico proteolysis generated nine theoretical peptide sequences with molecular weights ranging from 849.00–1,508.64 Da. GDSPSGVQC, SDPTHETK, and QNIVVAASIICR were predicted to have antibacterial potential, while eight peptides showed anti-inflammatory potential. GDSPSGVQC and DHGCTEEEACMA were predicted to be toxic. SDPTHETK and QNIVVAASIICR showed the most favorable profiles, combining antibacterial and anti-inflammatory potential with predicted non-toxicity. **Conclusion:** SDPTHETK and QNIVVAASIICR were prioritized as putative peptide candidates based on their predicted antibacterial, anti-inflammatory, and non-toxic profiles. However, these findings are based exclusively on computational analyses and do not demonstrate actual biological activity. Experimental validation is required to confirm their endogenous occurrence, biological activity, safety, and mechanisms of action.

Keywords: Antibacterial; Anti-inflammatory; Betel leaf; Bioactive peptides; Computational; *Piper betle* L.

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INTRODUCTION

Piper betle L. leaf has been utilized by various communities as a traditional medicine for generations. Beyond its medicinal uses, this plant holds significant social and cultural value, symbolizing respect for guests, reinforcing family bonds, and serving as an essential element in traditional ceremonies and weddings.¹ Among the Dayak people of West Kalimantan, a decoction of *Piper betle* L. is employed for medicinal purposes.² In Bojonegoro, East Java, the leaves are specifically used to treat toothaches.³

Previous research has demonstrated that *Piper betle* L. leaves contain various bioactive compounds, such as phenols, flavonoids, tannins, saponins, and essential oils, with eugenol and hydroxychavicol being particularly prominent.^{4,5} These constituents possess antioxidant and anti-inflammatory properties,⁶ which may support oral and dental health. *Piper betle* L. leaf extract has been reported to inhibit the growth of bacteria associated with plaque and dental caries, including *Streptococcus mutans*, as well as to reduce biofilm formation, gum inflammation, and halitosis.^{7,8} Therefore, *Piper betle* L. leaves are considered promising active ingredients for oral care products, such as mouthwashes, toothpastes, and periodontal gels.

Extensive research has demonstrated the significance of bioactive compounds in *Piper betle* L. leaves for maintaining oral health. However, the potential of peptide sequences encrypted within *Piper betle* proteins remains largely unexplored. In the present study, the peptides evaluated were not isolated or directly identified from leaf tissue but were generated theoretically through in silico proteolysis of a selected *Piper betle*-derived protein sequence. Such computationally generated peptides should therefore be regarded as putative bioactive candidates rather than naturally occurring peptides whose presence in the plant has been experimentally confirmed. Plant proteins can serve as precursors of bioactive peptides that may be released following proteolytic cleavage. Several classes of plant-derived peptides, including defensins, thionins, snakins, cyclotides, lipid-transfer proteins, and hevein-like peptides, have been reported to exhibit antimicrobial properties.^{9,10} Beyond their antibacterial activity, certain peptides also exhibit anti-inflammatory effects. For instance, lunasin and the VPY (Val-Pro-Tyr) tripeptide derived from soybeans have demonstrated such properties. Lunasin inhibits NF- κ B activation, resulting in decreased production of IL-6, IL-1 β , nitric oxide, COX-2, iNOS, and prostaglandin E₂ in lipopolysaccharide-induced macrophages.¹¹ The VPY peptide has been shown to suppress the secretion of IL-8 and TNF- α , as well as reduce the expression of IL-1 β , IL-6, IFN- γ , and IL-17 in a mouse colitis model.¹²

To the best of our knowledge, the antibacterial and anti-inflammatory potential of putative peptide sequences generated from *Piper betle* proteins has not been systematically investigated using an integrated computational approach. Therefore, this study aimed to identify theoretical peptide fragments generated through in silico proteolysis of a selected *Piper betle* protein sequence and to predict their antibacterial, anti-inflammatory, and toxicity profiles. Computational screening provides a rapid and cost-effective strategy for prioritizing candidate peptide sequences for subsequent experimental investigation. Nevertheless, all biological activities reported in this study represent computational predictions and should not be interpreted as evidence that these peptides naturally occur in *Piper betle* leaves or possess experimentally confirmed antibacterial or anti-inflammatory activity.

MATERIALS AND METHODS

This computational exploratory study aimed to predict the antibacterial and anti-inflammatory potential of theoretical peptides generated from a selected *Piper betle* L. protein sequence. The methodology included selecting a precursor protein sequence from *Piper betle* L., simulating its enzymatic hydrolysis by proteases into peptides, and subsequently assessing the resulting peptides for antibacterial and anti-inflammatory properties.

Choosing Protein Sources

The selection of protein sources is a critical step in computational exploratory research, as it directly influences the validity of subsequent analyses. Protein selection criteria include organism suitability, sequence completeness, biological function, and annotation status. The UniProt database (<https://www.uniprot.org/>) was used to retrieve and evaluate candidate precursor protein sequences based on organism suitability, sequence completeness, biological function, and annotation status. Through this database, the sesquiterpene synthase protein (accession: A0A1X9H811; entry name: A0A1X9H811_9MAGN) was identified. This protein comprises 561 amino acids and is involved in terpenoid biosynthesis.¹³

Sesquiterpene synthase is an enzyme that participates in the biosynthesis of sesquiterpenes. It is predicted to catalyse the conversion of farnesyl diphosphate into a sesquiterpene hydrocarbon skeleton, which includes precursors of volatile compounds. This enzymatic activity contributes to plants' characteristic aroma and supports their defence mechanisms.

Sesquiterpene synthase was selected as the precursor protein because this enzyme is biologically relevant to the terpenoid biosynthetic and defence-related processes of *Piper betle*. Previous experimental studies have demonstrated sesquiterpene synthase expression and associated sesquiterpene production in *Piper betle*.¹⁴ In the database search, three candidate protein records meeting the predefined search criteria were retrieved. Among these candidates, the 561-amino-acid sesquiterpene synthase sequence was selected because it was the longest complete sequence, thereby providing a broader sequence space for exploratory in silico proteolysis. This selection criterion was intended to maximize peptide discovery and does not imply that sesquiterpene synthase is more abundant or intrinsically more likely than other *P. betle* proteins to release bioactive peptides.

Protein Hydrolysis Simulation

Protein hydrolysis was simulated using trypsin, pepsin, and chymotrypsin to predict cleavage patterns within the sequence. Trypsin cleaves after lysine or arginine, pepsin primarily cleaves hydrophobic residues under acidic conditions, and chymotrypsin targets aromatic residues. The resulting hydrolysed peptides were systematically screened using computational methods to assess their potential antibacterial and anti-inflammatory activities.

Protein cleavage simulations were conducted using a web-based application¹⁵ (<https://services.healthtech.dtu.dk/services/AnOxPePred-1.0/>). In these simulations, the protease enzymes trypsin, pepsin, and chymotrypsin were employed to generate peptides consisting of 8 to 20 amino acids.

Prediction of Antibacterial Peptides

Antibacterial peptide predictions were conducted on protein hydrolysis fragments using parameters including activity, net charge, hydrophobicity, sequence length, and propensity to form amphipathic structures. The resulting peptides were evaluated for antibacterial potential using the web-based application AntiBP3 (<https://webs.iitd.edu.in/raghava/antibp3/>).¹⁶ AntiBP3 is a sequence-based tool designed to predict, screen, and design antibacterial peptides targeting Gram-positive, Gram-negative, and Gram-variable bacteria. The system analyses amino acid composition, terminal-residue binary profiles, motifs, sequence similarity, and fastText representations using machine learning algorithms. The optimal model classifies candidates based on terminal residue patterns and their activity against specific bacterial groups.

Prediction of Anti-Inflammatory Peptide Activity

The peptides were computationally evaluated for anti-inflammatory potential. The AIPpred tool (<http://thegleelab.org/AIPpred/index.html>)¹⁷ predicts anti-inflammatory activity based on the primary amino acid sequence. This system utilizes a random forest algorithm trained on selected dipeptide composition features to differentiate anti-inflammatory from non-anti-inflammatory peptides. The resulting output score represents the probability of anti-inflammatory activity for each candidate peptide.

Peptide Toxicity Prediction and LD50 Assessment

Peptide toxicity predictions are generated using the web-based application ToxinPred3 (<https://webs.iitd.edu.in/raghava/toxinpred3/>).^{18,19} ToxinPred3 identifies the potential toxic effects of peptide candidates based on their amino acid sequences. The application integrates BLAST-based similarity searches, toxic motif recognition via MERCI, and machine learning algorithms, including deep learning and protein language models. It uses features such as amino acid frequencies and sequence patterns to classify candidate peptides as toxic or non-toxic.

Predicted Acute Oral Toxicity

Predicted acute oral toxicity was additionally explored using ProTox 3.0.²⁰ Two-dimensional chemical structures of the peptide candidates were submitted to the server as SMILES strings. The predicted LD50 values correspond to computational estimates of acute oral toxicity in rats and should not be interpreted as experimentally determined lethal doses. Because ProTox 3.0 was primarily developed for chemical compounds, these outputs were considered exploratory and were not used as primary evidence of peptide safety.

RESULTS

The selected sesquiterpene synthase sequence retrieved from the UniProt database comprised 561 amino acid residues, with its structure shown in **Figure 1**.

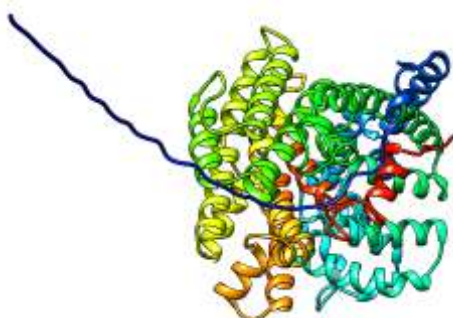


Figure 1. 3D Structure of Sesquiterpene Synthase

Table 1. Theoretical peptide sequences generated by in silico proteolysis

Peptides	Mol Wt	Hydrophobicity	Hydropathicity	Hydrophilicity	Charge	PI
SDTPIDPPQNVVAR	1508.64	-0.22	-0.72	0.29	-1.00	4.21
VTNAAIAAHKPPSK	1404.82	-0.11	-0.24	0.02	2.50	10.02
GDSPSGVQC	849.00	-0.12	-0.48	0.14	-1.00	3.80
SDPTHETK	914.04	-0.44	-2.24	1.00	-0.50	5.33
DHGCTEEEACMA	1295.33	-0.18	-0.65	0.57	-3.50	4.00
QAPEQVSNTIK	1214.50	-0.25	-0.95	0.25	0.00	6.35
QSIANDIEGM	1077.32	-0.08	-0.25	0.13	-2.00	3.67
EASTMTDSSK	1157.35	-0.30	-1.06	0.63	-1.00	4.38
QNIVVAASIICR	1286.73	0.04	1.31	-0.56	1.00	8.60

In silico proteolysis of the selected sesquiterpene synthase sequence generated nine theoretical peptide sequences. **Table 1** lists these sequences. **Table 1** presents the hydrolysis results, indicating that the nine theoretical peptide sequences have molecular weights ranging from 849.00 to 1508.64 Da and exhibit diverse physicochemical properties. Most peptides demonstrate negative hydrophobicity and hydropathicity, as well as positive hydrophilicity, which increases their likelihood of interacting with aqueous environments. Hydrophobicity reflects a peptide's tendency to interact with nonpolar environments or lipid membranes. Hydropathicity represents the balance between hydrophilic and hydrophobic properties; a positive value signifies a predominance of hydrophobic character. Hydrophilicity denotes the ability to interact with water, with higher values generally enhancing solubility. Charge refers to the net charge of the peptide under specific conditions, where a positive charge facilitates electrostatic interactions with negatively charged bacterial membranes. The isoelectric point (pI) is the pH at which the peptide's net charge is zero; when the environmental pH is below the pI, the peptide carries a positive charge. Antibacterial, anti-inflammatory, and toxicity prediction tests were subsequently conducted based on the peptide data in **Table 1**.

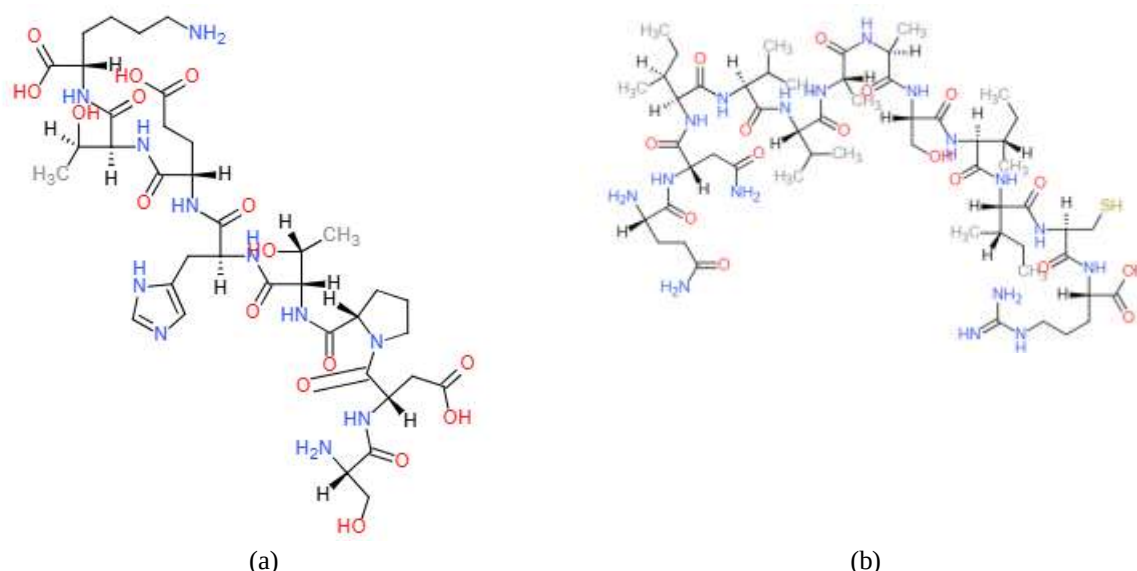
Table 2 summarizes the results of these computational prediction tests. The prediction results indicated that three of the nine peptides, specifically GDSPSGVQC, SDPTHETK, and QNIVVAASIICR, were predicted to have antibacterial potential. Eight peptides were predicted to possess anti-inflammatory potential, whereas EASTMTDSSK was predicted to have neither antibacterial nor anti-inflammatory potential. GDSPSGVQC and DHGCTEEEACMA were predicted to be toxic and were therefore not prioritized for further evaluation. SDPTHETK and QNIVVAASIICR presented the most favorable computational profiles because both were predicted to have antibacterial and anti-inflammatory potential and were classified as non-toxic by the prediction model. The remaining peptides were primarily predicted to have anti-inflammatory potential.

Table 2. Predicted antibacterial, anti-inflammatory, and toxicity profiles

Peptides	Antibacterial (score)	Anti-inflammatory (score)	Toxicity (score)	LD50 (mg/kg)
SDTPIDPPQNVVAR	No (0.45)	Yes (0.72)	No (0.43)	2000
VTNAAIAAHKPPSK	No (0.48)	Yes (0.65)	No (0.45)	3000
GDSPSGVQC	Yes (0.67)	Yes (0.62)	Yes (0.62)	1190
SDPTHETK	Yes (0.65)	Yes (0.63)	No (0.40)	3000
DHGCTEEEACMA	No (0.39)	Yes (0.74)	Yes (0.68)	3000
QAPQVSNTIK	No (0.48)	Yes (0.68)	No (0.39)	2000
QSIANDIEGM	No (0.46)	Yes (0.68)	No (0.43)	2000
EASTMTDSSK	No (0.45)	No (0.42)	No (0.42)	1190
QNIVVAASIICR	Yes (0.69)	Yes (0.72)	No (0.43)	1190

DISCUSSION

SDPTHETK and QNIVVAASIICR were prioritized for further discussion based on their combined computational prediction profiles. **Figure 2** presents their two-dimensional structures.

**Figure 2.** Peptide structures of (a) SDPTHETK and (b) QNIVVAASIICR

Among the peptide sequences evaluated, SDPTHETK and QNIVVAASIICR were computationally prioritized because they showed the most favorable combined prediction profiles for antibacterial activity, anti-inflammatory activity, and toxicity. Dental caries is associated with biofilm formation by cariogenic bacteria, primarily *Streptococcus mutans*, which produce extracellular polysaccharides and acids that cause enamel demineralization. Meanwhile, periodontitis involves bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans*, accompanied by an excessive inflammatory response that damages periodontal tissues and alveolar bone. Previous studies have shown that some antimicrobial and immunomodulatory peptides can disrupt bacterial membranes, form pores, interfere with intracellular processes, neutralize lipopolysaccharides, or modulate inflammatory signaling pathways such as TLR4, MAPK, and NF- κ B, which in turn reduce the production of mediators such as TNF- α , IL-1 β , IL-6, iNOS, and COX-2.^{21–23} However, these mechanisms were not directly investigated for SDPTHETK and QNIVVAASIICR in the present study and should therefore be regarded only as literature-based mechanistic hypotheses.

The QNIVVAASIICR peptide has a positive charge (+1), a pI of 8.60, and positive hydrophobicity. These physicochemical characteristics are compatible with features commonly reported for membrane-interacting antimicrobial peptides. In particular, a positive charge and hydrophobic residues may theoretically facilitate interaction with negatively charged bacterial surfaces and lipid membranes. However, membrane binding, membrane permeabilization, and intracellular leakage were not experimentally evaluated in this study.^{9,22,24,25} The present computational workflow did not include molecular docking, molecular dynamics simulation, or target-

binding analysis; therefore, no specific intracellular bacterial protein can be proposed as a validated molecular target of these peptides.^{21,26}

In contrast to QNIVVAASIICR, SDPTHETK is more hydrophilic, less hydrophobic, and slightly negatively charged. This physicochemical profile suggests that its predicted antibacterial activity may involve mechanisms different from those typically associated with strongly cationic membrane-disrupting peptides. However, the present study did not evaluate membrane interactions, cellular uptake, or specific molecular targets. Therefore, the antibacterial mechanism of SDPTHETK remains hypothetical and requires experimental validation.²⁶

The anti-inflammatory activities of SDPTHETK and QNIVVAASIICR were predicted using AIPpred based on their primary amino acid sequences. This prediction indicates that the sequences share features associated with previously characterized anti-inflammatory peptides, but it does not identify specific receptors, signaling proteins, or molecular pathways. Mechanisms such as LPS neutralization or modulation of TLR4, MAPK, NF- κ B, and NLRP3 signaling have been reported for other immunomodulatory peptides and may provide possible biological hypotheses for future investigation. However, none of these pathways were directly evaluated in the present study. Confirmation would require experimental analysis of peptide–LPS interactions, receptor binding, signaling-protein activation, and inflammatory mediator production in appropriate cellular or animal models.^{21,22,27} Immunomodulatory peptides suppress inflammation while preserving the body's overall defence response.²⁷

If their predicted antibacterial and anti-inflammatory activities are confirmed experimentally, SDPTHETK and QNIVVAASIICR could be further investigated as potential candidates for incorporation into oral-care formulations, including mouthwashes, periodontal gels, dental varnishes, restorative material coatings, or local delivery systems. However, their application must consider factors such as stability in saliva, susceptibility to protease degradation, fluctuations in oral cavity pH, biofilm penetration, impacts on the normal oral microbiota, and cytotoxicity toward gingival epithelial cells and fibroblasts. Consequently, the potential benefits of these peptides for oral and dental health remain theoretical and require validation through testing against oral bacteria, multispecies biofilms, inflammatory mediators, and periodontal disease models.

Currently, the findings regarding both peptides are based solely on computational predictions and lack experimentally validated biological efficacy. Furthermore, the present computational analyses did not identify or validate specific molecular targets or signaling pathways; therefore, all proposed antibacterial and anti-inflammatory mechanisms should be interpreted as hypothesis-generating rather than experimentally established mechanisms. Therefore, the peptides SDPTHETK and QNIVVAASIICR require validation through peptide synthesis, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) testing, membrane disruption assays, antibiofilm assays, and quantification of inflammatory mediators in lipopolysaccharide (LPS)-induced cells. Further evaluation of cytotoxicity, haemolytic activity, proteolytic stability, selectivity toward mammalian cells, and in vivo efficacy is necessary before these peptides can be considered safe and effective therapeutic candidates.

In silico proteolysis of the selected sesquiterpene synthase sequence generated nine theoretical peptide sequences with distinct physicochemical characteristics. Among these sequences, SDPTHETK and QNIVVAASIICR were prioritized because they showed favorable combined predictions for antibacterial activity, anti-inflammatory activity, and peptide toxicity. However, the present findings are exclusively computational and do not confirm the endogenous occurrence of these peptides in *Piper betle* leaves or demonstrate their biological activity, safety, or therapeutic efficacy. Therefore, experimental validation through peptide synthesis, antibacterial and anti-inflammatory assays, cytotoxicity assessment, stability evaluation, and mechanistic studies is required before their biological relevance or potential application in oral health can be established.

REFERENCES

1. Azzam MN, Azzahra FG, Fajeriadi H. Kajian etno-sosioantropologi tumbuhan Arecaceae pada ritual etnis suku di Kalimantan. In: Prosiding Seminar Nasional Pendidikan Biologi. Universitas Lambung Mangkurat; 2025. p. 23–31.
2. Pasmayay Y, Wardhani HAK, Ratnasari D, Setiawan H, Kurnianto AA. Kajian etnobotani tumbuhan obat Suku Dayak Desa Umin Jaya, Kecamatan Dedai, Kalimantan Barat. Biol Nat Resour J. 2026;4(2):31–40. doi:10.55719/binar.v4i2.2196
3. Andanalusia M, Izzatul Mukhlisah NR. Kajian literatur: Etnomedisin sebagai analgesik di Indonesia. J Syifa Sci Clin Res. 2023 Aug 10;5(2):313–26. doi:10.37311/jsscr.v5i2.21477

4. Prayoga T, Lisnawati N, Sari PE, Rohman DS, Shafa HF, Fadli T, et al. Analisis kandungan bioaktif dan bahan organik asing pada simplisia daun sirih merah (*Piper porphyrophyllum*). J Farm IKIFA [Internet]. 2024;3(3):115–20. Available from: <https://epik.ikifa.ac.id/jfi/article/view/221>
5. Ramdhani MochN, Firdaus A, Umami M. Analisis senyawa fitokimia dan tren penelitian pada daun sirih hijau (*Piper betle* L.): Pendekatan eksperimental dan bibliometrik. Bioed J Pendidik Biol. 2025 Sep 30;13(2):108–27. doi:10.25157/jpb.v13i2.19837
6. Seo J, Lee U, Seo S, Wibowo AE, Pongtuluran OB, Lee K, et al. Anti-inflammatory and antioxidant activities of methanol extract of *Piper betle* Linn. (*Piper betle* L.) leaves and stems by inhibiting NF- κ B/MAPK/Nrf2 signaling pathways in RAW 264.7 macrophages. Biomed Pharmacother. 2022 Nov;155:113734. doi:10.1016/j.biopha.2022.113734
7. Kandida I, Tari M, Fatiqin A. Effectiveness of the combination of green betel leaf extract (*Piper betle*) and mint leaf (*Mentha piperita*) as antibacterials against *Streptococcus mutans*. Bioactivities. 2023 Jun 30;1(1):32–8. doi:10.47352/bioactivities.2963-654X.184
8. Jalil V, Khan M, Haider SZ, Shamim S. Investigation of the antibacterial, anti-biofilm, and antioxidative effect of *Piper betle* leaf extract against *Bacillus gaemokensis* MW067143 isolated from dental caries, an in vitro-in silico approach. Microorganisms. 2022 Dec 15;10(12):2485. doi:10.3390/microorganisms10122485
9. Li J, Hu S, Jian W, Xie C, Yang X. Plant antimicrobial peptides: structures, functions, and applications. Bot Stud. 2021 Apr 29;62(1):5. doi:10.1186/s40529-021-00312-x
10. Tam J, Wang S, Wong K, Tan W. Antimicrobial peptides from plants. Pharmaceuticals. 2015 Nov 16;8(4):711–57. doi:10.3390/ph8040711
11. De Mejia EG, Dia VP. Lunasin and lunasin-like peptides inhibit inflammation through suppression of NF- κ B pathway in the macrophage. Peptides. 2009 Dec;30(12):2388–98. doi:10.1016/j.peptides.2009.08.005
12. Basson AR, Ahmed S, Almutairi R, Seo B, Cominelli F. Regulation of intestinal inflammation by soybean and soy-derived compounds. Foods. 2021 Apr 4;10(4):774. doi:10.3390/foods10040774
13. The UniProt Consortium. UniProt: the Universal protein knowledgebase in 2025. Nucleic Acids Res. 2025 Jan 6;53(D1):D609–17. doi:10.1093/nar/gkae1010
14. Woranoot K, Buaruang R, Aranyakanon K, Ratanasut K, Kongbangkerd A, Jannoey P, et al. *Fusarium solani* Upregulated Sesquiterpene Synthase Expression, Sesquiterpene Production and Allelopathic Activity in *Piper betle* L. Rice Sci. 2019 Sep;26(5):290–9. doi:10.1016/j.rsci.2019.08.003
15. Komari N, Suhartono E, Hadi S, Mustikasari K, Putera GMP. Antihypertensive activity of peptides derived from Toman Fish albumin (*Channa micropeltes*): In-silico angiotensin-converting enzyme inhibitory study. Int J Drug Deliv Technol. 2024 Sep 25;14(03):1505–10. doi:10.25258/ijddt.14.3.34
16. Bajiya N, Choudhury S, Dhall A, Raghava GPS. AntiBP3: A method for predicting antibacterial peptides against gram-positive/negative/variable bacteria. Antibiotics. 2024 Feb 8;13(2):168. doi:10.3390/antibiotics13020168
17. Manavalan B, Shin TH, Kim MO, Lee G. AIPpred: Sequence-based prediction of anti-inflammatory peptides using random forest. Front Pharmacol. 2018 Mar 27;9:276. doi:10.3389/fphar.2018.00276
18. Rathore AS, Choudhury S, Arora A, Tijare P, Raghava GPS. ToxinPred 3.0: An improved method for predicting the toxicity of peptides. Comput Biol Med. 2024;179:108926. doi:10.1016/j.compbimed.2024.108926
19. Gupta S, Kapoor P, Chaudhary K, Gautam A, Kumar R, Open Source Drug Discovery Consortium, et al. In silico approach for predicting toxicity of peptides and proteins. Patterson RL, editor. PLoS ONE. 2013 Sep 13;8(9):e73957. doi:10.1371/journal.pone.0073957
20. Banerjee P, Kemmler E, Dunkel M, Preissner R. ProTox 3.0: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2024 Jul 5;52(W1):W513–20. doi:10.1093/nar/gkae303
21. Luo Y, Song Y. Mechanism of antimicrobial peptides: antimicrobial, Anti-inflammatory and antibiofilm activities. Int J Mol Sci. 2021 Oct 22;22(21):11401. doi:10.3390/ijms222111401
22. Drayton M, Deisinger JP, Ludwig KC, Raheem N, Müller A, Schneider T, et al. Host defense peptides: Dual antimicrobial and immunomodulatory action. Int J Mol Sci. 2021 Oct 16;22(20):11172. doi:10.3390/ijms222011172
23. Li H, Niu J, Wang X, Niu M, Liao C. The contribution of antimicrobial peptides to immune cell function: A review of recent advances. Pharmaceuticals. 2023 Sep 4;15(9):2278. doi:10.3390/pharmaceutics15092278
24. Muthmainah N, Suhartono E, Putera GMP, Marisa D, Mashuri, Hayatie L, et al. Phytochemical profiling and antibacterial activity of Sungkai (*Peronema canescens*) leaf extract against *Staphylococcus aureus*. Dentino. 2026;XI(11):33–8.
25. Gan BH, Gaynord J, Rowe SM, Deingruber T, Spring DR. The multifaceted nature of antimicrobial peptides: current synthetic chemistry approaches and future directions. Chem Soc Rev. 2021;50(13):7820–80. doi:10.1039/D0CS00729C
26. Zhang QY, Yan ZB, Meng YM, Hong XY, Shao G, Ma JJ, et al. Antimicrobial peptides: mechanism of action, activity and clinical potential. Mil Med Res. 2021 Sep 9;8(1):48. doi:10.1186/s40779-021-00343-2
27. Liu W, Chen X, Li H, Zhang J, An J, Liu X. Anti-inflammatory function of plant-derived bioactive peptides: A review. Foods. 2022 Aug 6;11(15):2361. doi:10.3390/foods11152361