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Natural Polyphenol-Based Metal-Phenolic Capsules as a Drug Delivery System Containing Ethanol Extract of *Peronema canescens* Jack Bioactive Compounds

Regina Wan Azizah[1], Fashihah Maulida[1], Indra Lasmana Tarigan[1, 2], Madyawati Latief[1,2*]

[1]*Department of Chemistry, Faculty of Science and Technology, Universitas Jambi, Indonesia*
[2]*Natural Product and Bioactive Compound Laboratory, Faculty of Science and Technology, Universitas Jambi, Indonesia*

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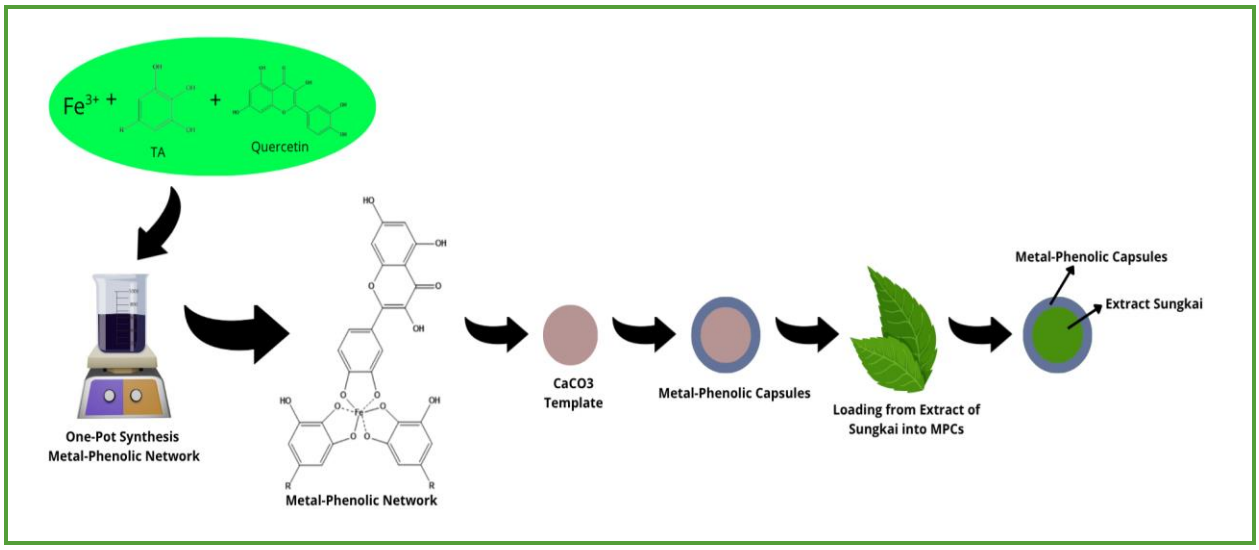
ABSTRACT

Sungkai leaves (*Peronema canescens* Jack) are rich in bioactive metabolites, particularly flavonoids such as quercetin, that exhibit antioxidant and immunomodulatory activities. In this study, a green chemistry-based metal–phenolic capsule (MPC) system was developed to enhance the therapeutic potential of *Sungkai* ethanol extract. The extract was characterized by HRMS, revealing approximately 454 compounds, including a candidate immunomodulator. MPCs were synthesized via coordination of Fe^{3+} with quercetin and tannic acid, yielding stable microcapsules (8.95–17.25 μm) as confirmed by FTIR, PSA, SEM, and XRD analyses. The system achieved high encapsulation efficiency (EE%) (98.38%) with a loading capacity (LC%) of 1.95%. *In silico* docking against the TLR4 receptor (PDB ID: 7AAH) indicated favorable binding, supporting the immunomodulatory potential of the extract. *In vitro* studies demonstrated rapid release under acidic conditions (pH 1.2) and sustained release at physiological pH (7.4). *In vivo* histopathological evaluation of mouse livers confirmed biocompatibility and hepatoprotective effects. Collectively, these findings highlight MPCs@Sungkai as a sustainable and biocompatible delivery platform, integrating natural polyphenols and plant extracts for immunotherapy applications with reduced risk of drug dependence.

Corresponding author, E-mail: madyawatilatief@unja.ac.id (M. Latief).
Tel.: +6281366197197.

Graphical Abstract



Introduction

The success of drug therapy depends on the ability of delivery systems to selectively transport active compounds to target tissues while minimizing systemic side effects [1,2]. Conventional administration routes, such as oral and injectable delivery, remain limited by metabolic degradation, low bioavailability, patient discomfort, and the lack of organ-specific targeting [3–6]. These shortcomings not only reduce therapeutic efficacy, but also increase the risk of adverse effects on healthy tissues. Consequently, there is an urgent need for innovative delivery platforms capable of controlled release and site-specific action, tailored to the patient's physiological and pathological condition. Metal-phenolic capsules (MPCs) are a drug delivery system gaining attention in the field of nanomedicine due to their multifunctional properties and design flexibility. One of the key advantages of their capsule structure is its ability to be tailored to specific physical and chemical characteristics based on therapeutic needs [6–9]. MPCs are made from natural materials such as tannic acid or other non-toxic phenolic compounds, as well as metals (Fe^{3+} and Ca^{2+}), making them relatively stable in biological systems and biodegradable in the body [10]. Phenolic modifications, such as hyaluronic acid and PEG enable the capsules to recognize specific receptors on the surface of target cells, such as cancer cells [11]. An innovative approach in the field of pharmacy is the development of nanotechnology-based drug delivery systems [3,12]. The integration of nanotechnology into drug-eluting stents can enhance the effectiveness and safety of cardiovascular treatments, improve biocompatibility, reduce restenosis risk, and increase drug delivery capacity [13,14]. Additionally, drug release also increases with the use of an alkaline medium (pH 7.4), and the concentration of silymarin in the medium pH plays an important role in the drug release profile [15,16]

Advances in nano- and microtechnology have enabled the development of innovative drug delivery systems that address the limitations of conventional approaches by providing controlled release, enhanced stability, and site-specific targeting [17]. One promising platform is MPCs, which are assembled through coordination between multivalent metal ions

(*e.g.,* Fe^{3+}, Cu^{2+}, and Zn^{2+}) and natural polyphenols such as tannic acid, yielding stable, biocompatible, and easily tunable structures [16-18]. The physicochemical properties and performance of MPCs—governed by parameters such as metal ion type, ligand ratio, and assembly conditions—highlight the interplay between nanostructure design and microscale functional behavior. Moreover, their responsiveness to pathological microenvironments (*e.g.*, acidic pH and enzymatic activity) positions MPCs as a bridge between the precision of nanotechnology and the functional advantages of micro-scale systems in therapeutic delivery. However, despite the growing interest in micro- and nano-structured carriers, no studies have yet explored MPCs formulated from Sungkai (*Peronema canescens*) polyphenols, even though these compounds are known to possess diverse bioactive potentials. Therefore, this study investigates both the fabrication and biological evaluation of Sungkai polyphenol–based MPCs to establish their suitability as targeted and stimuli-responsive drug delivery systems.

Experimental

Materials

Iron(III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$, ≥98%, Merck, Germany), quercetin (≥95%, Sigma-Aldrich, USA), tannic acid (ACS reagent grade, Sigma-Aldrich, USA), calcium carbonate ($CaCO_3$, analytical grade, Merck, Germany), commercial immunoglobulin (Immunos®, Kalbe Farma, Indonesia), dimethyl sulfoxide (DMSO, ≥99.9%, Sigma-Aldrich, USA), ethylenediaminetetraacetic acid (EDTA) buffer solution (0.1 M, pH 7.5, Merck, Germany), and phosphate buffer solutions (pH 1.2 and 7.4, Gibco, USA) were obtained from commercial suppliers and used without further purification. Ultrapure water (Milli-Q grade, Millipore, USA) was used throughout all preparations.

Plant material

Fresh *Sungkai* leaves were collected from healthy trees in Jambi Province, Indonesia. The plant material was authenticated at the Herbarium, Department of Biology, Faculty of Science and Technology, Universitas Jambi, and a voucher specimen (No. PCJ-2024) was deposited for future reference. Leaves were cleaned, air-dried at room temperature, and ground into fine powder before extraction.

Instrumentation and software

The primary instruments used included a UV-Vis spectrophotometer (UV-1800, Shimadzu, Japan), Fourier transform infrared spectrophotometer (IRTracer-100, Shimadzu, Japan), particle size analyzer (Zetasizer Nano ZS, Malvern Instruments, UK), scanning electron microscope (JSM-6510LA, JEOL, Japan), X-ray diffractometer (X'Pert PRO, PANalytical, Netherlands), and high-resolution mass spectrometer (Q Exactive Plus, Thermo Fisher Scientific, USA). Computational analyses, including molecular docking and visualization, were conducted using AutoDock Vina (The Scripps Research Institute, USA), PyRx v0.9.8, PyMOL v2.5 (Schrödinger, LLC, USA), and discovery studio visualizer (BIOVIA, Dassault Systèmes, France). Pharmacokinetics and toxicity predictions were performed using SwissADME and ProTox-II (accessed March 2025).

Preparation of polyphenol extract

Fresh Sungkai leaves were collected, washed with distilled water to remove adhering impurities, and air-dried in the shade at ambient temperature (approximately 28 °C) for five days, and then ground into fine powder. A total of 2.5 kg of powdered material was subjected to maceration with 96% ethanol at a solid-to-

solvent ratio of 1:5 (w/v) for 72 h at room temperature with occasional stirring. The extraction was repeated three times, and the combined filtrates were concentrated under reduced pressure at 40 °C to obtain a crude ethanolic extract. The extract was stored at 4 °C in an airtight container and used consistently for all subsequent experiments.

Synthesis of MPCs

Quercetin (100 mg) was dissolved in 20 mL of DMSO and subsequently diluted with 80 mL of distilled water under continuous magnetic stirring. Separately, tannic acid (170.12 mg, dissolved in 100 mL of distilled water) was added to the quercetin solution and stirred for 15 min. After that, $FeCl_3 \cdot 6H_2O$ (53.7 mg, in 100 mL distilled water) was added dropwise, resulting in the formation of a purple complex, indicating Fe^{3+} phenolic coordination. Calcium carbonate ($CaCO_3$, 4.5 g) was introduced as a sacrificial template due to its biocompatibility, mild solubility in EDTA, and ability to form uniform microspherical cores. The reaction mixture was incubated for 40, 60, or 80 h at ambient temperature without further agitation to allow capsule formation. The resulting product was collected by centrifugation (2000 rpm, 15 min) and washed three times with distilled water to remove unbound materials. The $CaCO_3$ cores were subsequently dissolved using EDTA buffer solution (0.1 M, pH 7.5) to generate hollow MPCs. The final product was purified by repeated washing, lyophilized at −50 °C, and stored in airtight containers at 4 °C [12].

Drug encapsulation, EE%, and LC%

The drug loading of MPCs with Sungkai extract and commercial Immunos was performed using a passive diffusion method in drug solution and incubating overnight (±24 h) at room temperature [19, 20]. After incubation, the suspension was centrifuged (3,000 rpm, 10 min at room temperature) to separate the loaded capsules from the supernatant. The concentration of free, unencapsulated drug in the supernatant was determined by UV-Vis spectrophotometry at 271 nm (Sungkai extract) and 247 nm (Immunos). The amount of encapsulated drug was calculated based on a standard calibration curve. EE% and LC% were determined using Equations 1 and 2 [11,12].

$$EE\% = \left(\frac{\text{weight of loaded rutin}}{\text{weight of initial rutin}}\right) \times 100\% \quad (1)$$

$$LC\% = \left(\frac{\text{weight of loaded rutin}}{\text{weight of sampel}}\right) \times 100\% \quad (2)$$

In silico studies revealed the interaction

Molecular docking was performed using Toll-like receptor 4 (TLR4, PDB ID: 7AAH) as the target protein. Ligand structures (quercetin, tannic acid, bioactive compounds from Sungkai extract, and Immunos) were prepared with Avogadro and converted to *pdbqt* format. Docking simulations were carried out with AutoDock Vina using a grid box centered on the active site. Binding affinities were analyzed, and interactions were visualized using PyMOL and Discovery Studio. Pharmacokinetics and toxicity were predicted using SwissADME and ProTox.

In vitro drug release

Drug release studies were conducted at pH 1.2 (simulated gastric fluid) and pH 7.4 (simulated blood plasma) at 37 °C. MPCs@ sungkai and MPCs@immunos were prepared at a concentration of 200 ppm in 50 mL and analyzed using UV-Vis spectroscopy in the wavelength range of 200-300 nm.

Antioxidant activity

The antioxidant activity was determined using the DPPH assay. A 0.1 mM ethanolic DPPH

solution was mixed with samples at various concentrations (10-200 µg/mL) and incubated in the dark for 30 min at room temperature. Ascorbic acid was used as a positive control. The absorbance of each mixture was measured at 517 nm, and all measurements were performed in triplicate. The percentage of DPPH inhibition was calculated using Equation 3:

$$\text{Percent of inhibition (\%)} = \left(\frac{\text{Ac of control - As of sample}}{\text{Ac of control}}\right) \times 100 \quad (3)$$

Where, Ac is the absorbance of the control, and As is the absorbance of the sample. The IC_{50} value (µg/mL), representing the concentration required to scavenge 50 % of DPPH radicals, was determined from the linear regression of the inhibition curve [21,22]

In vivo study

Male mice (*Mus musculus* 6-8 weeks, 25-30 g; n = 25) were housed under standard laboratory conditions (25 ± 2 °C, 12 h light/dark cycle) with free access to food and water. The animals were randomly divided into five groups (n = 5): normal control, MPCs, Immunos, MPCs@Immunos, and MPCs@Sungkai. Treatments were administered orally once daily a dose of 100 mg/kg body weight for seven days. After treatment, liver tissues were collected for histopathological examination to assess potential toxicity and hepatoprotective effects [23].

Result and Discussion

Preparation of sungkai leaf extract

The extract obtained was a thick green ethanol extract of sungkai leaves, which was diluted to 1,000 ppm for characterization using HRMS (High-resolution mass spectrometry). Based on the results of characterization using HRMS, ±454 compounds were obtained and proceeded to the stage of compound interpretation as drug candidates (Table S1). All detected compounds were evaluated using swissADME website for drug likeness according to Lipinski rule, ProTox for toxicity prediction, and PASSOnline for biological activity prediction. Five candidate compounds met Lipinski's criteria and were predicted to possess good oral bioavailability, low toxicity, and a high probability of antioxidant and immunomodulatory activity.

Synthesis of MPCs

MPCs were successfully synthesized by coordinating Fe^{3+} ions with phenolic groups from quercetin and tannic acid. The characteristic Fe–O stretching band appeared at 600–700 cm^{-1}, confirming the formation of the MPCs broad peaks around 3,200–3,400 cm^{-1} indicated –OH stretching, while bands at 1,600–1,650 cm^{-1} corresponded to C=O and C=C groups (Figure 1). These results are consistent with previous studies reporting Fe–phenolic coordination in capsule-based drug delivery systems. MPCs are designed on a micro scale for oral use, and particle size analysis (PSA) results confirm successful capsule formation, with MPCs40, MPCs60, and MPCs80 showing average sizes of 17.25 µm, 8.95 µm, and 10.22 µm, and MPCs@sungkai and MPCs@immunos showing sizes of 17.21 and 16.88 (Figure 2a). SEM analysis (Figure 2b) at 10,000x magnification revealed a spherical morphology with denser surface pores in drug-loaded MPCs compared to empty capsules. MPCs80 exhibited more aggregates than MPCs at a sufficiently short incubation time (MPCs40).

XRD patterns demonstrated increasing crystallinity with incubation time (71.76%, 88.01%, and 92.04% at 40, 60, and 80 h, respectively), although MPCs40 was considered

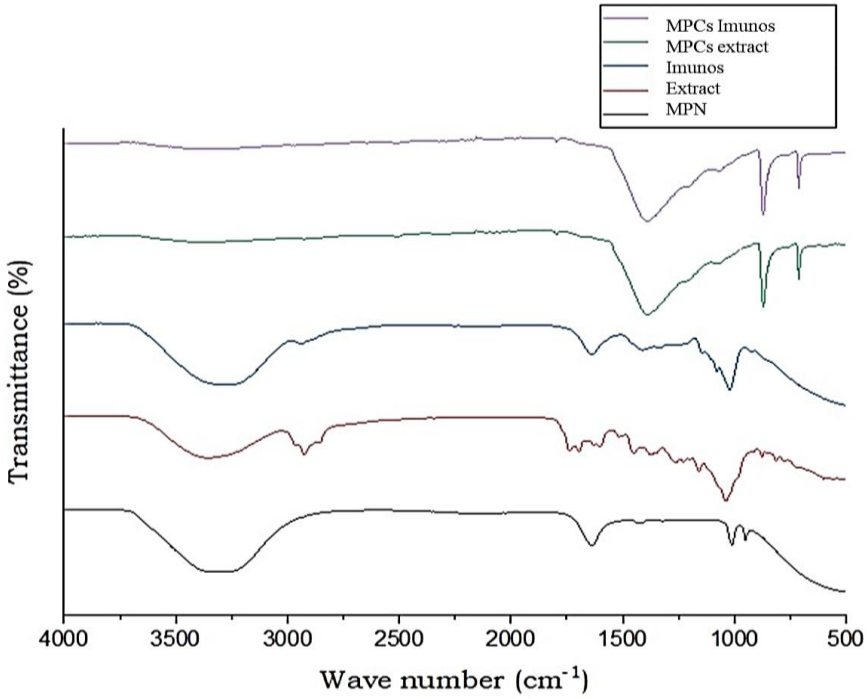
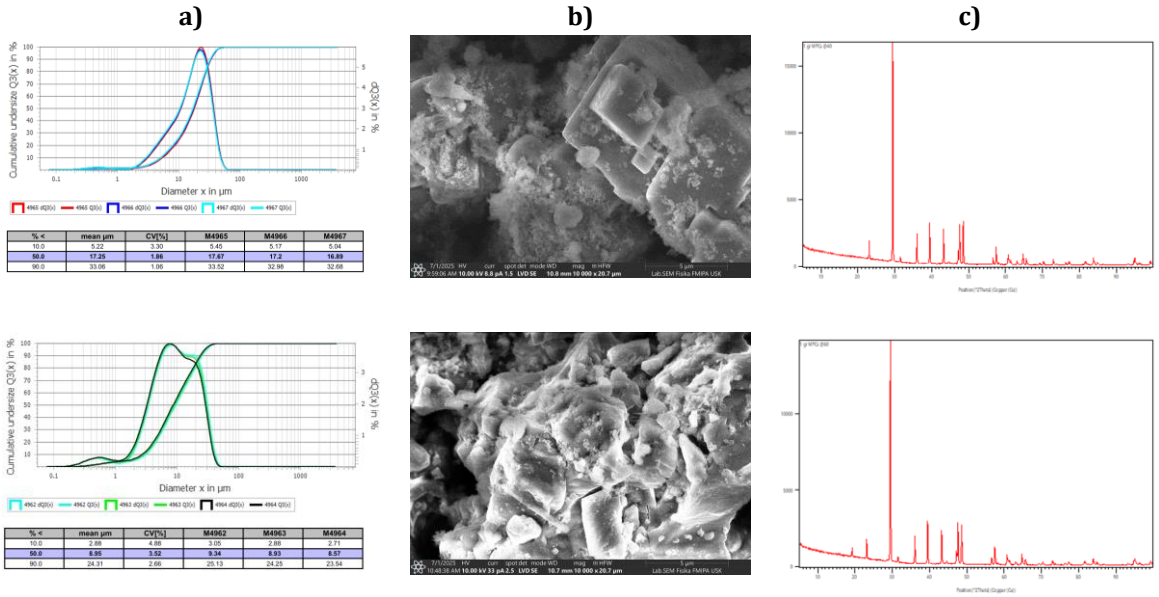


Figure 1. FTIR spectra of MPCs



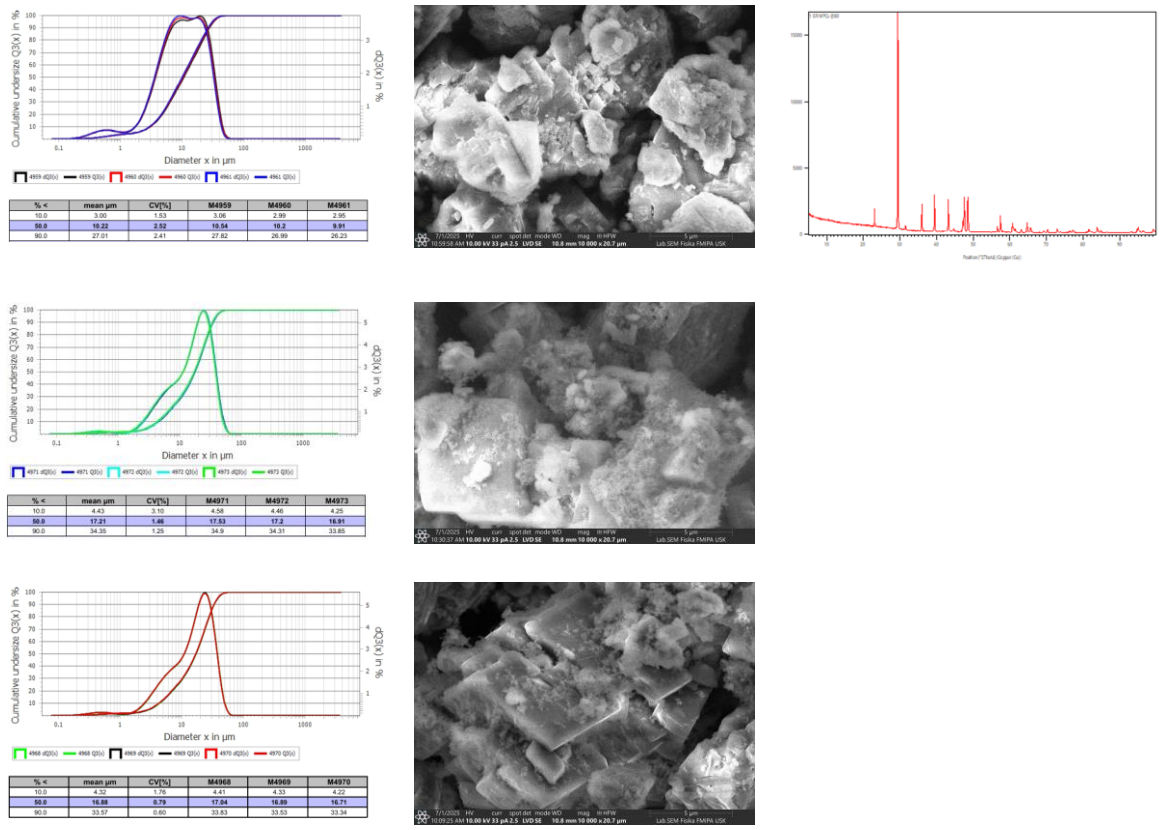


Figure 2. Particle size, morphological structure, and crystalline degree, a) PSA MPCs40, MPCs60, MPCs 80, and MPCs@sungkai dan MPCs@immunos, b) SEM MPCs40, MPCs60, MPCs 80, and MPCs@sungkai dan MPCs@immunos, c) XRD MPCs40 and MPCs60 dan MPCs 80

optimal due to its more amorphous structure, which favors drug loading and controlled release.

Drug encapsulation, EE%, and LC%

The drug loading of MPCs with Sungkai extract and commercial Immunos was successfully performed using the passive diffusion method. After incubation, UV-Vis spectrophotometric analysis of the supernatant confirmed that most of the drug had been entrapped within the capsules. The EE% of MPCs@Sungkai reached 98.38%, while MPCs@Immunos achieved 92%. In contrast, the LC% of MPCs@Sungkai was 1.95%, and MPCs@Immunos showed no detectable drug mass relative to the capsule weight. The high EE% values indicate that nearly all of the bioactive compounds were successfully incorporated into the MPCs, while the relatively low LC% reflects the larger contribution of the capsule matrix compared to the drug mass. These findings are consistent with previous studies using passive diffusion [19], which also reported high encapsulation but relatively low drug-to-carrier ratios. Overall, these results demonstrate that MPCs provide efficient entrapment of both natural extracts and protein-based drugs, ensuring structural stability and suitability for further controlled-release applications.

In silico studies of MPN

The ligands are quercetin, tannic acid, compounds from Sungkai leaf extract, and compounds from commercial Immunos extract. This process was carried out using Avogadro software, which will describe the molecular structure (if not already available), import from a database (in .mol or .sdf file format from ChemSpider or PubChem), and optimize the structure with the force field optimization feature so that the molecule is in a minimum energy geometry condition. After the structure is stable, polar hydrogen atoms are added, and the structure is saved in .pdb format, which will be used in the next stage. This step aims to ensure that the ligand structure used has chemically valid geometry and compatible with the docking process with the target protein. Meanwhile, the target protein structure, namely TLR4 (Toll Like Receptor 4) with PDB ID: 7AAH, was downloaded from the Protein Data Bank (PDB). The structure was selected based on its good resolution (≤2.5 Å), origin from humans (*Homo sapiens*), intact active site, and availability in .pdb format, allowing it to be used directly in the molecular docking process. The structure was processed using AutoDock Tools, where the author removed water molecules, added polar hydrogen atoms, and added Gasteiger charges. The next step was to determine the grid box, which is a 3D area on the receptor that serves to determine the space where the ligand molecule will attempt to interact. The determination of the grid box was focused on the active site of the receptor, so that the interactions observed were truly biologically relevant.

Molecular docking simulation

Molecular docking simulation was performed using PyRx software. Ligand structures such as quercetin, tannic acid, and compounds extracted from Sungkai leaves and commercial immunosorbents were imported into PyRx, along with the processed TLR4 receptor structure (PDB ID: 7AAH). Next, the interaction area (grid box) was determined. After docking was performed, PyRx displayed the binding affinity values of each compound to the receptor, sorted by binding strength. Visualization of molecular interactions can be observed in a 3D view.

Visualization and interpretation of molecular interactions

The results of the interaction between the ligand and the target protein were analyzed using Discovery Studio Visualizer and PyMOL software. In this stage, the author visualized the position of the active compound within the active site of the TLR4 protein, evaluated the types of interactions formed, such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions, each of which contributes to the strength and stability of the protein-ligand complex, and assessed whether the ligand occupied the optimal position in the active site of the receptor. This process is very important in understanding the relationship between molecular structure and function, as well as in estimating the pharmacological potential of the tested compounds. This visualization allows spatial observation of whether the ligand orientation is directed towards the correct active residue or not and helps assess the selectivity and strength of molecular bonds structurally.

Molecular docking and visualization of results

The final molecular docking results show the binding affinity values of each ligand, data on the types and number of interactions formed, and a display of the interaction structure in 2D and 3D (Figure 3).

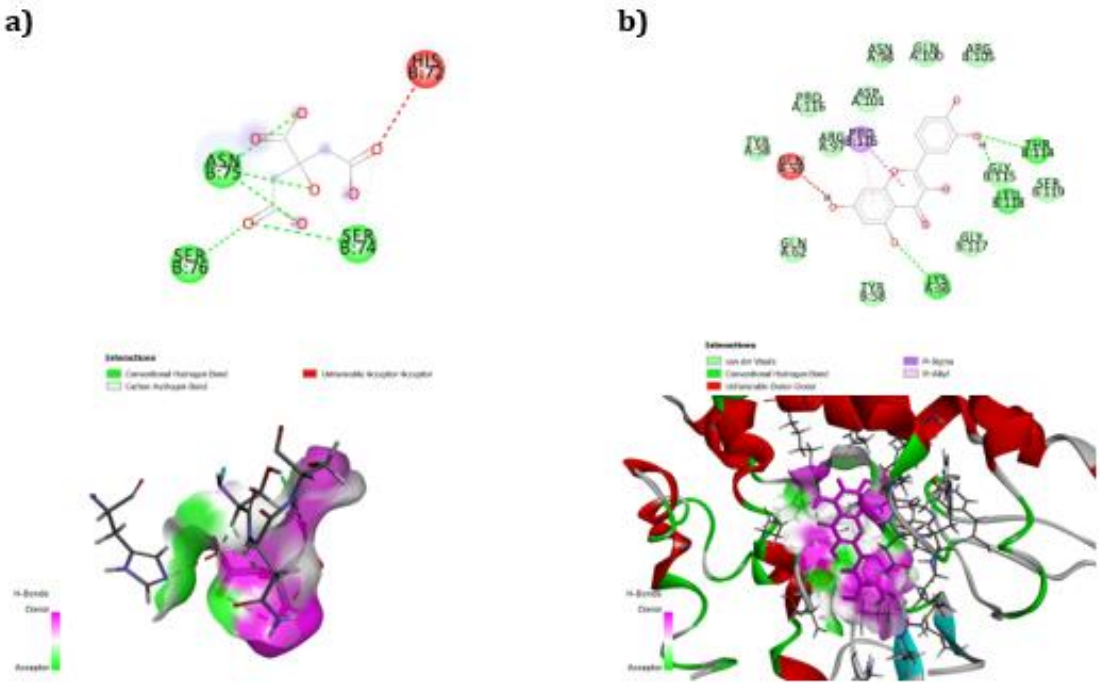


Figure 3. 2D and 3D visualization of a) Native-ligand and b) MPCs@Tert-butyl 2-hydroxy-3-[[1-[(2-methylpropan-2-yl)oxy]-3-propan-2-yloxy-2-(propan-2-yloxymethyl)propan-2-yl]amino]propane-1-sulfonate

In vitro study

The *in vitro* release profile of the encapsulated compounds was monitored using UV–Vis spectrophotometry at predetermined time intervals under simulated physiological (pH 7.4) and gastric (pH 1.2) conditions (Table 1). The release behavior exhibited a distinct pH-responsive pattern: a rapid and substantial release was observed in the acidic environment (pH 1.2), whereas a slower and more sustained release occurred at neutral pH (pH 7.4). This biphasic release characteristic indicates that the MPCs possess effective pH-sensitive properties, which are desirable for targeted drug delivery systems. The accelerated release in acidic conditions may be attributed to the protonation of phenolic groups and destabilization of MPCs bonds, leading to capsule disassembly and enhanced diffusion of the encapsulated bioactive molecules [14]. Conversely, the stability of the coordination network at near-physiological pH contributed to the controlled and prolonged release, preventing premature drug leakage in systemic circulation [7,11].

Such pH-responsive behavior is advantageous for oral drug delivery, as it facilitates efficient release in the stomach or targeted acidic microenvironments while maintaining stability in the bloodstream, thereby improving therapeutic efficacy and minimizing potential systemic toxicity [18].

Table 1. Percentage of bioactive compound release from MPCs under different pH conditions

Time (h)	Release of MPCs @extract	
	pH 1.2 (%)	pH 7.4 (%)
1	96.2	16.1
2	94.0	6.8
3	93.6	5.6

Antioxidant activity

The antioxidant activity of MPCs@Sungkai was assessed using the DPPH radical scavenging assay (Figure 4).

As expected, ascorbic acid, serving as the positive control, exhibited the highest activity at all tested concentrations, consistent with its well-established reducing capacity [24].

Free MPCs demonstrated moderate activity, attributable to the intrinsic antioxidant potential of the polyphenolic ligands (quercetin and tannic acid) incorporated during capsule assembly [25].

Notably, MPCs@Sungkai showed significantly higher radical scavenging activity than MPCs alone, indicating that the integration of *Peronema canescens* extract enhanced the antioxidant performance. This result suggests a synergistic interaction between the polyphenolic capsule matrix and bioactive compounds in Sungkai, reinforcing the potential of MPCs@Sungkai as a multifunctional drug delivery platform with added therapeutic benefits [23,24].

In vivo study

Histopathological examination is an essential approach in toxicological and pharmacological studies to evaluate tissue integrity, cellular morphology, and pathological alterations under microscopic observation. The liver, being the primary site of xenobiotic metabolism and detoxification, is highly sensitive to chemical and drug-induced injury, making it a reliable biomarker organ for assessing the safety profile of new therapeutic agents [26-28].

In this study, histopathological analysis revealed clear distinctions between the control and treatment groups. The normal control group exhibited hepatocytes with preserved cellular architecture, uniform size and shape, and normal sinusoidal spaces, consistent with healthy liver morphology (Figure 5). Conversely, the immunos control displayed signs of mild hepatic inflammation, including hepatocyte enlargement and cytoplasmic swelling, indicative of early hepatocellular stress responses [8]. Interestingly, the groups treated with MPCs, MPCs@immunos, and MPCs@sungkai demonstrated hepatocyte structures that closely resembled the normal control.

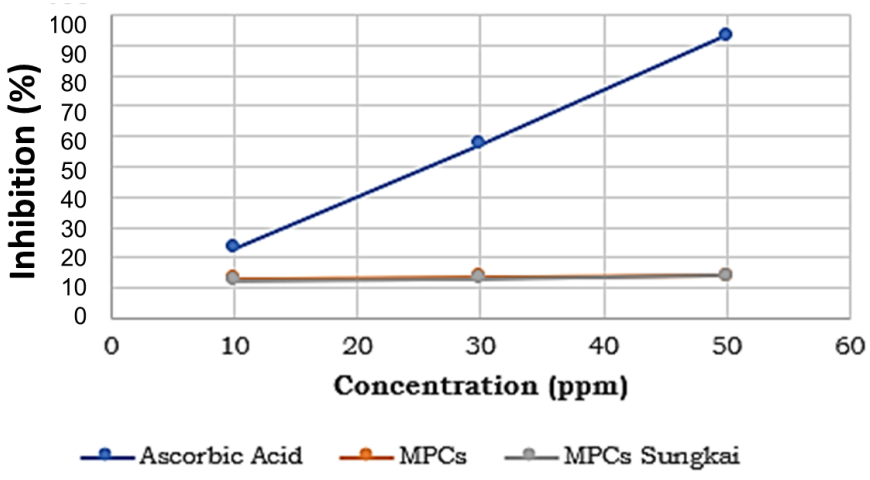


Figure 4. DPPH radical scavenging activity (%)

Hepatocytes appeared regular in size and organization, with no evident inflammatory infiltration or ballooning degeneration. These findings suggest that the tested formulations were non-toxic to hepatic tissue and may even exert protective effects against inflammation. The protective properties can be attributed to the phenolic compounds (quercetin and tannic acid) encapsulated within the MPCs, as these bioactive molecules are well-documented for their antioxidant and hepatoprotective activities [29]. Moreover, the synergistic role of Sungkai extract, which is reported to contain flavonoids and triterpenoids with anti-inflammatory activity, may further contribute to the observed hepatoprotective effect [30]. Overall, the histopathological evidence supports that MPCs, MPCs@immunos, and MPCs@sungkai are safe delivery systems with no hepatotoxicity under the tested conditions, while simultaneously offering potential anti-inflammatory and hepatoprotective benefits.

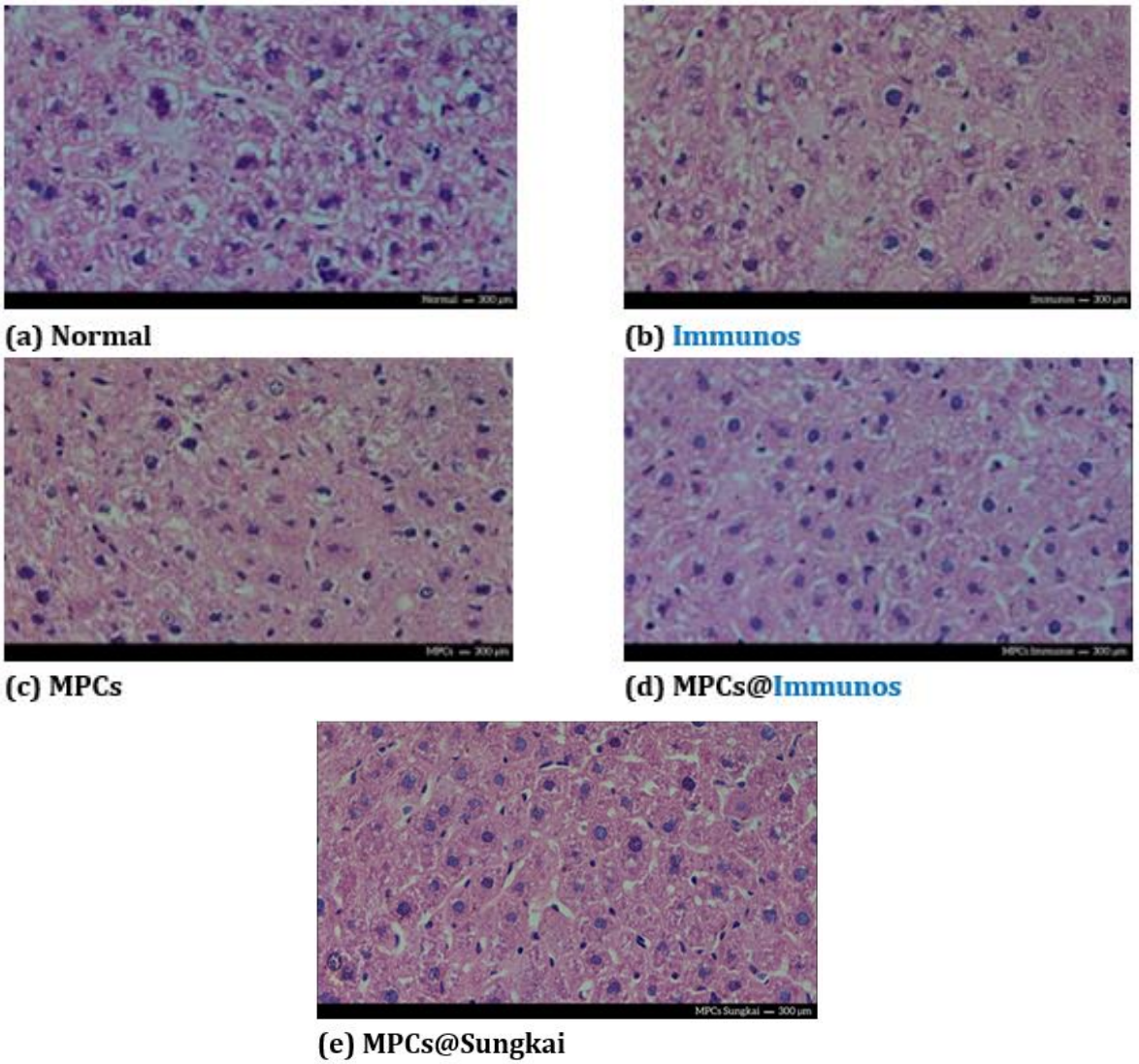


Figure 5. Histopathological results of mouse liver; (a) normal; (b) immunos; (c) MPCs; (d) MPCs@Immunos; (e) MPCs@Sungkai

Conclusion

This study reports, for the first time, the successful synthesis and comprehensive characterization of MPCs encapsulating bioactive compounds from *Peronema canescens* leaves. The resulting MPCs demonstrated favorable biocompatibility and multifunctional properties, including pronounced antioxidant, immunomodulatory, and hepatoprotective activities. These findings underscore the promise of MPCs as a safe, sustainable, and versatile platform for the delivery of natural bioactive compounds. Nevertheless, further investigations addressing pharmacokinetics, long-term toxicity, and formulation refinement are essential to advance this system toward clinical translation.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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ORCID

Regina Wan Azizah
https://orcid.org/0009-0006-7633-6573
Fashihah Maulida
https://orcid.org/0009-0000-0937-5317
Indra Lasmana Tarigan
https://orcid.org/0000-0002-7238-7780
Madyawati Latief
https://orcid.org/0000-0001-6023-4640

References

[1] Dong, P., Lv, H., Jia, W., Liu, J., Wang, S., Li, X., Hu, J., Zhao, L., Shi, Y. Polysaccharide dextran-based conjugate for selective co-delivery of two synergistic drugs docetaxel and docosahexaenoic acid to tumor cells. *Drug Delivery*, **2023**, 30(1), 40-50.

[2] Zheng, H., Zhang, Y., Liu, L., Wan, W., Guo, P., Nystrom, A.M., Zou, X. One-pot synthesis of metal–organic frameworks with encapsulated target molecules and their applications for controlled drug delivery. *Journal of the American Chemical Society*, **2016**, 138(3), 962-968.

[3] Lou, J., Duan, H., Qin, Q., Teng, Z., Gan, F., Zhou, X., Zhou, X. Advances in oral drug delivery systems: Challenges and opportunities. *Pharmaceutics*, **2023**, 15(2), 484.

[4] St Clair-Jones, A., Prignano, F., Goncalves, J., Paul, M., Sewerin, P. Understanding and minimising injection-site pain following subcutaneous administration of biologics: A narrative review. *Rheumatology and Therapy*, **2020**, 7(4), 741-757.

[5] Baryakova, T.H., Pogostin, B.H., Langer, R., McHugh, K.J. Overcoming barriers to patient adherence: The case for developing innovative drug delivery systems. *Nature Reviews Drug discovery*, **2023**, 22(5), 387-409.

[6] Bashiardes, S., Christodoulou, C. Orally administered drugs and their complicated relationship with our gastrointestinal tract. *Microorganisms*, **2024**, 12(2), 242.

[7] Xu, W., Pan, S., Noble, B.B., Lin, Z., Kaur Bhangu, S., Kim, C.J., Chen, J., Han, Y., Yarovsky, I., Caruso, F.

Engineering flexible metal-phenolic networks with guest responsiveness via intermolecular interactions. *Angewandte Chemie International Edition*, **2023**, 62(18), e202302448.
[8] Xu, K., Zhou, M., Li, M., Chen, W., Zhu, Y., Cai, K. Metal-phenolic networks as a promising platform for ph-controlled release of bioactive divalent metal ions. *Applied Surface Science*, **2020**, 511, 145569.
[9] Xie, W., Guo, Z., Zhao, L., Wei, Y. Metal-phenolic networks: Facile assembled complexes for cancer theranostics. *Theranostics*, **2021**, 11(13), 6407.
[10] Guo, Z., Xie, W., Lu, J., Guo, X., Xu, J., Xu, W., Chi, Y., Takuya, N., Wu, H., Zhao, L. Tannic acid-based metal phenolic networks for bio-applications: A review. *Journal of Materials Chemistry B*, **2021**, 9(20), 4098-4110.
[11] Imbia, A.S., Ounkaew, A., Mao, X., Zeng, H., Liu, Y., Narain, R. Tannic acid-based coatings containing zwitterionic copolymers for improved antifouling and antibacterial properties. *Langmuir*, **2024**, 40(7), 3549-3558.
[12] Guo, Z., Xiao, Y., Wu, W., Zhe, M., Yu, P., Shakya, S., Li, Z., Xing, F. Metal–organic framework-based smart stimuli-responsive drug delivery systems for cancer therapy: Advances, challenges, and future perspectives. *Journal of Nanobiotechnology*, **2025**, 23(1), 157.
[13] Li, L., Pan, J., Huang, M., Sun, J., Wang, C., Xu, H. Metal-phenolic networks: A promising frontier in cancer theranostics. *International Journal of Nanomedicine*, **2024**, 11379-11395.
[14] Mandsberg, N.K., Liao, W., Yamanouchi, Y.A., Boisen, A., Ejima, H. Encapsulation of chlamydomonas reinhardtii into a metal-phenolic network. *Algal Research*, **2022**, 61, 102569.
[15] Di Costanzo, A., Angelico, R. Formulation strategies for enhancing the bioavailability of silymarin: The state of the art. *Molecules*, **2019**, 24(11), 2155.
[16] Martanisa, M., Hastuti, B., Hadi, S. Silymarin encapsulation in alginate microspheres as a drug delivery matrix and its release kinetics. *Advanced Journal of Chemsitry, Section A*, **2026**, 9, 393–404.
[17] Hiremath, G., Sikkander, A.R.M., Upadhyay, R., Acharya, D., Singh, K.P., Wahi, N. Safety and efficacy of drug-eluting stents improved dramatically with application of nanotechnology. *Advanced Journal of Chemistry, Section A*, **2025**, 8, 378-391.
[18] Guo, J., Ping, Y., Ejima, H., Alt, K., Meissner, M., Richardson, J.J., Yan, Y., Peter, K., Von Elverfeldt, D., Hagemeyer, C.E. Engineering multifunctional capsules through the assembly of metal–phenolic networks. *Angewandte Chemie International Edition*, **2014**, 53(22), 5546-5551.
[19] Ju, Y., Cui, J., Sun, H., Mullner, M., Dai, Y., Guo, J., Bertleff-Zieschang, N., Suma, T., Richardson, J.J., Caruso, F. Engineered metal-phenolic capsules show tunable targeted delivery to cancer cells. *Biomacromolecules*, **2016**, 17(6), 2268-2276.
[20] Escobar-Avello, D., Avendaño-Godoy, J., Santos, J., Lozano-Castellón, J., Mardones, C., von Baer, D., Luengo, J., Lamuela-Raventós, R.M., Vallverdú-Queralt, A., Gómez-Gaete, C. Encapsulation of phenolic compounds from a grape cane pilot-plant extract in hydroxypropyl beta-cyclodextrin and maltodextrin by spray drying. *Antioxidants*, **2021**, 10(7), 1130.
[21] Sidoryk, K., Jaromin, A., Filipczak, N., Cmoch, P., Cybulski, M. Synthesis and antioxidant activity of caffeic acid derivatives. *Molecules*, **2018**, 23(9), 2199.
[22] Kolonas, A., Vareltzis, P., Kiroglou, S., Goutzourelas, N., Stagos, D., Trachana, V., Tsadila, C., Mossialos, D., Mourtakos, S., Gortzi, O. Antioxidant and antibacterial properties of a functional sports beverage formulation. *International Journal of Molecular Sciences*, **2023**, 24(4), 3558.
[23] Saputra, M.F.N., Nabila, A., Maulida, F., Ramadhani, S., Syafiq, M.H., Tarigan, I.L. Synthesis and characterization of insulin-mof-5 loaded into cellulose nanocrystalline-based dissolving microneedle as anti-diabetic delivery system. *Journal of Medicinal and Chemical Sciences*, **2025**, 8(2), 177-189.
[24] Shahidi, F., Ambigaipalan, P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects–a review. *Journal of Functional Foods*, **2015**, 18, 820-897.
[25] Cory, H., Passarelli, S., Szeto, J., Tamez, M., Mattei, J. The role of polyphenols in human health and food systems: A mini-review. *Frontiers in Nutrition*, **2018**, 5, 370438.
[26] Dai, J., Mumper, R.J. Plant phenolics: Extraction, analysis and their antioxidant and anticancer properties. *Molecules*, **2010**, 15(10), 7313-7352.

[27] Ejima, H., Richardson, J.J., Caruso, F. Metal-phenolic networks as a versatile platform to engineer nanomaterials and biointerfaces. *Nano Today*, **2017**, 12, 136-148.
[28] Thakur, S., Kumar, V., Das, R., Sharma, V., Mehta, D.K. Biomarkers of hepatic toxicity: An overview. *Current Therapeutic Research*, **2024**, 100, 100737.
[29] Huang, Z.Q., Chen, P., Su, W.-W., Wang, Y.G., Wu, H., Peng, W., Li, P.B. Antioxidant activity and hepatoprotective potential of quercetin 7-rhamnoside in vitro and in vivo. *Molecules*, **2018**, 23(5), 1188.
[30] Wrońska, N., Szlaur, M., Zawadzka, K., Lisowska, K. The synergistic effect of triterpenoids and flavonoids—new approaches for treating bacterial infections? *Molecules*, **2022**, 27(3), 847.

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