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***Musa Paradisiaca* var. *sapientum* STEM SAP PHYTOCHEMICALS AS CANDIDATE
 COX-2 INHIBITORS: AN IN SILICO STUDY FOR RECURRENT APHTHOUS
 STOMATITIS TREATMENT**

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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is a common ulcerative disorder of the oral mucosa in which cyclooxygenase-2 (COX-2)-derived prostaglandin E2 contributes to pain and inflammation. Stem sap of *Musa paradisiaca* var. *Sapientum* (Ambonese banana) is used ethnomedicinally for oral ulcers, but the constituents responsible for its anti-inflammatory effect are unidentified. **Objective:** To screen phytochemicals previously reported from *M. paradisiaca* stem sap for predicted binding to human COX-2 and to characterise their predicted pharmacokinetic (ADMET) profiles, in order to prioritise candidates for experimental testing. **Methods:** Nine phytochemicals compiled from published phytochemical reports, together with celecoxib and the co-crystallised ligand rofecoxib, were docked into human COX-2 (PDB ID 5KIR). The protocol was validated by redocking rofecoxib. ADME-T descriptors were predicted with SwissADME and ADMETlab 3.0. **Result:** The docking protocol was successfully validated (RMSD = 0.992 Å). The five best-scoring compounds were catechin (docking score = -8.76 kcal/mol; predicted K_i = 376.01 nM), gallicocatechin (-8.59; 504.97 nM), quercetin-3-O-glucoside (-8.43; 658.19 nM), quercetin (-8.38; 721.52 nM) and leucocyanidin (-8.37; 734.98 nM). Each formed hydrogen bonds with Tyr385, Ser530 or Gln192 and hydrophobic contacts with Leu352 and Val523. All five were predicted to have low Caco-2 permeability and low human intestinal absorption, and four carried a high predicted skin-sensitisation probability. **Conclusion:** Catechin and gallicocatechin were the best-scoring candidate COX-2 inhibitors. Their binding affinity and favorable topical pharmacokinetics support their potential as non-steroidal anti-inflammatory agents for RAS. Further evaluation of COX-1/COX-2 selectivity, in vitro, and in vivo experimental validation are required to confirm these findings.

Keywords: ADME-; Cyclooxygenase-2; Molecular docking; *Musa paradisiaca*; Recurrent aphthous stomatitis

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INTRODUCTION

Recurrent Aphthous Stomatitis (RAS), commonly known as canker sores, is a chronic inflammatory disorder of the oral mucosa characterized by the appearance of painful and recurrent ulcerative lesions on the non-keratinized mucosa.^{1,2} The typical lesion of RAS presents as a shallow, round or oval ulcer, defined by an erythematous halo and covered by a yellowish-grey pseudomembrane.³ The global prevalence of RAS is high, affecting up to 25% of the general population, with Indonesian prevalence estimates of approximately 12%.⁴ RAS can interfere with daily activities and reduce the quality of life of patients due to pain and discomfort during ulcerative episodes.⁵

While the exact etiology is multifactorial^{6,7}, a hallmark of RAS pathology is localized inflammation and elevated levels of inflammatory mediators in the ulcer tissue.⁷⁻⁹ Prostaglandin E2 (PGE₂) is found to be increased in oral ulcer models, suggesting an active arachidonic acid–COX pathway in these lesions.^{10,11} Cyclooxygenase-2 (COX-2) is an inducible enzyme that plays a key role in inflammation by converting arachidonic acid to pro-inflammatory prostaglandins.¹² COX-2 inhibition is a validated mechanism for pain relief and anti-inflammatory effects, supported by the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs).¹³ A study using Yangyin Shengji powder showed that COX-2 downregulation reduced ulcer size and inflammation through the COX-2/PGE₂ pathway in a chemotherapy-induced oral ulcer model.¹⁴ Topical *Kaempferia galanga* L. extract suppressed COX-2 expression and accelerated oral ulcer healing in rats, supporting COX-2 as a potential target for plant-derived RAS therapies.¹⁵

Current management of RAS is primarily symptomatic and aimed at reducing pain and inflammation to promote healing.^{3,16,17} Topical corticosteroids (e.g., triamcinolone acetonide paste) are the first-line treatment and can shorten ulcer duration by suppressing local inflammation.^{7,18} However, corticosteroids may cause side effects or are not suitable for long-term prophylaxis,¹⁹ which has prompted interest in natural-product alternatives with a more favourable safety profile.

In Indonesia, bananas (*Musa spp.*) have long been used in traditional medicine. The stem sap of *Musa paradisiaca* var. *sapientum* (Ambonese banana) is applied ethnomedicinally to stop bleeding, reduce oral pain, and accelerate mucosal healing.²⁰⁻²² Recent studies reporting that *M. paradisiaca* stem sap gel enhances oral wound repair by stimulating fibroblast proliferation, collagen deposition, and re-epithelialization while being safe for oral cells at therapeutic concentrations.²⁰ Published phytochemical characterisation of the sap and of related *M. paradisiaca* tissues has reported flavan-3-ols (catechin, epicatechin and gallocatechin), quercetin and its 3-O-glycosides, leucocyanidin and palmitic acid, tannins, saponins and terpenoids.^{20,22-27}

The molecular basis of the anti-inflammatory effects of *M. paradisiaca* var. *sapientum* stem sap remains undefined. It remains unclear which compounds interact with COX-2 and have suitable pharmacokinetic and toxicity profiles for oral mucosal use. In silico screening offers a faster and cost-effective approach to prioritize compounds for further in vitro and in vivo studies.²⁸ This study aimed to explore the potential of phytochemicals from *M. paradisiaca* var. *sapientum* stem sap as candidate COX-2 inhibitors for topical management of RAS through an in silico approach. The objectives were to evaluate their predicted binding affinity and molecular interactions with COX-2 using molecular docking and to assess their predicted pharmacokinetic and toxicity profiles, thereby identifying promising compounds for further experimental investigation.

MATERIALS AND METHODS

Research Design

This was a computational (in silico) study. Only publicly available structural and bioinformatic data were analysed, with no human participants, animals, or clinical specimens involved. Ethical approval was therefore not required.

Research Materials and Tools

Docking was performed on a workstation Intel® Core™ i7-1165G7, 16 GB RAM, 512 GB solid-state drive, Windows 10, 64-bit) using AutoGrid4 and AutoDock4 (The Scripps Research Institute) with AutoDockTools 1.5.7 (MGLTools).²⁹ BIOVIA Discovery Studio Visualizer v21.1 was used for receptor preparation and interaction analysis, Avogadro v1.2.0 for ligand geometry optimisation, Swiss-PdbViewer v4.1.0 for receptor minimisation and PyMOL v2.5 for pose superposition. SwissADME³⁰ and ADMETlab 3.0³¹ were used for pharmacokinetic, drug-likeness and toxicity prediction.

Step of Procedure

Protein Retrieval and Preparation

The crystal structure of human cyclooxygenase-2 (COX-2) (PDB ID: 5KIR) was retrieved from the RCSB Protein Data Bank (PDB).³² This structure was selected because it is the human COX-2 enzyme, is co-crystallised with a selective diaryl heterocyclic inhibitor occupying the cyclooxygenase channel and Val523-gated side pocket, has a 2.70 Å resolution that provides sufficient structural detail for docking compared with structures at ≥4.0 Å,³³ and retains the haem cofactor and catalytic residues Tyr385 and Ser530 required to reproduce canonical inhibitor interactions.³⁴ Preparation was carried out in Discovery Studio Visualizer. Chain B, all crystallographic water

molecules, the co-crystallised rofecoxib, the cobalt protoporphyrin IX prosthetic group, the N-acetylglucosamine glycans and the phosphate, glycerol and ammonium ions were removed, leaving chain A. The protoporphyrin occupies the peroxidase site, which is remote from the cyclooxygenase channel targeted here, so its removal does not alter the docking region. Polar hydrogens were added and Gasteiger partial charges assigned for a pH of 7.4, with aspartate and glutamate deprotonated, lysine and arginine protonated and histidine treated as neutral, as assigned by default in AutoDockTools.³⁵ The structure was then energy-minimised in Swiss-PdbViewer v4.1.0 with the GROMOS96 force field and saved in PDBQT format.^{32,35} The specific structures selected are in Table 1 and Figure 1.

Table 1. Protein Target Data ³⁶	
PDB ID	COX-2 (PDB ID: 5KIR)
Title	The Structure of Vioxx Bound to Human COX-2
DOI	https://doi.org/10.2210/pdb5KIR/pdb
Author(s)	Orlando, B.J., Malkowski, M.G.
Resolution	2.70 Å
Classification	Oxidoreductase
Organism	Homo sapiens
Method	X-Ray diffraction
Molecule	Prostaglandin G/H synthase 2
Chains	A, B
Total structure weight	131 kDa

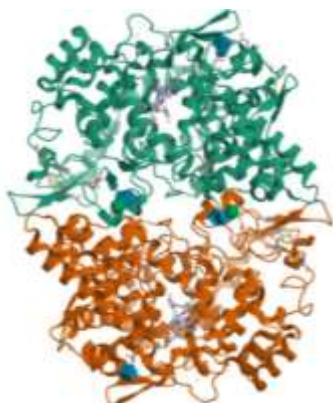


Figure 1. Three-dimensional crystal structure of the molecular target (COX-2) (PDB ID: 5KIR).³⁶

Ligand Retrieval and Optimization

The phytochemicals examined were not isolated or identified experimentally in the present study but were compiled from previously published literature about phytochemical analyses of *M. Paradisiaca*.^{20,22–27} Three-dimensional structures were downloaded from PubChem in SDF format. Phytochemicals of *Musa paradisiaca* var. *sapientum* stem sap analyzed in this study included palmitic acid (CID: 985), leucocyanidin (CID: 71629), quercetin (CID: 5280343) and its glycosides [quercetin-3-O-glucoside (CID: 5280804), quercetin-3-O-galactoside (CID: 5281643), rutin (CID: 5280805)], as well as flavan-3-ols [galocatechin (CID: 65084), catechin (CID: 9064), epicatechin (CID: 72276)].^{20,22–27} The stereochemical configuration annotated in each PubChem record was retained without modification: catechin as (2R,3S), epicatechin as (2R,3R) and galocatechin as (2R,3S); the quercetin glycosides retained their β -D-glucopyranosyl, β -D-galactopyranosyl and rutinosyl linkages as deposited; and leucocyanidin was used as the three-dimensional conformer deposited under CID 71629. No stereocentre was inverted and no alternative diastereomer was generated. Reference ligands celecoxib (CID: 2662) were also retrieved.

All ligands were prepared in their neutral forms. At pH 7.4 this corresponds to the predominant species for the eight polyphenolic compounds, whose phenolic hydroxyl groups have pKa values above 8. Palmitic acid is predominantly ionised at this pH, and its treatment as the neutral acid is a recognised simplification of the AutoDock 4 workflow; its low rank in this screen should be read with that in mind. Geometry was optimised in Avogadro v1.2.0 with the MMFF94 force field.³⁵ Gasteiger charges were assigned and rotatable bonds detected

automatically in AutoDockTools, with all acyclic single bonds free to rotate and ring systems held rigid, and the ligands saved in PDBQT format.

Docking Grid Preparation

A grid box was generated around the active site of COX-2 using coordinates based on the binding site of the native inhibitor. The grid box dimensions were adjusted to cover the catalytic residues and surrounding hydrophobic pocket, ensuring that potential ligand binding conformations could be fully explored. Docking validation steps start from setting grid box active site of protein, grid box dimension size was $40 \times 40 \times 40$ and coordinate's ($X = 23.206$, $Y = 1.318$, $Z = 34.258$) with a space of $0.5 \text{ \AA}$.

Molecular Docking Simulation

Molecular docking was performed using Autodock Tools (Autodock4 & Autogrid4) with the Lamarckian Genetic Algorithm (LGA). The protein and ligand were automatically parameterized with Kollman and Gasteiger charges once ligand torsions had been defined. Docking validation was initiated by setting the protein active site grid box at coordinates ($X = 23.206$, $Y = 1.318$, $Z = 34.258$) with dimensions of $40 \times 40 \times 40$ and a grid spacing of $0.5 \text{ \AA}$. For each ligand, 100 docking runs were conducted, with a maximum number of energy evaluations set at 2.5 million, to obtain reliable conformations. The most favorable conformation from the re-docking procedure was used for validation. Docking validation was considered successful when the Root Mean Square Deviation (RMSD) between the re-docked pose and the co-crystallized ligand was less than $2 \text{ \AA}$.³⁵ The resulting docking poses were ranked according to docking score.

Interaction Analysis and Visualization

The top-ranked poses of each ligand were analyzed to identify key interactions with amino acid residues in the COX-2 active site. Hydrogen bonding, hydrophobic interactions, and electrostatic contacts were examined. Two-dimensional binding orientations and interaction networks were visualized using BIOVIA Discovery Studio Visualizer (v21.1) and the three-dimensional representation was generated using PyMOL.

Pharmacokinetic and Toxicity Prediction

Canonical SMILES strings retrieved from PubChem were submitted to SwissADME (<http://www.swissadme.ch>) for physicochemical descriptors and for the Lipinski, Ghose, Muegge, Veber and Egan drug-likeness filters,^{30,37} 2 and to ADMETlab 3.0 (<https://admetlab3.scbdd.com>) for absorption, distribution, metabolism, excretion and toxicity endpoints.³¹

RESULTS

In silico molecular docking is a computational strategy used to estimate how small compounds interact with protein targets at specific binding sites. The magnitude of this interaction, indicating binding affinity, is measured through binding energy values. The reliability of the docking outcomes was assessed through RMSD validation, docking score, and the inhibition constant (K_i).

Validation of the Docking Protocol for Human COX-2 (5KIR)

Docking validation was performed to assess the reliability of the workflow by comparing the co-crystal pose of the native inhibitor with its redocked pose. Protein and ligand preparation were carried out in BIOVIA Discovery Studio Visualizer v21.1 and AutoDockTools 1.5.7, and docking was executed with AutoDock 4.2.6 from the command prompt using the same grid and search parameters subsequently applied to the test compounds. Redocking of rofecoxib (RCX601) into COX-2 (PDB ID: 5KIR) reproduced the crystallographic pose with a heavy-atom RMSD of $0.992 \text{ \AA}$, as reported in the reference RMSD column of the docking log file and confirmed by superposition in PyMOL v2.5. This is within the widely accepted success criterion of $\leq 2.0 \text{ \AA}$, indicating that the grid definition and scoring settings used here can faithfully reproduce the native binding orientation and are suitable for subsequent docking of *Musa paradisiaca* phytochemicals.³⁵

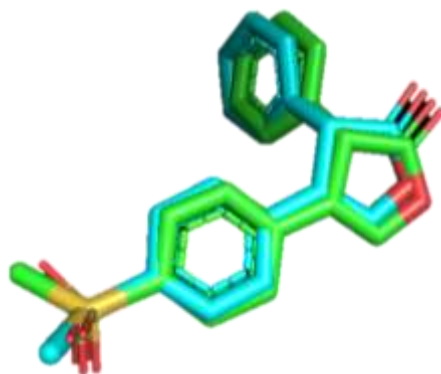


Figure 2. Docking Protocol Validation for COX-2 (PDB ID: 5KIR). Overlapping visualization of the native co-crystal ligand RCX601 (green) and the re-docked ligand pose (cyan) within the active site of human COX-2.

Predicted Binding Affinities and Predicted Inhibition Constants

Predicted binding affinities and the corresponding predicted K_i values are given in Table 2. The five highest-ranked phytochemicals were catechin (-8.76 kcal/mol), gallocatechin (-8.59), quercetin-3-O-glucoside (-8.43), quercetin (-8.38) and leucocyanidin (-8.37), a range of 0.39 kcal/mol; epicatechin followed closely at -8.20 . All were weaker than celecoxib (-10.77) and rofecoxib (-10.34) under the same protocol, by 1.58 – 2.40 kcal/mol. Quercetin-3-O-galactoside (-6.94) and palmitic acid (-6.09) ranked substantially lower. Rutin returned a positive score ($+1.18$), indicating that no favourable pose was found within the grid box; a predicted K_i was therefore not derived for it.

Table 2. Predicted binding affinities and derived predicted inhibition constants of *M. paradisiaca* var. *sapientum* phytochemicals and reference inhibitors against COX-2 (PDB ID: 5KIR), obtained with AutoDock4.

Category	Compound Name	Predicted Binding Affinity (Docking Score)	Predicted inhibition constant (K_i)
Native Ligand	Celecoxib	-10.77	12.81 nM
Reference Ligand	Rofecoxib	-10.34	26.24 nM
<i>Musa paradisiaca</i> var. <i>sapientum</i> phytochemicals	Catechin	-8.76	376.01 nM
	Gallocatechin	-8.59	504.97 nM
	Quercetin-3-O-Glucoside	-8.43	658.19 nM
	Quercetin	-8.38	721.52 nM
	Leucocyanidin	-8.37	734.98 nM
	Epicatechin	-8.20	978.49 nM
	Quercetin-3-O-Galactoside	-6.94	8.18 μ M
	Palmitic Acid	-6.09	34.34 μ M
	Rutin	+1.18	N/A
(Positive docking score)			

Molecular Interaction Analysis at the COX-2 Active Site

All five leading compounds occupied the cyclooxygenase channel and formed hydrogen bonds with at least one of Tyr385, Ser530 and Gln192, residues also engaged by celecoxib and rofecoxib in the same simulations (Table 3, Figure 3-5). Catechin formed hydrogen bonds with Phe518, Ser530, Gln192, Val349, Met522 and His90, together with π -sigma, π -sulfur, π - π T-shaped and π -alkyl contacts involving Val523, Met522, Trp387 and Leu352. Gallocatechin formed hydrogen bonds with Phe518, Tyr385, Ser353 and Gln192. Quercetin-3-O-glucoside formed hydrogen bonds with Tyr385, Met522 and Gln192 and a π -cation contact with Arg120 at the mouth of the channel, its glycosyl group projecting towards the membrane-binding lobby rather than into the channel. Quercetin formed hydrogen bonds with Phe518, Ser530, Gln192, Val349 and Met522, and leucocyanidin formed five, with His90, Tyr385, Tyr355, Gln192 and Ser530. Hydrophobic contacts with Leu352 and Val523 were common to all five. Among the lower-ranked compounds (Supplementary Figure 6), palmitic

acid bound in an extended conformation along the hydrophobic channel with hydrogen bonds only to Arg120 and Tyr355, and rutin formed an unfavourable steric contact at Ser530.

Table 3. Interactions of the reference inhibitors and the *M. paradisiaca* var. *sapientum* phytochemicals with amino acid residues of the COX-2 active site

Ligand	Hydrogen-bond residues	Hydrophobic and other contacts
Rofecoxib (native)	Ile517, Phe518, Arg513	Val523 (π -sigma), Phe518 (π - π stacked), Leu352 (amide- π stacked; π -alkyl), Val523 (π -alkyl)
Celecoxib (reference)	Phe518, Leu352, Gln192, His90, Ser353, Arg513	Ser353, Val523 (π -sigma); Leu352 (amide- π stacked); Leu384, Val349, Leu359 (alkyl); Tyr355, Trp387, Val349, Ala527, Leu352, Val523 (π -alkyl)
Catechin	Phe518, Ser530, Gln192, Val349, Met522, His90	Val523 (π -sigma); Met522 (π -sulfur); Trp387 (π - π T-shaped); Leu352, Val523 (alkyl); Phe518, Leu352 (π -alkyl)
Gallocatechin	Phe518, Tyr385, Ser353, Gln192	Leu352, Val523 (π -sigma); Trp387 (π - π T-shaped); Leu352, Val523 (alkyl); Ala516 (π -alkyl)
Quercetin-3-O-glucoside	Tyr385, Met522, Gln192, Unl1	Arg120 (π -cation); Val523 (π -sigma); Val349, Val523, Ala527, Leu531 (π -alkyl)
Quercetin	Phe518, Ser530, Gln192, Val349, Unl1, Met522	Leu352, Val523 (π -sigma); Met522 (π -sulfur); Trp387 (π - π T-shaped); Val523, Leu352, Ala516 (π -alkyl)
Leucocyanidin	His90, Tyr385, Tyr355, Gln192, Ser530	Leu352, Val523 (π -sigma); Val349 (π -alkyl)
Epicatechin	Phe518, Ser353, Gln192	Leu352, Val523 (π -sigma); Leu352, Val523 (alkyl); Val349 (π -alkyl)
Quercetin-3-O-galactoside	Ser530, Met522, Leu352, Unl1, Arg513	Val523, Ala527 (π -sigma); His90 (π -lone pair); Tyr355 (π - π T-shaped); Leu352 (amide- π stacked; π -alkyl); Ala516 (π -alkyl)
Palmitic acid	Arg120, Tyr355	Val344, Val349, Val523, Leu352, Leu534 (alkyl); Phe205, Phe209, Tyr348 (π -alkyl)
Rutin	Unl1, Leu384, Met522, Leu352, Ser353, Val523	Val349, Trp387 (π -sigma); Met522 (π -sulfur); Phe518 (π - π stacked); Tyr385 (π - π T-shaped); Gly526 (amide- π stacked); Val116, Arg120 (alkyl); Ala527, Leu384 (π -alkyl); Ser530 (unfavourable bump)

Physicochemical properties and drug-likeness

Catechin and quercetin satisfied all five drug-likeness filters with no violations (Table 4). Gallocatechin and leucocyanidin each violated the Muegge filter on hydrogen-bond donors and the Lipinski rule on the same descriptor. Quercetin-3-O-glucoside violated all five filters, chiefly on topological polar surface area (210.51 Å²) and hydrogen-bond count, and returned the lowest bioavailability score of the set (0.17).

Table 4. Physicochemical properties and drug-likeness filters for the five highest-ranked phytochemicals (SwissADME)

Compound	MW (g/mol)	HB A	HB D	TPSA (Å ²)	Lipinski	Filters failed	Bioavailability score
Catechin	290.27	6	5	110.38	0 violations	None	0.55
Gallocatechin	306.27	7	6	130.61	1 violation (NH/OH > 5)	Muegge (HBD > 5)	0.55
Quercetin-3-O-glucoside	464.38	12	8	210.51	2 violations (N/O > 10; NH/OH > 5)	Ghose, Muegge, Veber, Egan (TPSA; HBA/HBD)	0.17
Quercetin	302.24	7	5	131.36	0 violations	None	0.55
Leucocyanidin	306.27	7	6	130.61	1 violation (NH/OH > 5)	Muegge (HBD > 5)	0.55

MW, molecular weight; HBA, hydrogen-bond acceptors; HBD, hydrogen-bond donors; TPSA, topological polar surface area.

Predicted ADME and toxicity profiles

All five compounds were predicted to have low Caco-2 permeability ($\log P_{app}$ -6.03 to -6.44) and low human intestinal absorption (probability 0.016 – 0.194), with negligible predicted blood–brain barrier penetration (Table 5). Plasma protein binding ranged from 84.4% to 98.7% and was highest for quercetin, whose predicted unbound fraction was correspondingly lowest (1.13%). Quercetin was the only compound predicted to inhibit CYP1A2 (0.998) and CYP3A4 (0.937). Predicted plasma clearance ranged from 3.53 to $16.46 \text{ mL min}^{-1} \text{ kg}^{-1}$ and predicted half-life from 1.59 to 3.63 h .

Predicted carcinogenicity was low for all five compounds (0.216 – 0.600) and Ames mutagenicity was intermediate (0.459 – 0.856 , highest for quercetin-3-O-glucoside). Skin-sensitisation probability was high for quercetin-3-O-glucoside (0.999), gallocatechin (0.998), catechin (0.969) and quercetin (0.897), and moderate for leucocyanidin (0.521). Eye-irritation probability exceeded 0.88 for all five. Predicted drug-induced liver injury was highest for quercetin-3-O-glucoside (0.913) and quercetin (0.783).

Table 5. Predicted ADME and toxicity parameters for the five highest-ranked phytochemicals (ADMETlab 3.0)

Parameter	Catechin	Gallocatechin	Quercetin-3-O-glucoside	Quercetin	Leucocyanidin
Absorption					
Caco-2 permeability ($\log P_{app}$)	-6.169	-6.436	-6.255	-6.177	-6.029
Human intestinal absorption	0.016	0.086	0.194	0.134	0.034
Distribution					
Plasma protein binding (%)	89.28	84.87	84.36	98.66	89.77
Unbound fraction (%)	17.11	21.21	13.67	1.13	16.96
Blood–brain barrier ($\log BB$)	0.135	0.025	0.000	0.000	0.065
Metabolism					
CYP1A2 inhibitor	0.000	0.000	0.002	0.998	0.000
CYP3A4 inhibitor	0.000	0.000	0.723	0.937	0.104
Excretion					
Plasma clearance ($\text{mL min}^{-1} \text{ kg}^{-1}$)	16.455	12.148	3.528	8.289	13.051
Half-life (h)	2.443	2.349	3.634	1.586	1.975
Toxicity					
Drug-induced liver injury	0.223	0.424	0.913	0.783	0.163
Ames mutagenicity	0.459	0.538	0.856	0.586	0.527
Skin sensitisation	0.969	0.998	0.999	0.897	0.521
Carcinogenicity	0.226	0.216	0.239	0.600	0.286
Eye irritation	0.991	0.992	0.880	0.998	0.963

Classification endpoints are reported as probabilities between 0 and 1 ; Caco-2 permeability, plasma protein binding, unbound fraction, volume of distribution, blood–brain barrier penetration, clearance and half-life are regression outputs. All values are model predictions.

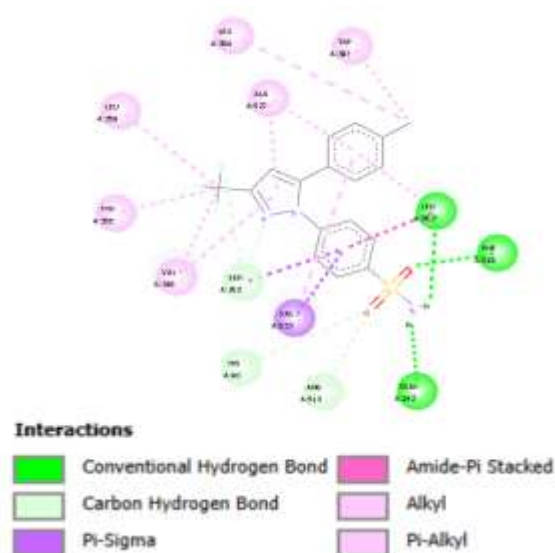


Figure 3. Molecular docking visualization of reference ligand (Celecoxib)

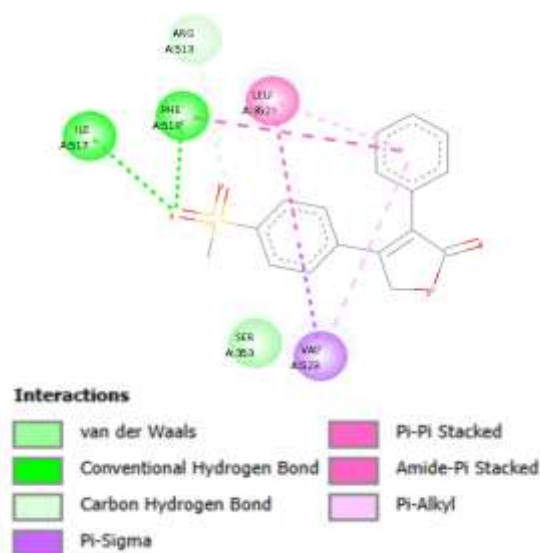
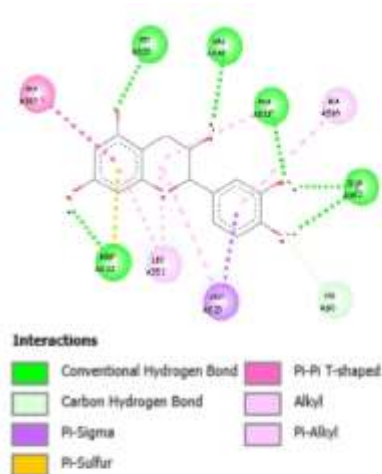
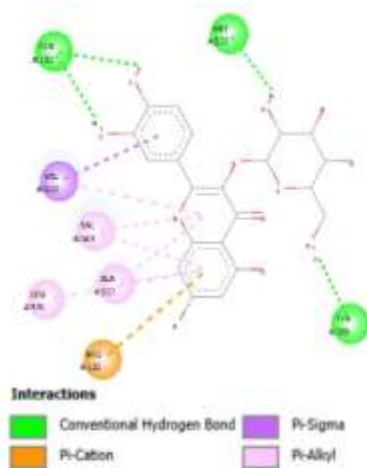


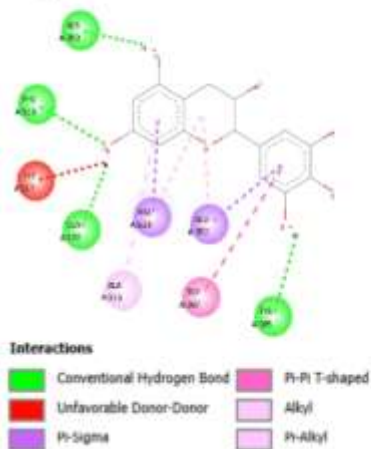
Figure 4. Molecular docking visualization of ligand native Rofecoxib (RCX601)



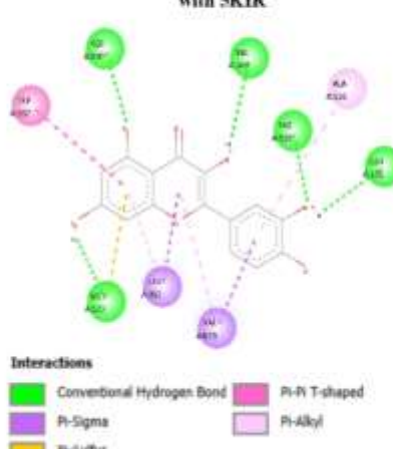
(a) Catechin interactions with SKIR



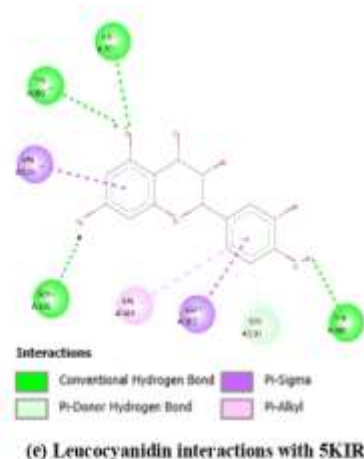
(b) Quercetin-3-O-Glucoside interactions with SKIR



(b) Gallocatechin interactions with SKIR



(d) Quercetin interactions with SKIR



(e) Leucocyanidin interactions with SKIR

Figure 5. Molecular docking visualization of top five *Musa paradisiaca* var. *sapientum* phytochemicals

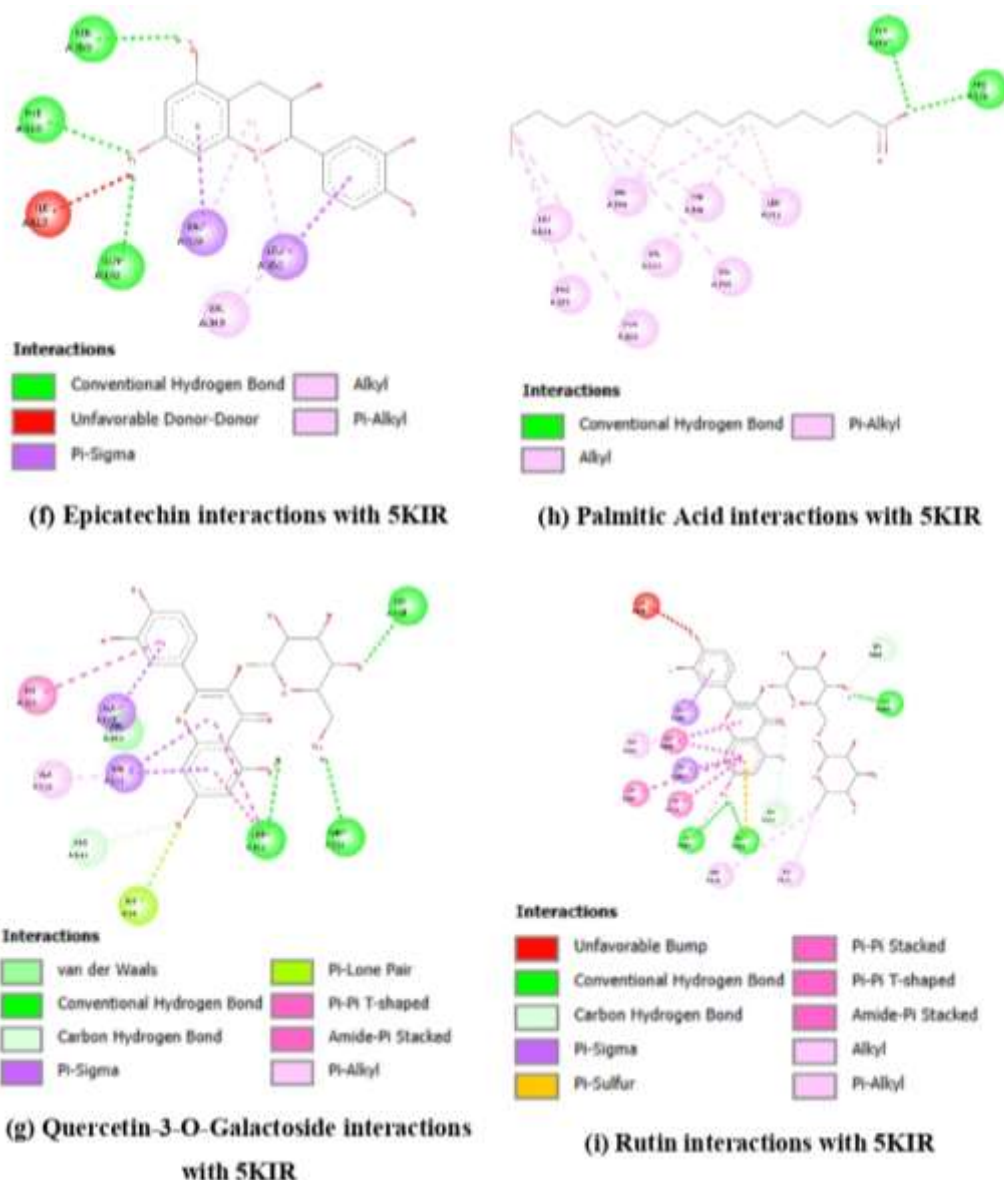


Figure 6. Molecular docking visualization of *Musa paradisiaca* var. *sapientum* phytochemicals

DISCUSSION

RAS ulceration is sustained by a local inflammatory infiltrate that induces COX-2 and converts arachidonic acid into PGE₂. PGE₂ sensitizes peripheral nociceptors, making the ulcer disproportionately painful relative to its size, and drives the vasodilatation and edema clinically observed as an erythematous halo. Suppressing COX-2-derived PGE₂ within the lesion directly targets the mechanism generating the symptoms, rather than merely protecting the ulcer surface. This effect is evident when COX-2 expression is down-regulated in experimental oral ulcers, resulting in reduced ulcer size and inflammation, as well as accelerated healing.^{10,15} Molecular docking identified five compounds, namely catechin, gallic acid, quercetin-3-O-glucoside, quercetin, and leucocyanidin, that occupied the COX-2 cyclooxygenase channel and showed predicted binding affinities ranging from -8.37 to -8.76 kcal/mol. Although these values were weaker than those of celecoxib and rofecoxib under the same docking protocol, the five phytochemicals showed comparable docking scores within a narrow range of 0.39 kcal/mol. This suggests that these compounds may have a similar capacity to interact with the COX-2 binding channel, although the docking results alone cannot establish their inhibitory activity.

The relevance of these interactions to COX-2 inhibition is supported by the involvement of residues associated with the catalytic function of the enzyme. COX-2 catalyses the conversion of arachidonic acid into

prostaglandin intermediates, which subsequently contribute to prostanoid production. Tyr385 has an essential role in the cyclooxygenase reaction, while Ser530 is located within the active-site region involved in interactions with substrates and inhibitors.³⁸ Ligand interactions with these residues may interfere with substrate positioning or access within the cyclooxygenase channel and provide a structural basis for the predicted inhibitory potential.

Catechin showed the most favourable predicted binding affinity (−8.76 kcal/mol) and formed hydrogen bonds with Ser530 and Gln192, together with interactions involving Phe518, Val349, Met522, His90, Val523, Trp387, and Leu352. The interaction with Ser530 is particularly relevant because this residue participates in the binding of several COX inhibitors.³⁸ The combination of hydrogen bonding and hydrophobic interactions may stabilize catechin within the cyclooxygenase channel and potentially interfere with access of arachidonic acid to the catalytic region. Catechin therefore represents a plausible candidate for further evaluation as a COX-2 inhibitor. This interpretation is also consistent with previous experimental evidence showing that catechin and related flavan-3-ols can inhibit cyclooxygenase-catalysed prostaglandin biosynthesis.³⁹

Gallocatechin showed the second-highest predicted affinity (−8.59 kcal/mol) and interacted with Tyr385, Ser353, Phe518, and Gln192 through hydrogen bonds, with additional contacts involving Leu352, Val523, Trp387, and Ala516. The interaction with Tyr385 is mechanistically relevant because this residue is essential for cyclooxygenase catalysis.³⁸ Its predicted binding within the cyclooxygenase channel may therefore hinder the molecular environment required for arachidonic acid oxygenation. Gallocatechin may consequently have potential as a COX-2 inhibitor candidate, although its additional hydrogen-bond donor and drug-likeness violations indicate that formulation and local tolerability should be investigated before topical development.

Quercetin-3-O-glucoside showed a predicted affinity of −8.43 kcal/mol and interacted with Tyr385, Met522, and Gln192, with an additional π -cation interaction involving Arg120. These interactions indicate that the compound can occupy the COX-2 channel despite its glycosyl group extending toward the membrane-binding lobby. Interaction with Tyr385 provides a structural basis for considering this compound as a potential modulator of COX-2 catalytic activity. However, its high topological polar surface area, multiple drug-likeness filter violations, and low predicted bioavailability score suggest that its physicochemical properties may limit development as a conventional drug. For topical RAS treatment, these systemic drug-likeness limitations may be less decisive than they would be for oral administration, but local formulation, mucosal retention, and safety would still require experimental assessment.

Quercetin showed a predicted affinity of −8.38 kcal/mol and formed hydrogen bonds with Phe518, Ser530, Gln192, Val349, and Met522, accompanied by hydrophobic interactions with Leu352, Val523, and Ala516. Its interaction with Ser530 and occupancy of the cyclooxygenase channel provide a plausible structural basis for COX-2 inhibition. Experimental studies have also reported that quercetin can reduce COX-2 expression and PGE2 production, supporting the biological relevance of its predicted interaction with COX-2.⁴⁰ In the context of RAS, reduced COX-2 activity or expression could theoretically decrease downstream prostaglandin production and thereby attenuate inflammatory signalling and pain associated with oral ulceration.⁴¹

Leucocyanidin showed a predicted affinity of −8.37 kcal/mol and formed hydrogen bonds with His90, Tyr385, Tyr355, Gln192, and Ser530, in addition to interactions with Leu352 and Val349. The simultaneous interaction with Tyr385 and Ser530 is notable because both residues are functionally associated with the COX catalytic site and inhibitor interactions. The multiple hydrogen bonds may contribute to stabilization of leucocyanidin within the cyclooxygenase channel and support its consideration as a potential COX-2 inhibitor.³⁸ Among the five compounds, leucocyanidin also showed the lowest predicted skin-sensitisation and drug-induced liver injury probabilities, although its predicted eye-irritation probability remained high. These predictions should be interpreted as screening signals rather than evidence of mucosal safety.

The potential relevance of these five compounds to topical RAS management can be explained through the role of COX-2 in prostanoid-mediated inflammation. Inflammatory stimulation can increase COX-2 activity and prostaglandin production, while prostaglandins contribute to vasodilatation, inflammatory signalling, and nociceptor sensitisation.^{42,43} Experimental evidence also demonstrates that PGE2 can influence recurrent aphthous ulceration, supporting the relevance of the prostaglandin pathway to RAS. Thus, inhibition of COX-2 by a locally delivered compound could theoretically reduce prostaglandin formation at the ulcer site and subsequently decrease inflammatory activity and pain. This provides the mechanistic rationale for investigating COX-2-binding phytochemicals as candidates for topical RAS management rather than interpreting their docking scores only as evidence of protein-ligand interaction.

From a topical-development perspective, the predicted ADME profiles provide additional context. All five compounds showed low predicted intestinal absorption and negligible predicted blood-brain barrier penetration, which may reduce the relevance of systemic exposure for a locally applied formulation. However, these parameters do not demonstrate favourable retention within oral mucosa. A topical formulation would need to maintain sufficient drug concentration at the ulcer surface despite saliva and oral clearance. Therefore, mucoadhesive formulation studies and measurements of local residence and mucosal permeation are required to determine whether the predicted COX-2 interactions can be achieved at therapeutically relevant concentrations.

The toxicity predictions also indicate that topical development requires caution. High predicted skin-sensitisation probabilities were observed for four compounds, while eye-irritation probabilities exceeded 0.88 for all five. Because these are computational predictions and the models are not specific to oral mucosa, they should not be interpreted as evidence that the compounds will cause oral mucosal irritation or sensitisation. Instead, they identify safety endpoints that require experimental evaluation. This is particularly important for RAS because the intended site of administration is damaged oral mucosa. Therefore, subsequent studies should evaluate cytotoxicity and irritation using oral keratinocytes or reconstructed oral mucosal models before proceeding to in vivo testing.

This study has several limitations. The compound list was compiled from published reports, and not all compounds were identified at the varietal level of *M. paradisiaca* var. *sapientum*, so some constituents present in the material may not have been identified. The docking approach also assumes a rigid receptor and does not fully account for molecular dynamics, so the docking results require experimental validation. Only COX-2 was targeted, and therefore selectivity toward COX-1 and other targets in the arachidonic acid pathway could not be determined. In addition, the ADME-T predictions do not reflect compound disposition in the oral mucosa. Further studies should evaluate COX-2 and COX-1 inhibition, followed by in vitro and in vivo testing in an oral ulcer model.

CONCLUSION

Five of the nine phytochemicals from *Musa paradisiaca* var. *sapientum* stem sap, namely catechin, gallocatechin, quercetin-3-O-glucoside, quercetin, and leucocyanidin, showed favourable predicted binding to the COX-2 catalytic channel. Catechin and gallocatechin showed the highest predicted binding affinities and interacted with key COX-2 residues. All five compounds showed low predicted intestinal absorption and high skin-sensitisation and eye-irritation probabilities. These findings identify catechin and gallocatechin as promising candidates for further experimental investigation as potential topical COX-2 inhibitors for RAS, with their predicted safety profiles requiring experimental validation.

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