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About the Journal

Focus and Scope

Pharmacy Education journal provides a research, development and evaluation forum for communication between academic teachers, researchers and practitioners in professional and pharmacy education, with an emphasis on new and established teaching and learning methods, new curriculum and syllabus directions, educational outcomes, guidance on structuring courses and assessing achievement, and workforce development. It is a peer-reviewed online open access platform for the dissemination of new ideas in professional pharmacy education and workforce development. Pharmacy Education supports Open Access (OA): free, unrestricted online access to research outputs. Readers are able to access the Journal and individual published articles for free - there are no subscription fees or 'pay per view' charges. Authors wishing to publish their work in Pharmacy Education do so without incurring any financial costs.

In addition we are listed in EBSCO, and indexed in the Emerging Sources Citation Index (ESCI - Web of Science), EMBASE and SCOPUS.

The Journal also recognises the importance of policy issues and current trends in the context of education, professional development and workforce.

The Journal publishes reports of research and innovation in all aspects of professional pharmacy education and training, case studies, country studies, innovations in laboratory and professional educational practice, workforce issues and development, reviews and reports on information technology in education and reviews of current literature.

The Journal has a clear international perspective, and has a longstanding policy of facilitating publication, in particular for younger Faculty, and those authors whose first language may not be English, and manuscripts from all regions seeking low cost engagement with the wider global community.

The Journal is published by the International Pharmaceutical Federation (FIP) and is aligned to the global mission of advancing education, advancing practice and advancing science.

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Pharmacy Education has adopted a double-blind peer review process - the identities of the Authors and Reviewers are kept from being known to each other. A step-by-step checklist is provided for Authors, Reviewers and Editors to ensure this (see Ensuring a Blind Review).

Peer Review Process: Once a submission is received, the assigned Editor will select appropriate Reviewers based on their expertise and proven ability to critique. The peer reviews received will assist the Editor in determining the validity, significance and originality of the work submitted. Reviewers will also provide comment on manuscript content for scientific value, check for adherence to general scientific practice as well as Pharmacy Education's specific guidelines. The Peer Review process will look closely at methodology and the data validity, and consider the ethical approach. Reviewers are encouraged to provide suggestions for improvement and recommend to Editors if manuscripts should be accepted, accepted with revisions, or rejected.

Please note that an invitation for Authors to submit a revised version is not a guarantee of acceptance. Ultimately, the final decision lies with the Editor assigned to each submission. An Editor can reject any article at any time before publication, including after acceptance if concerns arise about the integrity of the work.

As part of their agreement with Pharmacy Education, Reviewers will keep manuscripts and associated material strictly confidential, and will not appropriate Authors' ideas before the manuscript is published. Once a review has been completed, Reviewers will be directed and expected to permanently delete/destroy any retained copies of manuscripts they hold (see Privacy Statement).

Timeliness: Reviewers are expected to respond promptly to requests to review and to submit reviews within the time agreed. Reviewers are also required to declare their conflicts of interest and recuse themselves from the Peer Review process if a conflict exists. Editors will do their utmost to ensure timely processing of manuscripts. Authors will be notified on any unusual delays in publication of manuscripts via email. Authors will ne notified as soon as possible if a manuscript is going to be rejected, either by the Journal Manager or Editorial Team.

Journal Ownership and Editorial Scope

Pharmacy Education is published by the International Pharmaceutical Federation (FIP). Appointments and dismissals to the Editorial Team are made by the Editor-in-Chief in consultation with FIP.

Editorial roles and responsibilities

Editor-in-chief - The Editor-in-Chief has full authority over content publication in Pharmacy Education. In co-operation with the wider Editorial Team and publisher, they direct overall strategy of the journal. Together with the Editors and Associate Editors, the Editor-in-Chief reviews and decides upon submitted manuscripts, ensuring timely publication of submissions.

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Advisory Board – Pharmacy Education is currently engaged in establishing an Advisory Board who alongside the Editor-in-Chief, Editors and Associate Editors will assist with:

- Guidance on the peer review and publishing policies of Pharmacy Education and where necessary, suggest reviewers to the Editor-in-Chief.
- Developing the journal by providing expertise to the Editor-in-Chief and FIP on how to increase impact and reach
- Impartial Judgement in appeal cases by providing professional, independent scientific comments to the Editor-in-Chief and FIP
- Promoting Pharmacy Education

Managing Editor – The Managing Editor assumes day-to-day responsibility of managing the submissions flow to Pharmacy Education. They liaise with Authors and Reviewers where needed, clarifying the Submission and Publication process as well as responding to all general enquires. The Managing Editor also completes all typesetting, proofreading and online publication of accepted manuscripts once accepted by the Editors.

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Pharmacy Education does not provide opportunities for advertising on any of its platforms, including downloadable content. This policy maybe reviewed in future in conjunction with the publisher, FIP.

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To assist Pharmacy Education in ensuring public trust in the scientific process and the credibility of articles that it publishes, all those involved in the Submissions and Peer Review process are required to disclose perceived as well as actual conflicts of interest.

Authors: When submitting an article to Pharmacy Education, all Authors are required to disclose all financial and personal relationships that may bias their work (see Submission Preparation Checklist)

Peer Reviewers: Reviewers are asked at the time of conducting a review if they have conflicts of interest that may impact on their ability to provide an unbiased review. Reviewers are asked to disclose conflicts of interest to the assigned Editor. The assigned Editor will then cancel the review and reassign the article to another reviewer. Reviewers agree to not use knowledge of the work they are reviewing before its publication to further their own interests.

Editors and Journal Staff: Editors making final decisions on manuscripts will recuse themselves where conflicts of interest or relationships that pose potential conflicts are present. All editorial staff (including guest editors) provide the Editor-in-Chief with a completed Editorial Disclosure Form (up to date description of financial interests/conflicts). Editors will annually publish disclosure statements about potential conflicts of interests related to the commitments of journal staff.

Research involving Human participants and Informed Consent

It is the responsibility of the authors to ensure that research involving human subjects has been reviewed and approved by the appropriate research or ethics review committee, or that it has been determined to be exempt from such review.

Confirmation of this should be included in the Cover Letter and also included in the Methods section of the manuscript. Where informed consent is required, authors should include a statement in the manuscript detailing that informed consent was obtained from human subjects (see Submission Preparation Checklist)

Article Corrections, Replacement, Retractions & Removal Policy

Published articles are a permanent record that should remain unaltered. However, Pharmacy Education recognises that in exceptional circumstances, articles may need to be corrected, replaced, retracted or removed.

The Editor-in-Chief has full authority over content publication in Pharmacy Education. In making decisions regarding publication, the Editor-in-Chief is guided by the policies of the Journal as well as legal requirements such as libel, copyright, infringement and plagiarism.

Corrections

Detailed below are our procedures for managing requests for corrections post publication

Minor errors

If Authors identify a minor error once an article has been published online, they are advised to email their request for corrections to Pharmacy Education for consideration.

Minor errors include: errors in spelling, data, medical terms; missing text; amendments to tables, figures or appendices; errors in correspondence details, etc. The Journal may decline proposed corrections that are for aesthetic reasons; errors to text, typography tables, figures and appendices if the meaning is unchanged; errors in acknowledgments lists etc.

Significant Corrections

Corrections may be needed if honest errors have resulted in a portion of an article being misleading; if the author/contributor lists are disputed; or if potential conflicts of interest affecting authorship are disclosed post publication.

Where the Editor-in-Chief agrees that a correction is needed, the Journal will:

- Correct the error online, and to any article file for download, linking to a Correction Notice via a footnote
- The Correction Notice will detail the changes made to the original version, and the dates the changes were made.

Replacement

Honest errors such as mis-classification or miscalculation may lead to significant changes to the results, interpretations and conclusions. In such cases, the Journal will consider retraction with replacement of the article:

- The changed version of the article will undergo further editorial review;
- The authors will be required to detail and explain the changes made which will be published as supplementary material or in an appendix;
- The supplementary material/appendix will be attached to the changed version, allowing for complete transparency.

Retraction

An article will be retracted if the results or conclusions are unsound and/or where misconduct breaching professional ethical codes has occurred. The publisher and Editor-in-Chief will conduct an investigation into the errors or misconduct before retracting an article. The following steps will be taken where articles are retracted:

- A Statement of Retraction, giving the reasons for the retraction and signed by the authors and/or the Editor-in-Chief will be published online linking to the original article.
- The original article is preceded by a screen containing the Statement of Retraction. The reader can then proceed to the article itself.
- A watermark will be added to the original PDF indicating on each page that it is “RETRACTED”
- The Statement of Retraction will be included as a numbered page in the Table of Contents to ensure proper indexing, and will include the article title in its heading

Removal

Very occasionally, it may be necessary to remove an article from the online database as a consequence of legal action (e.g., defamatory content, infringement on legal rights, article is subject of a court order, or might pose a serious health risk if an article's content is acted upon).

In these circumstances:

- The article's metadata (title and author details) will be retained and the text replaced with an Article Removal Notice
- The Article Removal Notice will be included in the Table of Contents and prefix the metadata.

Expressions of Concern

If concerns or allegations of misconduct regarding a publication are raised, the Editor-In-Chief will consult the Committee on Publication Ethics (COPE) http://www.publicationethics.org and initiate the appropriate procedure based on the nature of the concern or allegation. The Editor-in-Chief, with appropriate support form the Editorial Team, will assess each situation individually.

The Editor-in-Chief will consider issuing an Expression of Concern if:

- the Editor judges that readers should be made aware of potentially misleading information contained in a published article;
- investigations into any concerns of misconduct remain inconclusive;
- concerns remain over the impartiality of any investigations into alleged misconduct;
- -an investigation is pending and a judgment is not expected for some time.

An Expression of Concern will be published and appear in the Table of Contents and include the title of the article in its heading. It should be noted that Pharmacy Education understands the potential repercussions that issuing an Expression of Concern can bring and will only take this action where it is deemed necessary.

If an investigation produces evidence of misconduct or reveals that the concerns raised are well founded after an Expression of Concern has been published, the Journal will instigate the Retraction process

Appeals and Complaints

Appeals

Authors are entitled to appeal editorial decisions if they believe their submission has been unfairly or inappropriately rejected. An appeal letter should be submitted to the Journal Manager (pej@fip.com)

The appeal letter should provide appropriate detail and context. For example, if an Editor has provided peer review comments it is worthwhile responding to each item in the letter. If the appeal is against the editorial decision made on the submission, explaining and justifying clearly the work's importance, relevance, and usefulness in the appeal letter is recommended.

An invitation to submit a revised version after sending an appeal letter does not guarantee acceptance; the revised article will proceed through the Peer Review process again.

Appeal letters will be ordinarily acknowledged within 5 working days, followed by a full response containing the appeal decision within 4 weeks.

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Pharmacy Education aims to respond quickly, courteously, and constructively to complaints about the Journal's procedures, policies, or actions.

Complaints will be considered if:

- the complainant defines their dissatisfaction as a complaint; and
- it concerns a failure of process, i.e. a long delay or a severe misjudgement; and is not simply disagreement with an editorial decision;
- the issue being raised is within the responsibility of Pharmacy Education's editorial remit
- Complaints should be directly emailed to the Journal Manager (pej@fip.com) who will ordinarily formally acknowledge receipt within 5 working days.
- The Journal Manager will forward the complaint to a relevant person within the Journal organisation who will aim to provide a full response within four weeks. If this is not possible, an interim response and update will be given within the four weeks.
- Following this action, if the complainant remains unhappy, complaints will be escalated to the Editor-in-Chief whose decision is final.
- If a complainant remains unhappy, they may complain to an external body such as the Committee on Publication Ethics (COPE) http://www.publicationethics.org. They will consider complaints against Editors once a Journal's own Complaints procedures have been exhausted.

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Pharmacy Education recognises that there may be legitimate reasons for individuals who wish to remain anonymous when raising issues relating to publication ethics. Concerns or allegations raised anonymously will be handled as they would be if the complaint were from another source, following the processes and procedures of the Journal.

If concerns remain after processes have been followed, The Editor-in-Chief will seek advice from Committee on Publication Ethics (COPE) http://www.publicationethics.org

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Journal History

Pharmacy Education has been publishing peer reviewed education, training, research and evaluation in the field of pharmaceutical education since 2000.

The Journal encourages manuscript submissions from younger career scientists, academics and practitioners and has a focus on supporting authors who do not have English as a first language.

Through our FIP publication platform we are able to reach out to over 3 million pharmacists and pharmaceutical scientist worldwide.

Editorial Team

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IAI SPECIAL EDITION

RESEARCH ARTICLE

Theobroma cacao L. (Cocoa) pod husk as a new therapy for transient receptor protein vanilloid-1 (TRPV1)-targeted diabetic neuropathy: An *in silico* study

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Abstract

Backgrounds: *Theobroma cacao* L. (cocoa) is one of the leading commodities found in Indonesia. Cocoa pod husk has many bioactive compounds with antinociceptive properties. One of the targets in treating pain, especially painful diabetic neuropathy, is the transient receptor potential vanilloid-1 (TRPV1). **Aim:** This study aimed to investigate the activity of active compounds from cocoa pod husk extracts against TRPV1 and their toxicity. **Methods:** Molecular docking was used to predict the activity of the test ligands, and the results were analysed with Molegro Virtual Docker 6.0. The TRPV 1 structure was taken from the Protein Data Bank (ID: 5IS0), with capsazepine as a native ligand. The toxicity prediction was evaluated using pkCSM. **Results:** The results showed that the active chemical compounds from cocoa pod husks with the strongest affinity for TRPV1 were phlorofucofuroeckol-A (-95.7785 ± 1.868), catechins (-92.6868 ± 2.681), 7-phloroeckol (-91.9788 ± 0.356), and resveratrol (-91.1921 ± 0.579), and the safest compounds were catechins, resveratrol, and 7-phloroeckol. **Conclusion:** Catechins, resveratrol, and 7-phloroeckol from cacao pod husks are safe and potential therapy for diabetic neuropathy.

Introduction

Painful Diabetic Neuropathy (PDN) is a common comorbidity among diabetic neuropathy patients, with a reported prevalence in Europe ranging from 0.7-34% in Type 1 or Type 2 diabetes mellitus patients overall (Alleman *et al.,* 2015). PDN can even be classified as an incurable disease due to its poor response to conventional analgesics and lack of working drugs based on the pathogenesis of the underlying illness. Current clinical strategies for PDN management include tricyclic compounds, serotonin noradrenaline reuptake inhibitors (SNRIs), anticonvulsants, opiates, and topical capsaicin, often inefficient because of their significant side effects (Carrasco *et al.,* 2018).

Transient receptor potential vanilloid-1 (TRPV1) is an ion channel in sensory neurons activated by protons, capsaicin, heat, and various endogenous lipids called endovanilloids (Palazzo *et al.,* 2010). TRPV1 activation is associated with chronic inflammatory and peripheral neuropathic pain, thereby controlling inflammation and reducing pain in diabetic patients (Brito *et al.,* 2014).

Of the 25,000-30,000 plant species in Indonesia, around 39,000 are estimated to include therapeutic substances. Only 6,000 plants have been recorded as ingredients for herbal medicine, among which roughly 1,000 varieties have been utilised in herbal medicine (Mustofa *et al.,* 2021). Biodiversity holds a lot of promise for discovering novel chemicals, such as cocoa pod husks, previously considered a waste product.

The most often studied part of cocoa was the seeds which are reported to contain active antioxidant compounds, such as phenolic compounds, procyanidins, and flavonoids (Urbanska & Kowalska, 2019), with a demonstrated antidiabetic activity (Olasope et al., 2016). Previous research showed that

cocoa pod husks contain 45.6-46.4 mg of GAE phenolic compounds, 32.3% carbohydrates, 21.44% lignin, 19.2% sugar, 8.6% protein, and 27.7% minerals and pectin in ranges of 6% to 15% from the dry weight (Karim *et al.,* 2014). A recent study could detect 49 bioactive compounds in cocoa extracts, including polyphenols (resveratrol, esculetin, catechins, (-)-epigallocatechin 3-O-Gallate), carbohydrates (pectin), and phlorotannin (phlorofucofuroeckol-A, 7-phloroeckol, DDBT, eckol, and 6,6'-dieckol) (Cadiz-Gurrea *et al.,* 2020). The specific mechanism of these compounds is uncertain, and the compounds involved have not been studied. This study aims to predict the activity of the test ligand against TRPV-1 and its toxicity.

Materials and methods

Hardware and software

The study was conducted *in silico* using the molecular docking method. The hardware used was an ASUS notebook with Intel(R) Core(TM), CPU at 1.80 GHz processor and Windows 8 operating system (64 bit, 4GB RAM). The software used included Molegro Virtual Docker 6.0 (free trial) and ChemOffice 2010, consisting of ChemBio Draw Ultra 12.0 and ChemBio3D Ultra 12.0. The IBM SPSS Statistics version 22 was used to analyse the data.

Molecular Structure and Optimisation

The molecular structure of test ligands was drawn using ChemBio Draw Ultra 12.0 2010 (Figure 1). Furthermore, optimisation was carried out on the geometry of the molecular structure using MM2 tools on ChemBio3D ultra 12.0 2010. The structure of the TRPV1 complex with capsazepine (PDB ID 5IS0) was obtained through the Protein Data Bank and saved in PDB format (Panggalih *et al.,* 2019).

Docking method validation

The re-docking method using Molegro Virtual Docker 6.0 was performed to validate the docking process. Validation was carried out on the active site of the result of 5IS0 crystallography. The 6ET 801 (B) ligand in the conformation found in the complex structure of crystal-ligand (Figure 2B) was extracted and put into the active side (cavity 5 vol. 228.352).

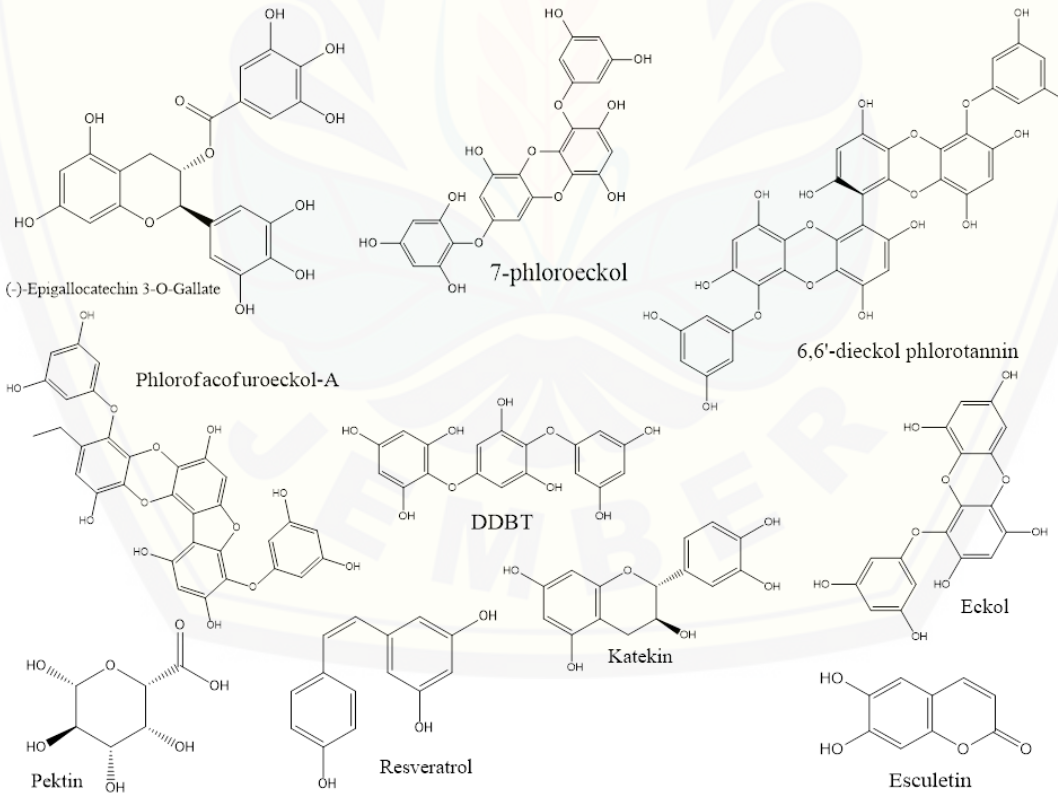
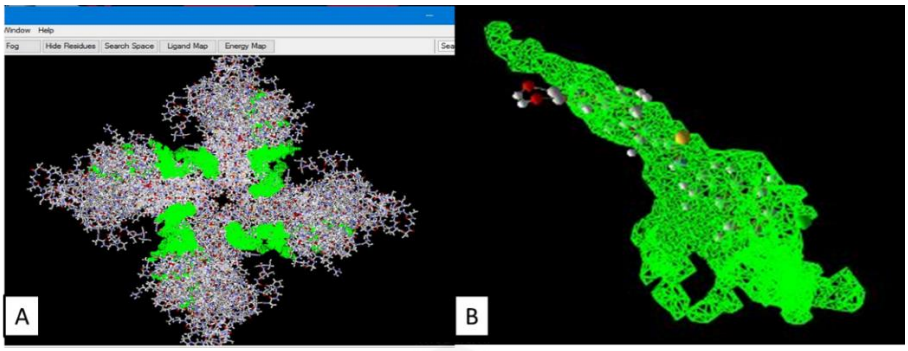


Figure 1: Chemical structure of bioactive compounds from cocoa pod husk



A) TRPV1 after detecting cavities and B) Capsazepin as a native ligand

Figure 2: Interaction between Capsazepine and TRPV1 in Cavity 5

Molecular docking

The molecular docking process was carried out to determine the binding location of the ligand to the TRPV1 as a receptor target in PDN. The test ligands were resveratrol, catechins, esculetin, pectin, 7-phloroeckol, phlorofucofuroeckol-A, (-)-epigallocatechin 3-O-Gallate, DDBT, eckol, and 6,6'-dieckol. Capsazepine, a TRPV1 antagonist, was chosen as a native ligand. The affinity of the test ligands against TRPV1 was indicated by the rerank score using Molegro Virtual Docker 6.0. The determination of the hydrogen bond was also evaluated.

Prediction of toxicity

All the test ligands were predicted for toxicity online using pkCSM. LD_{50} and ADMET values were the parameters used in pkCSM.

Statistical analysis

The rerank score was shown in mean±SD. It was analysed using one-way ANOVA, followed by Tukey's post hoc analysis with a 95% confidence level to evaluate the compound with the best affinity to TRPV1. The *p* - value of 0.05 indicated that the results were significantly different. Toxicity prediction analysis used pkCSM by comparing the lethal dose 50 (LD_{50}) of the tested compounds with ADMET values, such as the lowest-observed-adverse-effect level (LOAEL).

Results

Docking methods validation

The results of the docking method validation showed an average of Root Mean Square Deviation (RMSD) of 1.63271 ± 0.175. This value indicates that the docking method is valid.

Interaction prediction of bioactive compound from cocoa pod husk with TRPV1

The results of the docking analysis of the test ligands with their receptors (Table I) were calculated as a rerank score value described as the affinity of the ligand binds with the receptor. The rerank score is a value that reflects the energy required to form a bond between a ligand and its receptors and thus the compound's predictable activity. The stronger the ligand-receptor bond, the lower the rerank score value.

The test ligands with the strongest bond with TRPV1 are phlorofucofuroeckol-A (-95.7785 ± 1.868), catechins (-92.6868 ± 2.681), 7-phloroeckol (-91.9788 ± 0.356), and resveratrol (-91.1921 ± 0.579). The rerank score of the test compounds is higher than that of capsazepine (-96.3851 ± 1.047), as shown in Table I.

Table I: Rerank score of the test ligands and capsazepine on TRPV1 receptor

Compounds	Rerank score ± SD	No	Compounds	Rerank score ± SD
Capsazepine	-96.3851 ± 1.047[a]	7	Phlorofucofuroeckol-A	-95.7785 ± 1.868[a]
Resveratrol	-91.1921 ± 0.579[b]			
Catechin	-92.6868 ± 2.681[b]	8	(-)-Epigallocatechin 3-O-Gallate	-81.7869 ± 0.979[b]
Esculetin	-67.8644 ± 0.012[c]	9	DDBT	-85.3081 ± 6.531[c]
Pectin	-76.1119 ± 0.052[d]	10	Eckol	-82.3129 ± 0.116[c]
7-phloroeckol	-91.9788 ± 0.356[b]	11	6.6'-dieckol	-71.9141 ± 1.720[c]

Superscript letters indicate that there is a significant difference between groups using One Way ANOVA at the 95% confidence level.

The toxicity prediction of bioactive compounds from cocoa pod husks with TRPV1

The pkCSM study used the LD_{50} and LOAEL to predict toxicity (Table II). Oral LD_{50} (median lethal dose) is an acute toxicity parameter for oral rats. Based on the literature of the criteria for classifying test preparations, the range of LD_{50} values with mild toxicity is >2000-5000 mg and >5000 mg for non-toxic compounds (WHO, 2019). The compound with the highest LD_{50} value was eckol (2.704), indicating it has relatively low toxicity.

Table II: Toxicity prediction of compounds from cocoa pod husks using pkCSM

Compounds	Ames Toxicity	Max tolerated dose (log mg/kg/day)	LD_{50} (mol/kg)	LOAEL (log mg/kg bw/day)	Hepatotoxicity	Skin Sensitisation
Capsazepine	No	0.275	2.314	0.982	No	No
(-)-Epigallocatechin 3-O-Gallate	No	0.439	2.601	4.13	No	No
6.6-dieckol	No	0.438	2.482	6.96	No	No
7-phloroeckol	No	0.417	2.497	4.279	No	No
Catechin	Yes	0.197	2.261	1.587	No	No
DDBT	No	0.425	2.541	3.489	No	No
Eckol	No	0.497	2.704	3.571	No	No
Esculetin	No	0.6	2.054	2.886	No	No
Pectin	No	0.43	2.482	6.49	No	No
Phlorofucofuroeckol-A	No	0.438	2.482	5.458	No	No
Resveratrol	Yes	0.561	2.216	1.761	No	No

LOAEL (Lowest Observed Adverse Effect Level) was defined as the lowest dose at which chronic toxic effects of ingested compounds were observed in rats (WHO, 2017). The highest LOAEL value was 6.96 for 6.6-dieckol, indicating this compound is safer than others. However, capsazepine showed high toxicity.

The physicochemical properties of a ligand when it crosses the cell membrane in the body can be determined by performing the Lipinski test (Table III). The conditions that a ligand must have based on the Lipinski rule are molecular weight <500 Da (this value must be met so that the ligand penetrates the cell membrane more easily), LogP value <5 (related to the polarity of the ligand in fat, oil, or non-polar solvents; a negative LogP value cannot pass through the lipid bilayer membrane), donor hydrogen bonds <5, hydrogen bond acceptor <10, and a molar refractivity range from 40-130 (Benet *et al.,* 2016). Based on the prediction of toxicity according to the Lipinski rule, catechins, resveratrol, and 7-phloroeckol are the safest among all the compounds from cocoa pod husks.

Table III: The ligand properties based on the Lipinski rule through pkCSM

Ligand	Weight Molecule	LogP	Acceptor	Donor
(-)-Epigallocatechin 3-O-Gallate	458.375	2.2332	11	8
6,6-dieckol	742.554	7.2014	18	12
7-phloroeckol	496.38	4.814	12	8
Capsazepin	338.451	3.45792	4	3
Catechin	290.271	1.5461	6	5
DDBT	374.301	3.2104	9	7
Eckol	372.285	3.6105	9	6
Esculetin	178.143	1.2042	4	2
Pectin	588.468	-5.8995	17	8
Phlorofucofuroeckol-A	614.515	7.2758	13	8
Phlorotanin	498.396	3.1548	12	12
Resveratrol	228.247	2.9738	3	3

Discussion

PDN occurs as a result of damage or dysfunction of the nervous system that mediates pain. PDN is associated with metabolic changes due to long-term hyperglycemia. Glucose accumulation causes higher production of ROS (Farmer et al., 2012).

ROS formation activates TRPV1, distributed in the skin, dorsal root ganglia (DRG), and spinal cord dorsal horn (Pabbidi *et al.,* 2008). TRPV1 activation causes depolarisation and stimulation of the NMDA receptor subunit NR2B (NMDAR2B) in the spinal cord's dorsal horn, resulting in chronic pain (Luongo *et al.,* 2012; Zhuo, 2013).

This study explained that some compounds from cocoa pod husks, such as phlorofcofuroeckol-A, catechins 7-phloroeckol, and resveratrol, have a high affinity with TRPV-1. Antagonists or agonists at these receptors reduce pain in diabetic neuropathy (Carrasco *et al.,* 2018). Previous studies demonstrated that substances from

plants, such as capsaicin (Morera *et al.,* 2012) and 6-shogaol (Fajrin *et al.,* 2018), had a strong affinity with TRPV1 *in silico*. Deactivation of TRPV1 causes decreased NMDAR2B activation.

In drug development, activity and safety are the most important to find new candidate substances. This research showed that among ten compounds in cocoa pod husks, phlorofucofuroeckol-A had the best affinity with TRPV1. However, it did not follow the Lipinski rule, making it harder to explore further compared to catechins, resveratrol, and 7-phloroeckol.

Conclusion

This research found that phlorofucofuroeckol-A, catechins, 7-phloroeckol, and resveratrol have the strongest affinity for TRPV1. Moreover, catechins, resveratrol, and 7-phloroeckol are the safest among all the compounds from cocoa pod husks.

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