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Original Research Article

Gastroprotective Effects of Guava (*Psidium guajava* L.) Leaf Infusion in Aspirin-Induced Gastric Ulcer in Male Wistar Rats

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ABSTRACT

Gastric ulcers are characterized by damage to the mucosal and submucosal layers and arise from an imbalance between protective and injurious factors. Active constituents of *Psidium guajava* leaves have been reported to possess gastroprotective properties. The present study was undertaken to evaluate the efficacy of guava leaf infusion (GLI) in protecting against aspirin-induced gastric lesions in male *Wistar* rats. Twenty male *Wistar* rats were allocated into five groups (n=4) and administered orally by gavage one of the following once daily for seven days: GLI at doses of 675, 1350, or 2700 mg/kg body weight; ranitidine at 27 mg/kg body weight (positive control); or 2 mL distilled water (negative control). One hour after, gastric injury was induced by aspirin (9 mg/kg body weight) given orally in all groups. Lesion area percentage and ulcer depth were assessed. A significant reduction in the percentage of gastric mucosal lesion area was observed in the 1350 mg/kg GLI group compared to the positive control (p=0.040), and a more pronounced reduction was noted in the 2700 mg/kg GLI group (p= 0.008). Ulcer depth scoring indicated a significant difference between the 675 and 1350 mg/kg GLI groups (p=0.040), and a highly significant decrease was found in the 2700 mg/kg GLI group relative to the negative control (p=0.008). Administration of guava leaf infusion was demonstrated to confer gastroprotection by attenuating both the area and depth of aspirin-induced gastric mucosal lesions.

Keywords: Aspirin-induced injury, Gastric ulcer, Gastroprotection, *Psidium guajava*.

Introduction

In gastric ulceration, disruption of the tunica mucosa and exposure of the tunica submucosa are observed.[1–4] Such lesions develop when an imbalance occurs between endogenous defence mechanisms and injurious agents, notably nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, paracetamol/ acetaminophen, and diclofenac.[1,2,5] Worldwide, gastric ulceration constitutes a common gastrointestinal disorder.[6] The global prevalence of peptic ulcer disease (PUD) in 2019 was estimated at 8.09 million cases, with higher age-standardized rates in South Asia and among males, although overall morbidity and mortality have declined compared to 1990.[7] The global prevalence of peptic ulcer disease ranges between 0.12% and 1.5%, with higher rates in South Asia and among populations with risk factors such as H. pylori infection and chronic NSAID use.[3,4,7]

Both therapeutic and prophylactic strategies are employed in the management of gastric ulcers. Therapeutic regimens include antacids, proton-pump inhibitors, and H_2-receptor antagonists; however, adverse effects such as headache, nausea, vomiting, and diarrhea have been documented.

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Preventive measures encompass cessation of tobacco and alcohol use, avoidance of caffeinated beverages, and minimization of NSAID consumption.[2,3,7,8] Given the ulcerogenic potential of NSAIDs, administration of herbal preparations with gastroprotective properties has been advocated prior to their use.[9–12] The leaves of *Psidium guajava* L. (family *Myrtaceae*), (guava) long employed in traditional medicine, have been ascribed anti-inflammatory activity.[9,10,13–17] Both *in vitro* and *in vivo* studies have demonstrated that *Psidium guajava* L. leaf extract may confer therapeutic benefits in conditions such as diabetes mellitus, cardiovascular disease, cancer, and gastrointestinal disorders.[9,14–16,18] Phytochemical analyses have revealed the presence of flavonoids, tannins, triterpenoids, essential oils, guaijaverin, and phenolic acids in guava leaves; flavonoids and tannins exert antioxidant effects, mitigate free-radical damage, and reduce gastric inflammation.[9,10,17,19] Owing to their accessibility, low cost, and favourable safety profile,[9,19] guava leaves were evaluated for gastroprotective efficacy in an aspirin-induced gastric ulcer model using male *Wistar* rats.

Aspirin remains one of the most commonly prescribed non-steroidal anti-inflammatory drugs (NSAIDs) worldwide, yet its chronic use is strongly associated with gastrointestinal complications, particularly gastric ulceration.[15,20–24] Despite the availability of standard gastroprotective drugs such as proton pump inhibitors, long-term use is often limited by side effects and economic burden.[6,25] This has prompted the search for safer and more affordable alternatives derived from natural products. Guava leaf (*Psidium guajava* L.) has been widely used in traditional medicine for gastrointestinal disorders,[9,10,13,26] but its potential gastroprotective effect against NSAID-induced gastric injury has not been sufficiently validated through experimental studies. Therefore, the present study was conducted to evaluate the gastroprotective effects of guava leaf infusion in aspirin-induced gastric ulcers in *Wistar* rats, to provide scientific evidence to support its therapeutic potential as a natural gastroprotective agent.

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Materials and Methods

Plant Collection and Identification

Red guava leaves (*Psidium guajava L.*) were collected from trees in Pameungpeuk, Bandung, (40376, Indonesia) in November 2022. The plant sample was authenticated at the Herbarium Bandungense (FIPIA), School of Life Sciences and Technology (SITH), Institut Teknologi Bandung (ITB) and a voucher specimen was deposited under registration number 7573/IT1.C11.2/TA.00/2022". Twenty-seven grams of young leaves, harvested from shoot tips, were washed under running water and air-dried. The dried leaves were weighed, finely chopped, and transferred to an infusion flask containing 100 mL of distilled water. Infusion was performed in a water bath maintained at 90 °C for 15 minutes. The resulting infusion was filtered through Whatman filter paper; approximately 99 mL of filtrate, equivalent to 2700 mg/kg BW, was obtained. To prepare the lower doses (1350 mg/kg and 675 mg/kg BW), the infusion was serially diluted with distilled water. All preparations were stored at 4°C for up to 7 days.[27–29]

Preparation of Animals

Twenty male *Wistar* rats (8–12 weeks old; mean weight 190 g) were procured from the animal facility of Institut Teknologi Bandung, Indonesia. Animals were acclimatised for 7 days under controlled conditions (temperature 22–24 °C; relative humidity 50–60%; 12 h light/dark cycle) with *ad libitum* access to standard rat chow and drinking water. Rats were then randomly assigned to five groups (n = 4 per group): Group I (GLI I): 675 mg/kg BW guava leaf infusion, Group II (GLI II): 1350 mg/kg BW guava leaf infusion, Group III (GLI III): 2700 mg/kg BW guava leaf infusion, Positive control: 27 mg/kg BW ranitidine, and Negative control: 2 mL distilled water. Each treatment was administered once daily by orogastric gavage for 7 days. On day 7, aspirin (9 mg/kg BW) was administered orally one hour after the final treatment.[30–32] Four hours post-aspirin induction, animals were anesthetised with ketamine (75 mg/kg BW) and xylazine (10 mg/kg BW) via intraperitoneal injection and subsequently euthanised.[33,34]

Gastric tissues were excised, fixed in 10% neutral-buffered formalin overnight, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin.[35–37] A veterinary pathologist, blinded to group allocation, evaluated the percentage of mucosal damage and ulcer depth using a semi-quantitative scoring system.[38,39]

Ethical approval was granted by the Research Ethics Commission of the Faculty of Medicine, Maranatha Christian University Bandung – Immanuel Hospital Bandung (Decree No. 115/KEP/V/2021; dated 24 May 2021). All procedures adhered to the 3R principles of refinement, reduction, and replacement.

Statistical analysis

Statistical analysis was conducted using the Kruskal–Wallis test followed by pairwise comparisons with the Mann–Whitney U test ($\alpha = 0.05$).

Results and Discussion

The result for percentage of damaged area and depth of the gastric mucosal ulcer were differentiated using a scoring system and are listed in Table 1 and Table 2. Results are presented as mean ± standard deviation (SD), as shown in Table 6 and Table 7.

Table 1: Rat gastric mucosal damage scoring and depth scoring

Scoring Type	Score	Criteria
Damage scoring	0	No lesions (normal mucosa)
	1	Lesion area < 20%
	2	Lesion area > 20%
Depth scoring	0	No ulcer (normal mucosa)
	1	Erosion of the mucosal surface epithelium
	2	Ulcers up to the lamina propria
	3	Ulcer beyond the lamina propria

Table 2: Scoring results indicating percentage of gastric mucosal damage area

Rat/Group	Control (-)	GLI I	GLI II	GLI III	Control (+)
1	2	1	1	1	0
2	2	2	1	1	1
3	2	2	1	1	1
4	2	2	2	1	1
Median	2	2	1	1	1

Control (-), rats administered with 2 mL of distilled water; GLI I, rats administered with 2 mL of guava leaf infusion (675 mg/kg BW); GLI II, rats administered with 2 mL of guava leaf infusion (1350 mg/kg BW); GLI III, rats administered with 2 mL of guava leaf infusion (2700 mg/kg BW); Control (+), rats administered with ranitidine (27 mg/kg BW).

Percentage of Damaged Area of Male Wistar Rats Gastric Mucosa

The extent of mucosal injury was quantified by calculating the percentage of damaged area under a LEICA ICC_{50} HD microscope (×100 magnification) and scored according to the system.(35) Median scores for each treatment group are summarised in Figure 1, and detailed scoring results are provided in Table 3. A Kruskal–Wallis test indicated a statistically significant difference among groups ($p = 0.011$), prompting pairwise comparisons by the Mann–Whitney U test (Table 4). A highly significant reduction in lesion area was observed in the GLI III group (2700 mg/kg BW) relative to the negative control ($p = 0.008$), and a significant reduction was noted in the GLI II group (1350 mg/kg BW) compared with the negative control ($p = 0.040$) (Table 4). These findings demonstrate that GLI at 2700 mg/kg BW provides a highly significant gastroprotective effect, whereas the 1350 mg/kg BW dose confers a significant protective effect.

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Table 3: Mann-Whitney post hoc test results for scoring percentage of gastric mucosa damaged area

Group of Rats	Control (-)	GLI I	GLI II	GLI III	Control (+)
Control (-)		0.317[c]	0.040[a]	0.008[b]	0.011[a]
GLI I			0.186[c]	0.040[a]	0.040[a]
GLI II				0.317[c]	0.186[c]
GLI III					0.317[c]
Control (+)					

[a]. significant ($p < 0.05$); **, highly significant ($p < 0.01$); NS, not significant ($p > 0.05$); Control (-), rats administered with 2 mL of distilled water; GLI I, rats administered with 2 mL of guava leaf infusion (675 mg/kg BW); GLI II, rats administered with 2 mL of guava leaf infusion (1350 mg/kg BW); GLI III, rats administered with 2 mL of guava leaf infusion (2700 mg/kg BW); Control (+), rats administered with ranitidine (27 mg/kg BW).

Table 4: Gastric ulcer depth scoring results

Rat/Group	Control (-)	GLI I	GLI II	GLI III	Control (+)
1	2	2	1	1	0
2	2	1	1	1	1
3	2	1	1	1	1
4	2	1	2	1	1
Median	2	1	1	1	1

Control (-), rats administered with 2 mL of distilled water; GLI I, rats administered with 2 mL of guava leaf infusion (675 mg/kg BW); GLI II, rats administered with 2 mL of guava leaf infusion (1350 mg/kg BW); GLI III, rats administered with 2 mL of guava leaf infusion (2700 mg/kg BW); Control (+), rats administered with ranitidine (27 mg/kg BW).

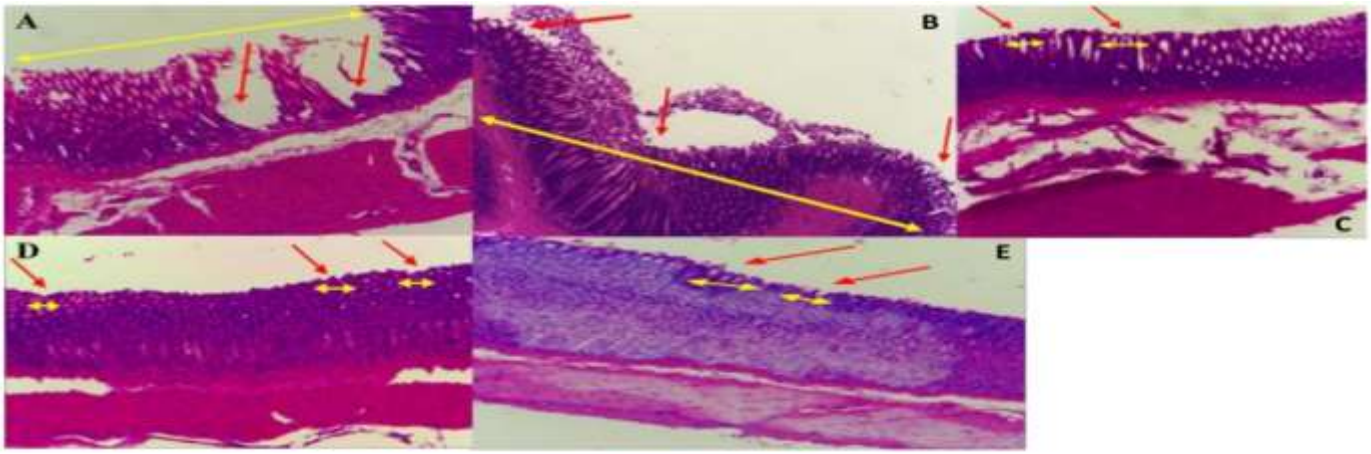

Figure 1: Histopathological overview of male *Wistar* rats. A: distilled water group (negative control), B: GLI I group; D: GLI III group; E: ranitidine group (positive control); the yellow arrow indicates the percentage of gastric mucosa damage area; the red arrow indicates the depth of gastric mucosa ulcer. Sections of rat stomach tissues were stained with hematoxylin-eosin. (magnification: 100X)

Depth of Gastric Mucosa Ulcers in Male Wistar Rats

The depth of the gastric mucosa ulcer was observed using a microscope and accessed using a scoring system. Median depth scores are depicted in Figure 2, and individual group scores appear in Table 5. The overall difference among groups was confirmed by a Kruskal–Wallis test ($p = 0.018$), and subsequent Mann–Whitney U comparisons are listed in Table 6. A highly significant decrease in ulcer depth was detected in the GLI III (2700 mg/kg BW) group relative to the negative control ($p = 0.008$). Additionally, significant reductions were observed in both the GLI I (675 mg/kg BW) and GLI II (1350 mg/kg BW) groups compared with the negative control ($p = 0.040$ for each comparison) (Table 6). These results indicate that all tested GLI doses imparted gastroprotection, with the highest dose yielding the most pronounced effect on ulcer depth.

Histological Findings

Representative micrographs illustrating the gastric mucosal architecture of each group are presented in Figure 3. Sections from treated animals exhibited preservation of mucosal integrity and reduced infiltration of inflammatory cells, in contrast to extensive epithelial disruption and submucosal exposure observed in the negative control group.

Sex-related differences play a pivotal role in gastric ulcer healing, with testosterone shown to impair gastric microcirculation and delay mucosal repair. In contrast, estrogen and progesterone enhance angiogenesis, improve mucosal blood flow, and accelerate tissue regeneration, thereby contributing to the lower incidence and faster healing rates observed in females compared to males.[40–42] A single batch of guava leaf administration was prepared to ensure consistency across the treatment period. Human-equivalent doses were converted to three experimental levels to identify the optimal gastroprotective effect.[17,18,29] The 1350 and 2700 mg/kg BW doses conferred greater protection than the negative control, whereas residual mucosal injury persisted in the ranitidine group, reflecting the fact that H_2-receptor antagonism does not afford complete mucosal defence.[10,28,43] Marked reductions in lesion area and ulcer depth were observed across all GLI-treated groups. Unlike previous investigations employing concentrated guava leaf extracts,[10,18,26] the present study employed a simple treatment, yet comparable gastroprotective efficacy was achieved, as evidenced by significant improvements in both quantitative endpoints.

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Table 5: Mann-Whitney post hoc test results for gastric ulcer depth scoring

Group of Rats	Control (-)	GLI I	GLI II	GLI III	Control (+)
Control (-)		0.040 (*) (NS)	0.040 (*)	0.008 (**)	0.011 (*)
GLI I			1.000 (NS)	0.317 (*)	0.186 (NS)
GLI II				0.317 (NS)	0.186 (NS)
GLI III					0.317 (NS)
Control (+)					

*, significant ($p < 0.05$); **, highly significant ($p < 0.01$); NS, not significant ($p > 0.05$); Control (-), rats administered with 2 mL of distilled water; GLI I, rats administered with 2 mL of guava leaf infusion (675 mg/kg BW); GLI II, rats administered with 2 mL of guava leaf infusion (1350 mg/kg BW); GLI III, rats administered with 2 mL of guava leaf infusion (2700 mg/kg BW); Control (+), rats administered with ranitidine (27 mg/kg BW).

Table 6: Mean ± SD of Gastric Mucosal Damage Scores in Male Wistar Rats

Group of Rats	Mean ± SD
Control (-)	2 ± 0
GLI I	1.75 ± 0.43
GLI II	1.26 ± 0.43
GLI III	1 ± 0
Control (+)	0.75 ± 0.43

Table 7: Mean ± SD of Gastric Mucosal Depth Scores in Male Wistar Rats

Group of Rats	Mean ± SD
Control (-)	2 ± 0
GLI I	1.26 ± 0.43
GLI II	1.26 ± 0.43
GLI III	1 ± 0
Control (+)	0.75 ± 0.43

The phytochemical constituents of *Psidium guajava* leaves, including flavonoids, tannins, triterpenoids, alkaloids, essential oils, phenolic acids, quercetin, vitamins, and saponins, have been implicated in gastroprotection.[9,10,15,16,19] Flavonoids, present in guava leaves, exhibit preventive and therapeutic effects on gastric ulcers. Flavonoids exhibit gastric cytoprotective activity by regulating the biosynthetic pathway of prostaglandins (PG), such as PGE2, that are the main metabolites of arachidonic acid. Two isoforms of cyclooxygenase (COX), COX-1 and COX-2, are the main enzymes in PG biosynthesis. The COX-1 isoform is expressed in most tissues, including the gastrointestinal tract, and produces PG that regulates gastric mucus and bicarbonate production, reduce gastric acid secretion, restores gastric mucosa by dilating blood vessels, increases mucosal blood flow, and accelerates mucosal healing. In contrast, COX-2 has no or little expression in most tissues; however, it is rapidly induced during inflammation, thereby reducing gastric inflammation.[5,9,10,19] In addition, flavonoids also reduce the levels of acetylcholine, gastrin, histamine, somatostatin, and inhibit the activity of H^+K^+-ATPase, which inhibits proton pumps in parietal cell membranes, catalyzes H^+ transport during ATP production, inhibits gastric acid secretion, increases mucus and bicarbonate secretion, inhibits pepsin activity, and accelerates the healing of gastric mucosal injuries by increasing mucosal blood flow.[5,15,16,19]

Moreover, tannins exhibit antioxidant and anti-secretory properties, reducing acid secretion and directly inhibiting *Helicobacter pylori*, thus preventing ulcer formation.[9,10,19] Alkaloids further enhance prostaglandin and mucus output, improve mucosal perfusion, and scavenge free radicals.[10,19,44,45] Quercetin's dual antioxidant and anti-inflammatory actions contribute to preservation of mucosal integrity.[9,19,26,46] The concerted action of these bioactives underpins the gastroprotective effects observed with guava leaf infusion. The present findings highlight the importance of sex-related factors in gastric ulcer pathophysiology, as hormonal modulation significantly influences mucosal repair and angiogenesis. Estrogen and progesterone have been shown to enhance mucosal blood flow and accelerate healing, whereas testosterone delays repair by impairing microcirculation.[41,42] By utilizing only male rats, which are more prone to ulcer persistence, the efficacy of guava leaf infusion (GLI) was demonstrated under stringent experimental conditions. In contrast to ranitidine, which primarily acts through H_2-receptor antagonism and provides incomplete mucosal protection,[4,21] GLI exerted multimodal effects, including antioxidative, anti-secretory, and cytoprotective actions mediated by its phytochemical constituents.[9,19,46] These multimodal mechanisms are consistent with prior reports on the gastroprotective roles of flavonoids, tannins, and alkaloids from Psidium guajava, but the use of a simple infusion preparation underscores its translational potential in traditional and clinical contexts.[18,29]

Conclusion

Administration of *Psidium guajava* leaf infusion conferred significant gastroprotection in an aspirin-induced ulcer model, as demonstrated by reductions in both lesion area and ulcer depth. Future perspectives of this study include validating the findings in larger cohorts involving both sexes and longer treatment durations, while also elucidating the molecular mechanisms and active phytoconstituents responsible for the observed effects. Comparative studies with standard anti-ulcer therapies and eventual translation into clinical trials are warranted to establish the therapeutic potential of guava leaf infusion.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J. Harrison's principle of internal medicine. 20th ed. New York: McGraw-Hill Education; 2018. p.2220–2226.
2. Laucirica I, Garcia Iglesias P, Calvet X. Peptic ulcer. Med Clin (Engl Ed). 2023;161(6):260–266. Doi: 10.1016/j.medcle.2023.05.015
3. Vakil N. Peptic Ulcer Disease: A Review. *JAMA*. 2024;332(21):1832–1842. doi:10.1001/jama.2024.19094
4. Almadi MA, Lu Y, Alali AA, Barkun AN. Peptic ulcer disease. *Lancet (London, England)*. 2024;404(10447):68–81. Doi: 10.1016/S0140-6736(24)00155-7
5. Zhang W, Lian Y, Li Q, Sun L, Chen R, Lai X, Zhang J, Zhu X, Xu X, Chen J, Zhao Y. Preventative and therapeutic potential of flavonoids in peptic ulcers. Molecules. 2020;25(20):1–24. Doi: 10.3390/molecules25204626
6. Shanmugapriya K, Kim H, Kang HW. EGFR-conjugated hydrogel accelerates wound healing on ulcer-induced burn wounds by targeting collagen and inflammatory cells using photoimmunomodulatory inhibition. Mater Sci Eng C. 2020;118(2021)1115114:1-14. Doi: 10.1016/j.msec.2020.111541
7. Xie X, Ren K, Zhou Z, Dang C, Zhang H. The global, regional and national burden of peptic ulcer disease from 1990 to 2019: a population-based study. BMC Gastroenterol. 2022;58(2022):1-12. Doi: 10.1186/s12876-022-02130-2
8. Kuna L, Jakab J, Smolic R, Raguz-Lucic N, Vcev A, Smolic M. Peptic ulcer disease: a brief review of conventional therapy and herbal treatment options. J Clin Med. 2019;8(2),179:1-13. Doi: 10.3390/jcm8020179
9. Díaz-de-Cerio E, Verardo V, Gómez-Caravaca AM, Fernández-Gutiérrez A, Segura-Carretero A. Health effects of *Psidium guajava* L. leaves: an overview of the last decade. Int J Mol Sci. 2017;18(4),897:1-24. Doi: 10.3390/ijms18040897
10. Liu C, Jullian V, Chassagne F. Ethnobotany, phytochemistry, and biological activities of *Psidium guajava* in the treatment of diarrhea: a review. Front Pharmacol. 2024;15(2024), 1459066:1-18. Doi: 10.3389/fphar.2024.1459066
11. Cherrada N, Chemsa AE, Gheraissa N, Laib I, Gueboudji Z, El-Shazly M, Zaater A, Abid A, Sweilam SH, Bin Emran T, Nani S, Benamor B, Amara DG, Atoki AV, Messaoudi M. Gastroprotective efficacy of North African medicinal plants: a review on their therapeutic potential for peptic ulcers. Food Sci Nutr. 2024;12(11):8793–8824. Doi: 10.1002/fsn3.4536
12. Ruiz-Hurtado PA, Garduño-Siciliano L, Domínguez-Verano P, Balderas-Cordero D, Gorgua-Jiménez G, Canales-Álvarez O, Canales-Martínez MM, Rodríguez-Monroy MA. Propolis and its gastroprotective effects on NSAID-induced gastric ulcer disease: a systematic review. Nutrients. 2021;13(9),3169:1-34. Doi: 10.3390/nu13093169
13. Daswani PG, Gholkar MS, Birdi TJ. *Psidium guajava*: a single plant for multiple health problems of rural Indian population. Pharmacogn Rev. 2017;11(22):167–174. Doi: 10.4103/phrev.phrev_17_17
14. Yumita A, Hikmawanti NPE, Hanani E, Saputri CW, Hanana PH, Ero JND, Marcelena M, Baytisani T, Sofiana FA, Shania AF, Saputri ESA, Islami FPN. Exploring the polyphenol contents and antioxidant capacity of the leaf extracts of selected Indonesian *Syzygium species*. Trop J Nat Prod Res. 2023;7(6):1034–1040. Doi: 10.26538/tjnpr/v7i6.8
15. Ogbiko C, Usman D, Eboka J, Igbe I. Anti-ulcer activity of methanol extract of *Plantago rugelii Decne*. (Plantaginaceae). Trop J Nat Prod Res. 2017;1(2):84–88. Doi: 10.26538/tjnpr/v1i2.9
16. Nweze C, Lay T, Muhammad A, Ubhenin A. Hypoglycemic, hepatoprotective and hypolipidemic effects of *Pleurotus ostreatus* in alloxan-induced hyperglycemic rats. Trop J Nat Prod Res. 2017;1(4):163–167. Doi: 10.26538/tjnpr/v1i4.8
17. Gutierrez-Montiel D, Guerrero-Barrera AL, Chávez-Vela NA, Avelar-Gonzalez FJ, Ornelas-García IG. *Psidium guajava* L.: from byproduct and use in traditional Mexican medicine to antimicrobial agent. Front Nutr. 2023;10,1134561:1-18. Doi: 10.3389/fnut.2023.1108306
18. Ibeh LN, Ijioma SN, Emmanuel O, Timothy CO, Ugbogu EA. *Psidium guajava* leaf extract improves gastrointestinal functions in rats and rabbits: an implication for ulcer and diarrhoea management. Biomarkers. 2021;26(8):737–746. Doi: 10.1080/1354750X.2021.1992651
19. Vimala G, Shoba FG. A review on antiulcer activity of few Indian medicinal plants. Int J Microbiol. 2014;2014(1):1–12. Doi:10.1155/2014/519590
20. Tai FWD, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clin Med. 2021;21(2):131–134. Doi: 10.7861/clinmed.2021-0039
21. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020;180,114147:1-21. Doi: 10.1016/j.bcp.2020.114147
22. Shim YK, Kim N. Nonsteroidal anti-inflammatory drug and aspirin-induced peptic ulcer disease. Korean J Gastroenterol. 2016;67(6):300–312. Doi: 10.4166/kjg.2016.67.6.300
23. Sha'aban A, Zainal H, Khalil NA, Abd Aziz F, Ch'ng ES, Teh CH, Mohammed M, Ibrahim B. Prediction of low-dose aspirin-induced gastric toxicity using nuclear magnetic resonance spectroscopy-based pharmacometabolomics in rats. Molecules. 2022;27(7),2126:1-11. Doi: 10.3390/molecules27072126
24. McEvoy L, Carr DF, Pirmohamed M. Pharmacogenomics of NSAID-induced upper gastrointestinal toxicity. Front Pharmacol. 2021;12,667223:1-15. Doi: 10.3389/fphar.2021.684162
25. O'Brien CW, Juraschek SP, Wee CC. Prevalence of aspirin use for primary prevention of cardiovascular disease in the United States: Results from the 2017 National Health Interview Survey. Ann Intern Med. 2019;171(8):596–598. Doi: 10.7326/M19-0953
26. Uduak EU, Timbuak JA, Musa SA, Ikyembe DT, Abdurrashid S, Hamman WO. Ulceroprotective effect of methanol extract of *Psidium guajava* leaves on ethanol induced gastric ulcer in adult Wistar rats. Asian J Med Sci. 2012;4(2):75–78.
27. Manekeng HT, Mbaveng AT, Ntyam Mendo SA, Agokeng AJD, Kuete V. Evaluation of acute and subacute toxicities of *Psidium guajava* methanolic bark extract: a botanical with in vitro antiproliferative potential. Evid Based Complement Alternat Med. 2019; 2019(1):1–13. Doi: 10.1155/2019/8306986
28. Birdi T, Krishnan GG, Kataria S, Gholkar M, Daswani P. A randomized open label efficacy clinical trial of oral guava leaf decoction in patients with acute infectious diarrhoea. J Ayurveda Integr Med. 2020;11(2):163–172. Doi: 10.1016/j.jaim.2020.04.001
29. Janhavi P, Divyashree S, Sanjailal KP, Muthukumar SP. DoseCal: a virtual calculator for dosage conversion between human and different animal species. Arch Physiol Biochem. 2022;128(2):426–430. Doi: 10.1080/13813455.2019.1687523
30. Lu S, Wu D, Sun G, Geng F, Shen Y, Tan J, Sun X, Luo Y. Gastroprotective effects of Kangfuxin against water-immersion and restraint stress-induced gastric ulcer in rats: Roles of antioxidation, anti-inflammation, and pro-survival. Pharm Biol. 2019;57(1):770–777. Doi: 10.1080/13880209.2019.1682620

31. Kim YS, Park HJ, Kim H, Song J, Lee D. Gastroprotective effects of Paeonia extract mixture HT074 against experimental gastric ulcers in rats. Evid Based Complement Alternat Med. 2019;2019(1):1–13. Doi: 10.1155/2019/3546258
32. Turner PV, Vaughn E, Sunohara-Neilson J, Ovari J, Leri F. Oral gavage in rats: animal welfare evaluation. J Am Assoc Lab Anim Sci. 2012;51(1):25–30.
33. Colby LA, Nowland MH, Kennedy LH. Clinical laboratory animal medicine. 5th ed. New Jersey: Wiley Blackwell; 2020. p.138-142.
34. Flecknell P. Examples of dilutions of anaesthetic mixtures for small rodents. In: Laboratory animal anaesthesia. 4th ed. Amsterdam: Elsevier; 2016. p.265–270. Doi: 10.1016/B978-0-12-800036-6.00023-5
35. Adefisayo MA, Akomolafe RO, Akinsomisoye SO, Alabi QK, Ogundipe OL, Omole JG, Olamilosoye KP. Gastroprotective effect of methanol extract of *Vernonia amygdalina* leaf on aspirin-induced gastric ulcer in Wistar rats. Toxicol Rep. 2017;4:625-633. Doi: 10.1016/j.toxrep.2017.11.004
36. Ercan G, Tartar RI, Solmaz A, Gulcicek OB, Karagulle OO, Meric S, Caroyen H, Kusaslan R, Kemik A, Kayali DG, Cetinel S, Celik A. Potent therapeutic effects of ruscogenin on gastric ulcer established by acetic acid. Asian J Surg. 2020;43(2):405-416. Doi: 10.1016/j.asjsur.2019.07.001
37. Khayyal MT, Wadie W, El-Haleim EA, Ahmed KA, Kelber O, Ammar RM, Aziz HA. STW 5 is effective against nonsteroidal anti-inflammatory drug-induced gastro-duodenal lesions in rats. World J Gastroenterol. 2019;25(39):5926–5935. Doi: 10.3748/wjg.v25.i39.5926
38. Masbuchin AN, Nurdiana, Suryana BPP. Gastroprotective Effect of Welsh Onion (*Allium fistulosum*) Toward Gastropathy in Indomethacin-Induced Rat. Health Journal of the Faculty of Medicine, Brawijaya University. 2014;1(3):181–187.
39. Usman S. The extent of gastric mucosal damage in ethanol-induced model rats. Mutiara Medika. 2016;16(1):34–39.
40. Tarnawski AS, Ahluwalia A. The critical role of growth factors in gastric ulcer healing: the cellular and molecular mechanisms and potential clinical implications. Cells. 2021;10(8),1964:1-19. Doi: 10.3390/cells10081964
41. Périco LL, Rodrigues VP, Ohara R, Bueno G, Nunes VVA, dos Santos RC, Camargo ACL, Justulin Júnior LA, de Andrade SF, Steimbach VMB, da Silva LM, da Rocha LRM, Vilegas W, dos Santos C, Hiruma-Lima CA. Sex-specific effects of *Eugenia punicifolia* extract on gastric ulcer healing in rats. World J Gastroenterol. 2018;24(38):4369–4383. Doi: 10.3748/wjg.v24.i38.4369
42. Zarricueta ML, Fagundes FL, Pereira QC, Pantaleão SQ, Santos RC. Relationship between hormonal modulation and gastroprotective activity of malvidin and cyanidin chloride: in vivo and in silico approach. Pharmaceutics. 2022;14(3),565:1-25. Doi: 10.3390/pharmaceutics14030565
43. Alazzouni AS, Abdel Aziz EA, Elnabtity S, Salem AI. Comparative histological and histochemical studies between ranitidine and nizatidine in treatment of peptic ulcer with evaluation of their adverse effects on male sex hormones. J Basic Appl Zool. 2020;81(61):4–16. Doi: 10.1186/s41936-020-00196-6
44. Asnaashari S, Dastmalchi S, Javadzadeh Y. Gastroprotective effects of herbal medicines (roots). Int J Food Prop. 2018;21(1):902-920. Doi: 10.1080/10942912.2018.1473876
45. Sudira IW, Merdana IM, Qurani SN. Preliminary phytochemical analysis of guava leaves (*Psidium guajava* L.) extract as antidiarrheal in calves. Adv Trop Biodivers Environ Sci. 2019;3(2):21–23. Doi: 10.24843/atbes.2019.v03.i02.p01
46. Ruksiriwanich W, Khantham C, Muangsanguan A, Phimolsiripol Y, Barba FJ, Sringarm K, Rachtanapun P, Jantanasakulwong K, Jantrawut P, Chittasupho C, Chutoprapat R, Boonpisuttinant K, Sommano SR. Guava (*Psidium guajava* L.) leaf extract as bioactive substances for anti-androgen and antioxidant activities. Plants. 2022;11(24),3514:1-14. Doi: 10.3390/plants11243514