



Effect of *Phyllanthus emblica* L. stem bark extract on diabetic nephropathy and hyperlipidemia in rats

[Efecto del extracto de corteza de tallo de *Phyllanthus emblica* L. sobre la nefropatía diabética y la hiperlipidemia en ratas]

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Abstract

Context: *Phyllanthus emblica* stem barks are rich in antioxidants, but its utilization for antidiabetic and diabetic complications remains understudied.

Aims: To evaluate the efficacy of extracts from *P. emblica* stem barks in improving diabetic nephropathy and hyperlipidemia *in vivo*.

Methods: *P. emblica* stem bark powder was dried and macerated using n-hexane, ethyl acetate, and methanol simultaneously. The diabetic condition was induced by streptozotocin (STZ) in male Wistar rats. Treatment interventions included the oral administration of metformin (60 mg/kg body weight) or *P. emblica* stem bark extracts (200 mg/kg) once a day, where the fasting blood glucose (FBG) and total cholesterol levels were measured before and after the treatment.

Results: Rats receiving the ethyl acetate extract exhibited a significantly lower FBG than the control (113.7 ± 15.04 versus 195 ± 19.97 mg/dL; p<0.05). Rats treated with ethyl acetate extract and methanol showed a significant decrease in total cholesterol levels with p-values of 0.037 and 0.004, respectively. Cellular damages observed on the histological images of the kidney were found to be significantly attenuated in all treated rats (p<0.001).

Conclusions: *P. emblica* stem bark extracts are efficacious in treating diabetic complications, including nephropathy and hyperlipidemia.

Keywords: antioxidant; diabetes; inflammation; kidney injury; necrosis; *Phyllanthus emblica*.

Resumen

Contexto: La corteza del tallo de *Phyllanthus emblica* es rica en antioxidantes, pero su utilización como antidiabético y contra las complicaciones diabéticas sigue sin estudiarse lo suficiente.

Objetivos: Evaluar la eficacia de los extractos de corteza de tallo de *P. emblica* para mejorar la nefropatía diabética y la hiperlipidemia *in vivo*.

Métodos: El polvo de corteza de tallo de *P. emblica* se secó y maceró utilizando simultáneamente n-hexano, acetato de etilo y metanol. Se indujo la condición diabética mediante estreptozotocina (STZ) en ratas Wistar macho. Las intervenciones de tratamiento incluyeron la administración oral de metformina (60 mg/kg de peso corporal) o de extractos de corteza de tallo de *P. emblica* (200 mg/kg) una vez al día, y se midieron los niveles de glucemia en ayunas (FBG) y de colesterol total antes y después del tratamiento.

Resultados: Las ratas que recibieron el extracto de acetato de etilo mostraron una FBG significativamente menor que el control (113,7 ± 15,04 frente a 195 ± 19,97 mg/dL; p<0,05). Las ratas tratadas con extracto de acetato de etilo y metanol mostraron una disminución significativa de los niveles de colesterol total con valores p de 0,037 y 0,004, respectivamente. Los daños celulares observados en las imágenes histológicas del riñón se atenuaron significativamente en todas las ratas tratadas (p<0,001).

Conclusiones: Los extractos de corteza de tallo de *P. emblica* son eficaces en el tratamiento de las complicaciones diabéticas, incluidas la nefropatía y la hiperlipidemia.

Palabras Clave: antioxidante; diabetes; inflamación; lesión renal; necrosis; *Phyllanthus emblica*.

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INTRODUCTION

Chronic hyperglycemia in diabetic patients may progress to diabetic nephropathy and hyperlipidemia, among other complications such as retinopathy and neuropathy (Brownlee, 2005). Patients having diabetic nephropathy are characterized by slower filtration of the glomerular as well as kidney failure (Dabla, 2010). In addition, glomerular sclerosis, tubulointerstitial fibrosis, and loss of podocytes are common findings in patients with diabetic nephropathy (Dabla, 2010). As for hyperlipidemia, other than higher total cholesterol, the condition is characterized by higher triglyceride, higher low-density lipoprotein cholesterol, and lower high-density lipoprotein cholesterol (Geberemeskel et al., 2019; Yibru, 2014). Mechanisms underlying these complications involved the overproduction of reactive oxygen species (ROS), resulting in oxidative stress imbalance (Manna et al., 2019). Hence, it is important to develop antidiabetic drugs capable of reducing blood glucose level and improving oxidative stress.

Natural products have been used as the inspiration to develop drugs for multiple diseases (Harahap et al., 2022; Nasution et al., 2022), even for type 2 diabetes mellitus (Andalia et al., 2022; Baker et al., 2021). Among many phytomedicines, *Phyllanthus emblica* L. (family *Phyllanthaceae*) emerges as a strong candidate due to its potent antioxidant activities (Ahmad et al., 2021; Saini et al., 2022). In regards to its antidiabetic potential, multiple studies have observed only the fruit and seeds of *P. emblica* (Huang et al., 2021; Sriwatcharakul, 2020). To the best of our knowledge, the antidiabetic potentials of *P. emblica* stem bark have never been reported before, hence the novelty of this present study. Using stem barks has more advantages as compared to fruit or seeds since their availability is not seasonal. The pharmacological properties of *P. emblica* stem barks have been associated with their antioxidant and antimicrobial activities (Adak et al., 2018; Chaphalkar et al., 2017; Fitriansyah et al., 2018). The antioxidant activity of *P. emblica* has been found efficacious in ameliorating ethanol-induced hepatic damage in a rat model (Chaphalkar et al., 2017). In our previously published preliminary study using *in silico* approach, we reported the drug-likeness and low cytotoxicity of the extracts (Quranayati et al., 2022). As diabetes and its complications are underlined by oxidative stress imbalance, the antioxidant activity of *P. emblica* stem barks is considered a potential therapeutic agent. Based on the explanations, this present study aimed to evaluate the efficacy of *P. emblica* stem bark extracts against diabetic nephropathy and hyperlipidemia *in vivo*.

MATERIAL AND METHODS

Plant material

Upon its collection from the area in Aceh Besar Regency (503'1.2"-5045'9.007"N and 95055'43.6"-94059'50.13"E), the plant sample of *Phyllanthus emblica* was appraised taxonomically in Laboratory of Biology, Universitas Syiah Kuala, Indonesia with the registration number of 150/UN11/1/8.4/TA.00.01/2022. The sample collection and its taxonomy identification were carried out in October 2022. Stem barks were taken from the plant after observing its apparent maturity level.

Extraction

The extraction of *P. emblica* stem barks was performed after the samples were dried (40-50°C for 24 h) and crushed into fine powder. The extraction was carried out on the dried powder (400 g) through maceration using n-hexane, ethyl-acetate, and methanol solvents simultaneously. Maceration for each solvent required 72 h (at room temperature) before the filtrate was collected, and the residue was re-macerated with the next solvent. To remove the solvent, the extract was treated using a rotary evaporator. This procedure yielded n-hexane, ethyl-acetate, and methanol extracts of *P. emblica* stem bark, named after the solvent used during the maceration.

Animal adaptation

The animal treatment in this study followed the Global Guiding Principles of Laboratory Animals (Guillén and Vergara, 2018). The adaptation phase was carried out after retrieving male *Rattus norvegicus* (Wistar rats) (body weight: 200-300 g; age: 2-3 months old). The acclimation was sustained for 1 week (7 days of light-dark cycles), carried out at ambient room temperature (25 ± 1°C), where the rats were fed with fat-rich feed consisting of 45% rice, 5% cheese, 5% vegetable oil, 10% egg yolk, 20% standard feed, and 15% cow's fat. Water was given *ad libitum*. After the 1-week adaptation, the rats were weighed to ensure they were still eligible for the study (body weight above 200 g).

Group randomization and allocation

Group allocation was performed randomly utilizing a web-based randomizer tool (<https://www.randomizer.org/>). The allocation was concealed from the researchers who measured the treatment and parameters. In this study, the rats were allocated into 6 groups: normal, control, n-hexane, ethyl acetate, and methanol. Rats in the normal group

were not injected with STZ and received no treatments. In group control, the rats were only injected with STZ. Meanwhile, groups n-hexane, ethyl acetate, and methanol, other than receiving STZ injection, the rats were treated with n-hexane, ethyl acetate, and methanol extracts of *P. emblica* stem barks, respectively.

Intervention

Except for those treated as healthy control (normal group), after 10-h fasting, all rats were injected with STZ (30 mg/kg body weight; CMC 0.5%) in the lower abdomen following the recommendation from a previously published report (El Maleky et al., 2021). The fasting blood glucose (FBG) was determined on the fourth day after injection. Rats with FBG of more than 200 mg/dL were considered diabetic and included in the study. Rats in the group metformin were given metformin orally with a daily dosage of 60 mg/kg body weight. The extracts (CMC 1% suspension, with administration volume, was adjusted to the rat's body weight) were given to their respective group (n-hexane, ethyl acetate, and methanol) with a daily oral dosage of 200 mg/kg body weight. The consideration of using a single extract concentration was based on our preliminary studies that increasing the concentration would result in toxicity (unpublished). Rats receiving only STZ without metformin or extract were taken as control. The venous blood from each rat was drawn from the tail to inspect the change in blood glucose and total cholesterol levels. At the end of the observation period, the rats were sacrificed by dislocating their cervical spine and dissected to harvest the kidney.

Determination of blood glucose and total cholesterol levels

The freshly collected venous blood was analyzed for blood glucose and total cholesterol levels using GlucoDr.auto© (All Medicus Co., Ltd. Gyeonggi-do, Republic of Korea) and Authocheck© (MDSS GmbH, Hannover, Germany), respectively. These parameters were determined before and after the treatment and expressed as mg/dL.

Histopathological analysis of the kidney

Histopathological analysis was performed to inspect the presence of fat degeneration, hemorrhage, necrosis, and infiltration of inflammatory cells in the kidney. The histology slide of the kidney was stained with Mayer's hematoxylin and Eosin sequentially. The presence of histological abnormalities was observed with the help of a microscope (Olympus CX21, Waltham, MA, USA) magnified for 400×.

Statistical analysis

Statistical analysis was performed on GraphPad Prism 9.2.0 software (GraphPad Software, San Diego, CA, USA) to obtain the descriptive and inferential data. The numerical data were presented as mean ± standard deviation (SD). Statistical significance was assessed based on ANOVA and *post hoc* Tukey analysis. Data obtained before and after the intervention were compared based on paired *t*-test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Reduction of blood glucose

The lowering effect of *P. emblica* stem bark extracts on fasting blood glucose (FBG) level has been presented in Fig. 1. Due to the acute nature of the induced diabetes by STZ, the blood glucose reduced significantly ($p < 0.01$) in the fourth week of observation. On the final day of observation, only the ethyl acetate extract had a significantly lower FBG as compared with group STZ (113.7 ± 15.04 versus 195 ± 19.97 mg/dL; $p < 0.05$). Others, n-hexane and methanol extracts yielded FBG levels of 182 ± 44.31 and 187.7 ± 19.66 mg/dL, respectively, which did not achieve statistical significance ($p > 0.05$). Rats receiving metformin also did not have a significantly lower FBG level than those receiving STZ (158.3 ± 33.17 versus 195 ± 19.97 mg/dL; $p > 0.05$). Taken altogether, the ethyl acetate extract has antihyperglycemic potential. Further analysis, such as the median effective dose of 50, needs to be carried out to confirm the efficacy of the extract.

Previous studies utilizing the fruits of *P. emblica* also indicate the potential of this plant to ameliorate diabetes (Mohanty et al., 2021; Qureshi et al., 2009). Besides blood glucose, the *P. emblica* fruit has been reported to reduce glycosylated hemoglobin (HbA1c) levels (Mohanty et al., 2021; Qureshi et al., 2009). Further, the reduction of HbA1c and advanced glycation end products (AGEs) *in vitro* by the extract from *P. emblica* fruit has been reported (Alsahli et al., 2021). The study also reported high total phenolic and flavonoid contents (39.54 ± 0.046 mg gallic acid equivalent/g and 33.58 ± 0.01 mg quercetin equivalent/g, respectively) (Alsahli et al., 2021). AGEs are elevated in patients with diabetes, and their accumulation has been associated with hyperglycemia and dysregulation of oxidative stress, which could worsen the diabetic condition (Younus and Anwar, 2016). In previous research, phytochemicals identified in *P. emblica*, such as

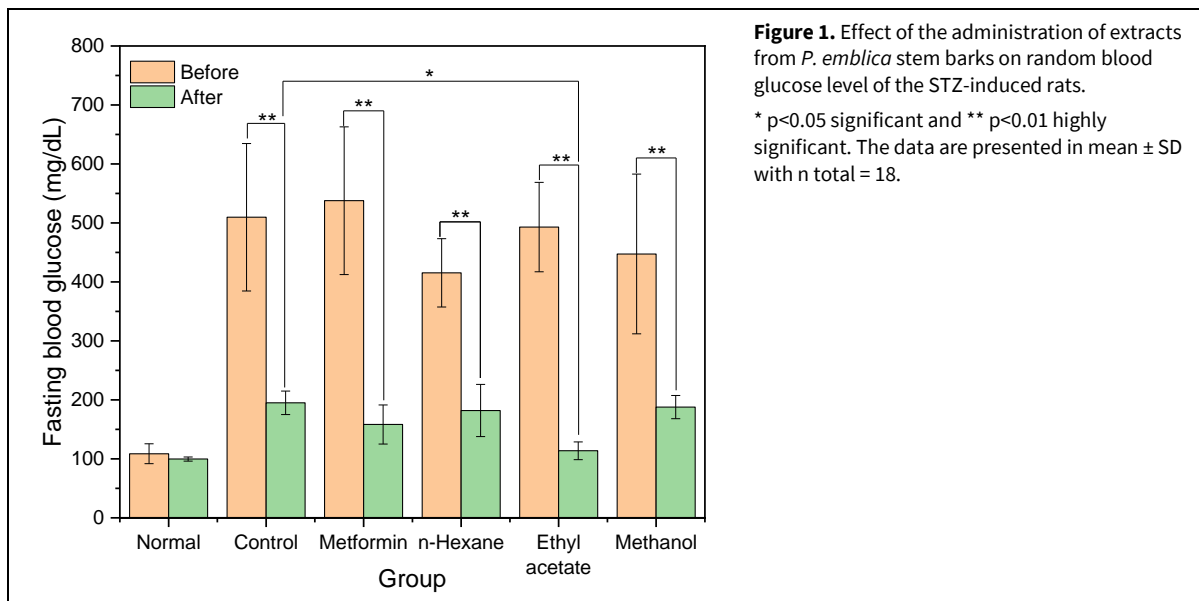


Figure 1. Effect of the administration of extracts from *P. emblica* stem barks on random blood glucose level of the STZ-induced rats. * p<0.05 significant and ** p<0.01 highly significant. The data are presented in mean ± SD with n total = 18.

Table 1. Effect of the administration of extracts from *P. emblica* stem barks on total cholesterol of the STZ-induced rats.

Group	Total cholesterol, mean ± SD (mg/dL)		p-value
	Before	After	
Normal	108.7 ± 16.86 (Ref)	119.3 ± 9.02 (Ref)	0.417
Control	126.7 ± 6.11 [#] (p=0.004)	129.3 ± 18.48 [#] (p=0.008)	0.824
Metformin	126.3 ± 6.66 [#] (p=0.002)	117.0 ± 8.54 (p=0.135)	0.210
n-Hexane	133.7 ± 14.98 [#] (p=0.005)	115.3 ± 14.47 [#] (p=0.021)	0.206
Ethyl acetate	136.3 ± 8.51 [#] (p=0.005)	112.7 ± 13.58 (p=0.984)	0.037*
Methanol	144.0 ± 7.55 [#] (p=0.013)	107.0 ± 7.55 [#] (p=0.014)	0.004*

n total = 18. Control: STZ injection only. [#]Statistically significant at p<0.05 based on *post hoc* Tukey as compared with normal. *Statistically significant at p<0.05 based on paired *t*-test.

gallic acid, quercetin, kaempferol, and catechin, are responsible for antidiabetic activity (Saini et al., 2022).

Profile of blood total cholesterol

After several years of onset, patients with insulin-dependent diabetes are at risk for developing a dyslipidemic condition concomitant to disrupted lipid metabolism (Adiels et al., 2008). This condition is characterized by abnormally increased cholesterol, triglyceride, low-density lipoprotein cholesterol, and a decreased level of high-density lipoprotein cholesterol (Geberemeskel et al., 2019; Yibru, 2014). This condition and the oxidative imbalance could lead to several vascular complications (Iqhrammullah et

al., 2023; Yang et al., 2021). Hence, this study has examined the blood total cholesterol level of the investigated animal, where the results have been presented in Table 1. After the STZ injection, all rats experienced significant increases (p<0.05) in total cholesterol from the baseline. The levels remained stable in control and normal groups at the end of the observation. In rats administered with metformin, even though the reduction of total cholesterol level was not significant (p=0.210), but the level became similar to those in group normal (117.0 ± 8.54 *versus* 119.3 ± 9.02 mg/dL; p=0.135). In the case of ethyl acetate, the total cholesterol was significantly reduced from 136.3 ± 8.51 mg/dL to 112.7 ± 13.58 mg/dL with

p=0.037. The total cholesterol levels between the group normal and group ethyl acetate were not significantly different (119.3 ± 9.02 versus 112.7 ± 13.58 mg/dL). Interestingly, rats treated with methanol had a significant decrease in total cholesterol level (144.0 ± 7.55 versus 107.0 ± 7.55 mg/dL; p=0.004), where the final cholesterol level was even lower as compared with those in group normal (p=0.014).

Effects on diabetic nephropathy

Injection of STZ may induce diabetic nephropathy through an inflammatory cascade involving pro-inflammatory cytokines such as tumor necrosis factor-α and interferon-γ (Mensah-Brown et al., 2005). This allows several studies to employ STZ to induce diabetic nephropathy in animal models (Mestry et al., 2017; Tzeng et al., 2013). In this present study, the histopathological images of the kidney from STZ-

induced diabetic rats and those receiving the treatment have been presented in Fig. 2. The reading results of this histopathological analysis have been presented in Table 2. The pathological findings were found to be significantly higher (p<0.0001) in group STZ, but then reduced significantly (p<0.001) after receiving either metformin or *P. emblica* stem bark extracts. The efficacy of metformin and extracts may be associated with their antioxidant properties. In a clinical trial, metformin has been revealed to significantly reduced the oxidative stress markers among diabetic patients, and it is more efficacious as compared with the healthy lifestyle implementation alone (Esteghamati et al., 2013). As for the extract, the *P. emblica* plant has been found to possess antioxidant properties associated with high contents of phenolic and flavonoid compounds (Alsahli et al., 2021; Ahmad et al., 2021).

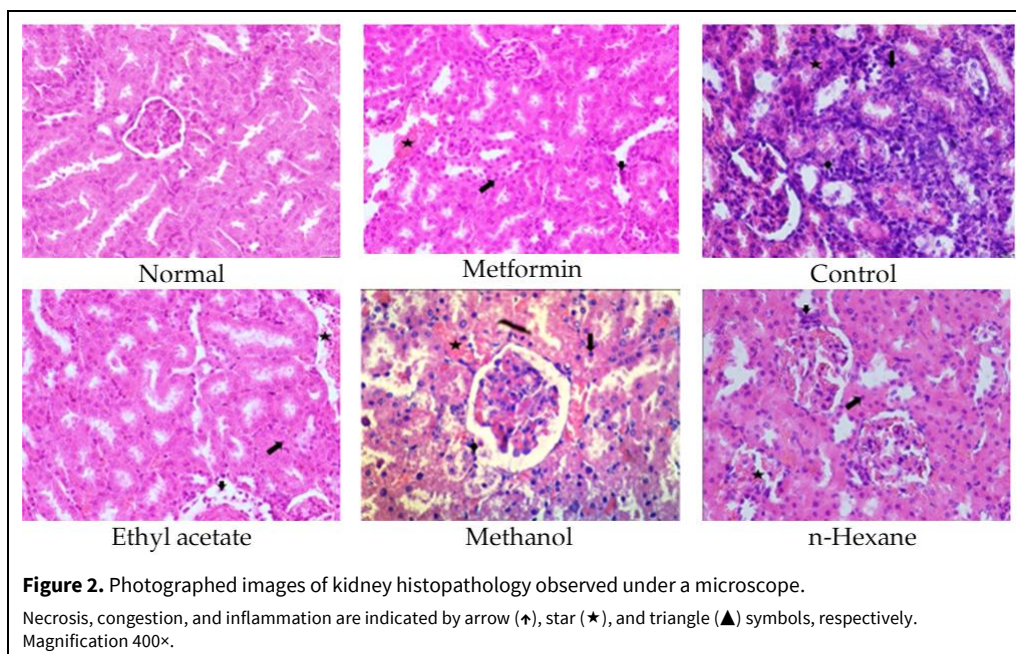


Table 2. Effect of the administration of extracts from *P. emblica* stem barks on the histopathological profile of the kidney.

Group	Necrosis		Inflammation cell		Congestion	
	Mean ± SD	p-value ^a	Mean ± SD	p-value ^a	Mean ± SD	p-value ^a
Normal	8.00 ± 1.000	Ref	6.11 ± 0.5092	Ref	7.89 ± 0.1924	Ref
Control	36.11 ± 0.5092	<0.0001 ^{b*}	38.22 ± 1.953	<0.0001 ^{b*}	31.22 ± 0.8389	<0.0001 ^{b*}
Metformin	15.44 ± 1.644	<0.0001 [*]	8.44 ± 0.3849	<0.0001 [*]	15.67 ± 2.728	<0.0001 [*]
n-Hexane	18.44 ± 0.3849	<0.0001 [*]	20.00 ± 1.528	<0.0001 [*]	17.67 ± 1.764	<0.0001 [*]
Ethyl acetate	16.00 ± 1.856	<0.0001 [*]	17.00 ± 1.732	<0.0001 [*]	17.67 ± 1.202	<0.0001 [*]
Methanol	26.56 ± 1.925	<0.0001 [*]	21.67 ± 1.453	<0.0001 [*]	21.67 ± 1.155	<0.0001 [*]

Total n = 18. Control: STZ injection only. ^aOtherwise stated, the p-value was obtained through a comparison with the control. ^bObtained through a comparison with the healthy group. ^{*}Statistically significant at p<0.05 based on *post hoc* Tukey.

CONCLUSION

The *P. emblica* stem bark extracts prepared in this study could ameliorate STZ-induced nephropathy in a rat model. Hyperlipidemia could be improved by the ethyl acetate and methanol extracts of *P. emblica* stem barks. The ethyl acetate extract exhibited the blood glucose-lowering effect. These findings have never been reported before for *P. emblica* stem barks (previous studies only investigated the fruits or seeds). Further studies are required to elucidate the antidiabetic activity of *P. emblica* stem bark, particularly in the case of diabetic nephropathy.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

- Adak S, Chakraborty D, Maji HS, Basu S, Roy P, Mitra S, Mukherjee N, Barik S, Goswami A (2018) Comparison of the antimicrobial activity of the phyto-constituents obtained from the stem bark and leaf extracts of *Phyllanthus emblica* L. against different strains of *Staphylococcus aureus* and *Salmonella typhi*. Res J Pharmacol Pharmacodyn 10: 53–60. <https://doi.org/10.5958/2321-5836.2018.00009.5>
- Adiels M, Olofsson S-O, Taskinen M-R, Borén J (2008) Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. Arterioscler Thromb Vasc Biol 28: 1225–1236. <https://doi.org/10.1161/atvbaha.107.160192>
- Ahmad B, Hafeez N, Rauf A, Bashir S, Linfang H, Rehman MU, Mubarak MS, Uddin MS, Bawazeer S, Shariati MA, Daglia M, Wan C, Rengasamy KRR (2021) *Phyllanthus emblica*: A comprehensive review of its therapeutic benefits. S Afr J Bot 138: 278–310. <https://doi.org/10.1016/j.sajb.2020.12.028>
- Alsahli M, Anwar S, Alzahrani FM, Almatroudi A, Alfheaid H, Khan AA, Allemailem KS, Almatroodi SA, Rahmani AH (2021) Health promoting effect of *Phyllanthus emblica* and *Azadirachta indica* against advanced glycation end products formation. App Sci 11(19): 8819. <https://doi.org/10.3390/app11198819>
- Andalia N, Salim MN, Saidi N, Ridhwan M, Iqhrammullah M, Balqis U (2022) Molecular docking reveals phytoconstituents of the methanol extract from *Muntingia calabura* as promising α -glucosidase inhibitors. Karbala Int J Mod Sci 8(4): 330–338. <https://doi.org/10.33640/2405-609X.3236>
- Baker C, Retzik-Stahr C, Singh V, Plomondon R, Anderson V, Rasouli N (2021) Should metformin remain the first-line therapy for treatment of type 2 diabetes? Ther Adv Endocrinol Metab 12: 2042018820980225. <https://doi.org/10.1177/2042018820980225>
- Brownlee M (2005) The pathobiology of diabetic complications: a unifying mechanism. Diabetes 54: 1615–1625. <https://doi.org/10.2337/diabetes.54.6.1615>
- Chaphalkar R, Apte KG, Talekar Y, Ojha SK, Nandave M (2017) Antioxidants of *Phyllanthus emblica* L. bark extract provide hepatoprotection against ethanol-induced hepatic damage: A comparison with silymarin. Oxid Med Cell Longev 2017: 3876040. <https://doi.org/10.1155/2017/3876040>
- Dabla PK (2010) Renal function in diabetic nephropathy. World J Diabetes 1(2): 48. <https://doi.org/10.4239/wjd.v1.i2.48>
- El Maleky W, Mahfoz AM, Osman AO, Abd El-Latif HA (2021) Investigation of the impacts of Zamzam water on streptozotocin-induced diabetic nephropathy in rats. In-vivo and in-vitro study. Biomed Pharmacother 138: 111474. <https://doi.org/10.1016/j.biopha.2021.111474>
- Esteghamati A, Eskandari D, Mirmiranpour H, Noshad S, Mousavizadeh M, Hedayati M, Nakhjavani M (2013) Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: A randomized clinical trial. Clin Nutr 32(2): 179–185. <https://doi.org/10.1016/j.clnu.2012.08.006>
- Fitriansyah SN, Aulifa DL, Febriani Y, Sapitri E (2018) Correlation of total phenolic, flavonoid and carotenoid content of *Phyllanthus emblica* extract from Bandung with DPPH scavenging activities. Pharmacog J 10(3): 447–452. <https://doi.org/10.5530/pj.2018.3.73>
- Geberemeskel GA, Debebe YG, Nguse NA (2019) Antidiabetic effect of fenugreek seed powder solution (*Trigonella foenum-graecum* L.) on hyperlipidemia in diabetic patients. J Diabetes Res 2019: 8507453. <https://doi.org/10.1155/2019/8507453>
- Guillén J, Vergara P (2018). Global Guiding Principles: A Tool for Harmonization. In: Guillén, J. (Ed.), Laboratory Animals 2nd ed. Massachusetts: Academic Press. <https://doi.org/10.1016/B978-0-12-849880-4.00001-5>
- Harahap D, Niaci S, Mardina V, Zaura B, Qanita I, Purnama A, Puspita K, Rizki DR, Iqhrammullah M (2022) Antibacterial activities of seven ethnomedicinal plants from family Annonaceae. J Adv Pharm Technol Res 13(3): 148. <https://doi.org/10.4103/japtr.japtr.111.22>
- Huang HZ, Qiu M, Lin JZ, Li MQ, Ma XT, Ran F, Luo CH, Wei XC, Xu RC, Tan P (2021) Potential effect of tropical fruits *Phyllanthus emblica* L. for the prevention and management of type 2 diabetic complications: A systematic review of recent advances. Eur J Nutr 60: 3525–3542. <https://doi.org/10.1007/s00394-020-02471-2>
- Iqhrammullah M, Rizki DR, Purnama A, Duta, TF, Harapan H, Idroes R, Ginting B (2023) Antiviral molecular targets of essential oils against SARS-CoV-2: A systematic review. Sci Pharm 91(1): 15. <https://doi.org/10.3390/scipharm91010015>
- Manna K, Mishra S, Saha M, Mahapatra S, Saha C, Yenge G, Gaikwad N, Pal R, Oulkar D, Banerjee K (2019) Amelioration of diabetic nephropathy using pomegranate peel extract-stabilized gold nanoparticles: assessment of NF- κ B and Nrf2 signaling system. Int J Nanomed 14: 1753–1777. <https://doi.org/10.2147/IJN.S176013>
- Mensah-Brown E, Obineche E, Galadari S, Chandranath E, Shahin A, Ahmed I, Patel S, Adem A (2005) Streptozotocin-induced diabetic nephropathy in rats: The role of inflammatory cytokines. Cytokine 31(3): 180–190. <https://doi.org/10.1016/j.cyto.2005.04.006>
- Mestry SN, Dhodi JB, Kumbhar SB, Juvekar AR (2017) Attenuation of diabetic nephropathy in streptozotocin-induced diabetic rats by *Punica granatum* Linn. leaves extract. J Tradit Complement Med 7(3): 273–280. <https://doi.org/10.1016/j.jtcm.2016.06.008>
- Mohanty IR, Kumar CS, Borde M (2021) Antidiabetic activity of *Commiphora mukul* and *Phyllanthus emblica* and computational analysis for the identification of active principles with dipeptidyl peptidase IV inhibitory activity. Indian J Pharmacol 53(5): 384–387. <https://doi.org/10.4103/ijp.IJP.69.19>

- Nasution R, Mailidar D, Bahi M, Saidi N, Marianne M, Iqhrammullah M (2022) Isolation of the active compound from the bark of *Cinnamomum burmannii* as a sunscreen. *Rasayan J Chem* 15(1): 557-563. <https://doi.org/10.31788/RJC.2022.1516619>
- Quranayati Q, Iqhrammullah M, Saidi N, Nurliana N, Idroes R, Nasution R (2022) Cytotoxicity and phytochemical profiles of *Phyllanthus emblica* stem barks with *in silico* drug-likeness: Focusing on antidiabetic potentials. *J Adv Pharm Technol Res* 13(4): 281. <https://doi.org/10.4103/japtr.japtr.319.22>
- Qureshi SA, Asad W, Sultana V (2009) The effect of *Phyllanthus emblica* Linn on type - II diabetes, triglycerides and liver-specific enzyme. *Pak J Nutr* 8: 125-128. <https://doi.org/10.3923/pjn.2009.125.128>
- Saini R, Sharma N, Oladeji OS, Sourirajan A, Dev K, Zengin G, El-Shazly M, Kumar V (2022) Traditional uses, bioactive composition, pharmacology, and toxicology of *Phyllanthus emblica* fruits: A comprehensive review. *J Ethnopharmacol* 282: 114570. <https://doi.org/10.1016/j.jep.2021.114570>
- Sriwatcharakul S (2020) Evaluation of bioactivities of *Phyllanthus emblica* seed. *Energy Rep* 6 (Supplement 1): 442-447. <https://doi.org/10.1016/j.egyr.2019.08.088>
- Tzeng T-F, Liou S-S, Chang CJ, Liu IM (2013) The ethanol extract of *Zingiber zerumbet* attenuates streptozotocin-induced diabetic nephropathy in rats. *Evid Based Complementary Altern Med* 2013: 340645. <https://doi.org/10.1155/2013/340645>
- Yang Y, Xu P, Liu Y, Chen X, He Y, Feng J (2021) Vascular inflammation, atherosclerosis, and lipid metabolism and the occurrence of non-high albuminuria diabetic kidney disease: A cross-sectional study. *Diab Vasc Dis Res* 18(1): 1479164121992524. <https://doi.org/10.1177/1479164121992524>
- Yibru E (2014) The effects of *Coriandrum sativum* seed extracts on hyperglycemia, lipid profile and renal function in streptozotocin induced type-2 diabetic Swiss albino mice. Thesis: Addis Ababa University.
- Younus H, Anwar S (2016) Prevention of non-enzymatic glycosylation (glycation): Implication in the treatment of diabetic complication. *Int J Health Sci (Qassim)* 10(2): 262-277.

AUTHOR CONTRIBUTION:

Contribution	Quranayati Q	Saidi N	Nurliana N	Idroes R	Gusti N	Nasution R
Concepts or ideas	x	x	x	x		x
Design	x	x	x	x		x
Definition of intellectual content	x					
Literature search	x					
Experimental studies	x					
Data acquisition	x					
Data analysis	x	x	x	x	x	x
Statistical analysis					x	
Manuscript preparation	x					
Manuscript editing		x	x	x	x	x
Manuscript review	x	x	x	x	x	x

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