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Mechanism of Alkaloids and Flavonoids in Bajakah (Uncaria nervosa Elmer) as Antidiabetic Agents

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Abstract
Purpose: Diabetes mellitus is a metabolic disease characterized by hyperglycemic resulting from defects of insulin secretion, insulin action, or both. One of the alternative treatments is bajakah which has antidiabetic activity. This study aims to further discuss the potential and mechanism of alkaloids and flavonoids in bajakah as antidiabetic agents.
Method: This study used the literature review method by searching research data on database and 5 articles included for the review.
Results: Alkaloids have antidiabetic activity through inhibition of AR, PTP1B, activating AMPK, inhibiting DPP-4 and AGEs, increasing glucose absorption, regenerating pancreatic β-cells, inhibiting and inducing GLUT-4, GSK-3, SREB-1, ACC, PPAR, and glucokinase mechanisms. Meanwhile, flavonoids have activity in pancreatic β-cell degradation, increasing insulin secretion and sensitivity, glucose homeostasis, glucose absorption through GLUT-2, inhibiting phosphodiesterase, inhibiting α-glucosidase and α-amylase enzymes, inhibiting apoptosis of pancreatic β-cells, encouraging proliferation, and lowering blood glucose.
Limitation: The limitation in this study is that it only used the literature review method which had a scarcity of the data studied, with lack of research on the cytotoxicity of the bajakah contents, information on the specific doses of the bajakah used, and the duration of treatment. Researcher suggests that more rigorous or experimental research methods be used in further studies to discuss and further explore the effectiveness of bajakah in lowering blood glucose in patients with diabetes mellitus.
Contribution: The findings of this study are expected to be a reference in scientific development in the diabetes mellitus treatment using herbal plants. In addition, it is expected that it can increase further knowledge about the mechanism of bajakah as antidiabetic agents.
Keywords: *antidiabetic, bajakah, diabetes mellitus, secondary metabolites*
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1. Introduction

Diabetes mellitus is a hyperglycemia syndrome accompanied by abnormalities in fat and protein metabolism, caused by defects in insulin secretion and quantity or its combination with insulin resistance (Tjokroprawiro et al., 2015). Diabetes mellitus is classified into four types according to the American Diabetes Association (ADA), namely type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus, and other types of diabetes mellitus. T1DM is caused by destruction of pancreatic β-cells which are mostly caused by autoimmune or idiopathic processes, while T2DM is caused by insulin resistance which eventually leads to pancreatic decompensation to secrete insulin. Diabetes mellitus is diagnosed when the results of the A1C test ≥ 6.5%, impaired fasting glucose (IFG) ≥ 7 mmol/L (≥ 126 mg/dL), 2-h plasma glucose ≥ 11,1 mmol/L (≥ 200 mg/dL), or random blood glucose (RBG) ≥ 11,1 mmol/L (≥ 200 mg/dL) (Tjokroprawiro et al., 2015). Diabetes mellitus

affects 422 million people worldwide, and 1.5 million people die from it each year (World Health Organization, 2023). In Indonesia, diabetes mellitus prevalence has risen from 1.5% in 2013 to 2% in 2018 (Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI, 2018).

One of the treatments for diabetes mellitus is using oral hypoglycemic drugs (Tjokroprawiro et al., 2015). Although synthetic oral hypoglycemic drugs have effectiveness in controlling diabetes mellitus, they have bad side effects. Several drawbacks have been reported associated with the use of these synthetic oral hypoglycemic drugs, including drug resistance or reduced efficiency, side effects, and toxicity. Sulfonylureas, for example, are known to lose effectiveness after 6 years of treatment in around 44% of patients, while glucose-lowering drugs are believed to be ineffective in controlling hyperlipidemia (Salehi et al., 2019). Antidiabetic drugs also have an adverse impact on bone metabolism such as thiazolidinediones which can increase bone loss and fracture risk through activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) in bone marrow cells and inhibit osteoblastogenesis through decreasing runt-related transcription factor-2 (RUNX2), insulin-like growth factor-1 (IGF-1) and wingless-related integration site (Wnt)/β-catenin signaling pathways (Adil et al., 2017; Palermo et al., 2015). In addition, several antidiabetic drugs, such as anagliptin, alogliptin, saxagliptin, linagliptin, vildagliptin, sitagliptin and teneligliptin which belong to gliptin or dipeptidyl peptidase-4 (DPP-4) inhibitors, are associated with varying degrees of adverse or severe cardiovascular side effects (Fisman & Tenenbaum, 2015). It can be concluded that long-term usage of antidiabetic drug therapy can have negative side effects, so developing novel alternative sources of antidiabetic agents from natural sources is an important goal, one of which is using bajakah which has a high content of alkaloids and flavonoids which can be used as antidiabetic agents (Faoziyah et al., 2019).

Bajakah (*Uncaria nervosa* Elmer) is one of the herbal plants that are widely used by the public as herbal medicines because it has activity in curing various conditions, such as wound healing, headaches, ulcers, gastrointestinal disorders, microbial infections, neurological diseases, hypertension, anticancer, asthma medications, antidiabetics, stroke medications, and rheumatism (Ravipati et al., 2014; Zhang et al., 2015). Indole type alkaloids are the most common type of secondary metabolites found in bajakah (Qin et al., 2020; Wang et al., 2018). The main components of indole alkaloids are rhynchophylline and isorhynchophylline with a combination of these two types of alkaloids contributing more than 40% of the total types of alkaloids present (Qin et al., 2020). Meanwhile, flavonoids are phenolic substances that exhibit biological activity, including antidiabetic agents (Panche et al., 2016; Wang et al., 2018), and are found in certain plants that have antioxidant effects (David et al., 2016). Bajakah has 40 types of flavonoids which are classified into flavanol and flavonol. Compound components belonging to the flavanol type include catechins, gallocatechins, catechins-3-gallate, epicatechins, and epigallocatechins. While compounds belonging to the flavonol type include kaempferol, myricetin, and quercetin (Veeramuthu et al., 2017; Zhang et al., 2015).

Based on the description above, it is known that bajakah contains secondary metabolites which have various benefits, one of which is used as antidiabetic agents. Given the increasing prevalence of diabetes mellitus in Indonesia, and synthetic oral hypoglycemic drugs have several negative side effects, treatment efforts to control and normalize blood glucose level in patients with diabetes mellitus must continue. Therefore, researcher wants to discuss further about the potential and mechanism of the alkaloids and flavonoids contained in bajakah as antidiabetic agents.

2. Method

This literature review of published studies on the mechanism of alkaloids and flavonoids in bajakah as antidiabetic agents was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted on the Google Scholar database. The keywords used in the research were “alkaloids”, “flavonoids”, “bajakah”, and “antidiabetic”. The inclusion and exclusion criteria were used during screening. Inclusion criteria include articles with a 5-year term (2018-2023), written in Indonesian or English, and full-text articles, and those that did not meet the inclusion criteria were excluded.

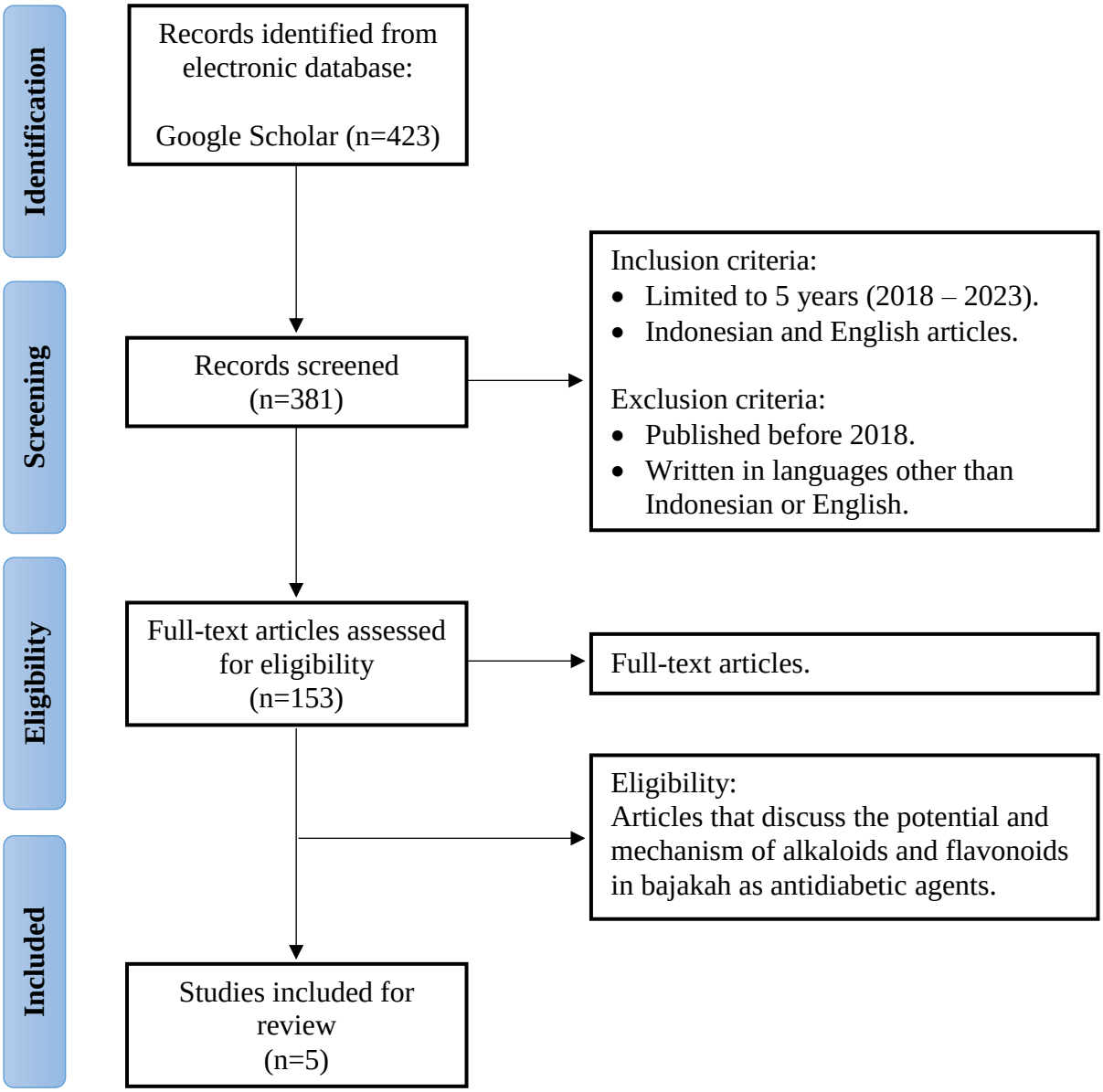

Figure 1. The flow chart of the PRISMA diagram for the study selection process.

3. Result and Discussion

After using a combination of keywords, 423 articles were identified from the database. The articles were then screened acording to the inclusion and exclusion criteria, resulting in 381 remaining articles. Following the review involving inclusion and exclusion criteria, 153 full-text articles were further assessed for eligibility. After this process, only 5 articles included for the review (Figure 1).

Table 1. Summary of the studies included in the review.

No.	Researcher(s)	Title	Result
1.	Annastasya Azzahra, Nurhafiza Farhani, Wulan Syahfitri, Sudana Fatahillah Pasaribu (2022)	Potensi Kandungan Flavonoid dalam Kayu Bajakah Sebagai Antidiabetes	Flavonoids are able to degrade damaged pancreatic β-cells and are able to increase insulin sensitivity and improve insulin receptor performance. Flavonoids inhibit glucose absorption through GLUT-2 in the intestine which can reduce glucose absorption. Flavonoids are able to inhibit phosphodiesterase which results in an increase in cAMP in pancreatic β-cells.

2.	Hamidreza Ardalani, Fatemeh Hejazi Amiri, Amin Hadipanah, Kenneth T. Kongstad (2021)	Potential antidiabetic phytochemicals in plant roots: a review of in vivo studies	Alkaloids have antidiabetic activity as AR inhibitors. In addition, alkaloids are able to activate AMPK. Meanwhile, flavonoids have antidiabetic activities such as glucose homeostasis, use of glucose in peripheral tissues, increase insulin secretion and sensitivity, and inhibit intestinal absorption of glucose.
3.	Francisca Diana Alexandra, Agnes Frethernety, Winney Amiani, Reza Nathasya Aprelea (2023)	Uji Aktivitas Antihiperglikemia Ekstrak Batang *Uncaria gambir* (W.Hunter) Roxb. pada Tikus Diabetes	Flavonoids have effectiveness in lowering blood glucose levels by the mechanism of insulin secretion in pancreatic β-cells. Administration of bajakah stem extract showed activity in reducing blood glucose levels in experimental rats with a decrease of 44.85% (group P3), 40.12% (group P1), 35.12% (group K+), 27.27% (group K-), and 7.12% (group P2).
4.	Dwi Nursyafitri, Ade Ferdinan, Fitri Sri Rizki (2021)	Skrining Fitokimia dan Parameter Non Spesifik Ekstrak Etanol Akar Bajakah (*Spatholobus littoralis* Hassk.)	The results of the screening showed that bajakah contains alkaloids, flavonoids, phenols, saponins and tannins, and there are no terpenoids and steroids in it.
5.	Ni Luh Kade Arman Anita Dewi, Putu Nimas Dyiah Prameswari, Erna Cahyaningsih, Fitria Megawati, Ni Putu Dewi Agustini, Debby Juliadi (2022)	Review: Pemanfaatan Tanaman Sebagai Fitoterapi pada Diabetes Mellitus	Some plants contain metabolites that have antidiabetic activity. Alkaloids have hypoglycemic activity which can regenerate pancreatic β-cells, increase insulin secretion, and lower blood glucose with an extra-pancreatic mechanism. Meanwhile, flavonoids have a role as inhibitors of the enzymes α-glucosidase, maltase and α-amylase, and stimulate glucose uptake in the muscles.

Bajakah contains more than 200 secondary metabolites, among which the most common are alkaloids and flavonoids (Flores-Sanchez & Ramos-Valdivia, 2017; Maulina et al., 2019). Phytochemical testing conducted by Maulina et al. (2019) showed the results of the secondary metabolite content in bajakah in the form of alkaloids, flavonoids, and terpenoids. Meanwhile, in the research of Nursyafitri et al. (2021), the phytochemical screening on bajakah contained secondary metabolites of alkaloids, flavonoids, saponins, tannins, and phenols. Qin et al. (2020) added that alkaloids and flavonoids are the most abundant secondary metabolites in bajakah. From the studies above showed that alkaloids and flavonoids are the most abundant secondary metabolites contained in bajakah. In a literature review conducted by Ridho (2020), it added that secondary metabolites in bajakah are classified more specifically, with the most common alkaloids being rhynchophylline and isorhynchophylline, and the most common flavonoids being flavanol and flavonol. It can be seen that of the more than 200 secondary metabolites contained in bajakah, two of them, alkaloids and flavonoids, are most commonly found in bajakah. With various studies on the potential of existing, it seems that bajakah is still rarely studied regarding its potential and mechanism as antidiabetic agents. Several studies have shown a lot of potential of alkaloids and flavonoids in lowering blood glucose levels in people with diabetes mellitus. In bajakah, alkaloids have antidiabetic activity through inhibiting aldose reductase (AR) and protein tyrosine phosphatase-1B (PTP1B). Inhibition of AR can decrease intracellular sorbitol and its metabolite, fructose, resulting in osmotic swelling and cell malfunction. Inhibition of PTP1B by alkaloids aids in the treatment of diabetes mellitus and its related complications because inhibition of this protein results in increased insulin receptor and insulin receptor substrate 1 and 2 phosphorylation leading to increased glucose uptake in the blood (Adhikari, 2021). In addition, alkaloids are able to

activate 5-adenosine monophosphate-activated protein kinase (AMPK) in the liver which can significantly reduce gluconeogenic and lipogenic gene, which functions to increase insulin sensitivity and lower blood glucose levels (Ardalani et al., 2021). Alkaloids also have activity in inhibiting DPP-4, digestive enzymes, increasing glucose absorption, and inhibiting advanced glycation end products (AGEs) and antioxidant activity (Adhikari, 2021). Thus, if DPP-4 is inhibited by alkaloids, it will convert glucagon-like peptide-1 (GLP-1) into its metabolites which play a role in stimulating insulin release and improving insulin sensitivity, which results in regulating blood glucose levels. In addition, inhibition of AGEs will also limit tissue damage, slow disease progression and improve quality of life (Mulatsari et al., 2019).

Alkaloids have the ability to regenerate pancreatic β-cells, lower blood glucose, and increase insulin secretion by extra-pancreatic mechanisms by stimulating glycogen synthesis, the mechanism of glucose transport in the intestine, and inhibiting glucose synthesis by inhibiting glucose 6-phosphatase and fructose 1,6-bisphosphatase which are enzymes that have a role in gluconeogenesis, and increase glucose oxidation through glucose 6-phosphate dehydrogenase. The inhibition of the glucose 6-phosphatase and fructose 1,6-bisphosphatase enzymes will result in a decrease in the formation of glucose from non-carbohydrate substrates. Other than that, alkaloids work by inhibiting or inducing glucose transporter-4 (GLUT-4), glycogen synthase kinase-3 (GSK-3), sterol regulatory element-binding proteins-1 (SREBP-1), glucokinase, acetyl-CoA carboxylase (ACC), and peroxisome proliferator-activated receptor (PPAR). In muscle cells and adipose tissue, insulin stimulates the delivery of GLUT-4 from intracellular locations to the cell surface, where GLUT-4 facilitates the reduction of plasma glucose levels, so that the administration of this alkaloid will affect GLUT-4 which in turn helps lower blood glucose levels. Whereas GSK-3 has an important role in regulation of the cell cycle of the Wnt and Hedgehog pathways, stem cell renewal and differentiation, apoptosis, circadian rhythms, transcription, and including regulation of insulin action, so that inhibition of GSK-3 by alkaloids can regulate blood glucose levels, accompanied by with increased expression of PPAR which can increase insulin sensitivity (Dewi et al., 2022; Kumar et al., 2019; Muhammad et al., 2021). So, it can be seen that besides alkaloids can lower blood glucose levels through extra-pancreatic mechanisms, they are also able to regenerate pancreatic β-cells.

Flavonoids are able to degrade damaged pancreatic β-cells and are able to increase insulin secretion and sensitivity, improve insulin receptor performance, glucose homeostasis, and use of glucose in peripheral tissues. Flavonoids can also inhibit glucose absorption through glucose transporter-2 (GLUT-2) in the intestinal mucosa which can reduce glucose absorption. Epigallocatechin 3-gallate, a type of flavonoids, are able to inhibit phosphodiesterase which results in an increase in cyclic adenosine monophosphate (cAMP) in pancreatic β-cells. Flavonoids have antidiabetic activities such as glucose homeostasis, increasing insulin secretion and sensitivity, glucose utilization in peripheral tissues, and inhibiting glucose absorption in the intestine (Al-Ishaq et al., 2019; Ardalani et al., 2021; Azzahra et al., 2022; Hussain et al., 2020; Jain et al., 2021; Sari, 2022). Many of the physiological effects of cAMP enhanced by flavonoids will be mediated via cAMP-dependent protein kinase (PKA) activation. Glucose homeostasis is regulated by the cAMP/PKA signaling pathway on numerous levels, including insulin and glucagon release, glucose absorption, glycogen synthesis and breakdown, gluconeogenesis, and neural control of glucose homeostasis (Yang & Yang, 2016). So, it can be concluded that flavonoids can also degrade damaged pancreatic β-cells besides being able to regulate blood glucose levels through GLUT-2 and cAMP.

Another role of flavonoids is as inhibitors of α-glucosidase and α-amylase enzymes (Dewi et al., 2022). The α-glucosidase and α-amylase enzymes are involved in the breakdown of starch into glucose, which causes an insulin response to lower blood glucose levels when the concentration of glucose increases in the blood. This is related to diabetes mellitus when there is insulin resistance. As a result, if the activity of these enzymes can be lowered, the risk of diabetes mellitus in people is decreased (Cahyana & Adiyanti, 2021). In addition, quercetin, a type of flavonoid found in bajakah, has activity in increasing insulin resistance by reducing oxidative stress and pancreatic β-cell death. Besides that, the flavonoid kaempferol has the ability to protect pancreatic β-cells, inhibit pancreatic β-cell apoptosis, encourage

proliferation, and lower blood glucose and blood lipids (Li et al., 2019). This is in accordance with research that gave bajakah stem extract to experimental rats and showed activity in reducing blood glucose levels in experimental rats with a decrease of 44.85% (group P3), 40.12% (group P1), 35.12% (group K+), 27.27% (group K-), and a decrease of 7.12% (group P2) (Alexandra et al., 2023). Based on the results of the review of the articles above, it showed that alkaloids and flavonoids in bajakah have activity in lowering blood glucose levels in people with diabetes mellitus. It is possible that bajakah has good potential to be used as antidiabetic agents. Moreover, research on the activity of the content of secondary metabolites in bajakah is still rarely conducted in Indonesia, thus providing a great opportunity for further research to explore more about the activity of bajakah, especially its activity as antidiabetic agents.

4. Conclusion

This literature review used 5 reviewed articles and the conclusion from this literature review indicates the potential of bajakah to be used as a treatment for diabetes mellitus because secondary metabolite content, such as alkaloids and flavonoids, can lower blood glucose levels through inhibiting AR, PTP1B, DPP-4, AGEs, phosphodiesterase, α-glucosidase and α-amylase enzymes, and apoptosis of pancreatic β-cells, inhibiting and inducing GLUT-4, GSK-3, SREB-1, ACC, PPAR, and glucokinase mechanisms, activating AMPK, increasing glucose absorption, insulin secretion and sensitivity, glucose homeostasis, and glucose absorption through GLUT-2. In addition, bajakah also has activity in pancreatic β-cell degradation and pancreatic β-cells regeneration. The findings in this literature review allows the opportunity to conduct further research regarding the effectiveness of bajakah as antidiabetic agents.

Limitation and Suggestion

The limitation in this study is that it only used the literature review method which had a scarcity of the data studied, with lack of research on the cytotoxicity of the bajakah contents, information on the specific doses of the bajakah used, and the duration of treatment. Researcher suggests that more rigorous or experimental research methods be used in further studies to discuss and further explore the effectiveness of bajakah in lowering blood glucose in patients with diabetes mellitus.

References

Adhikari, B. (2021). Roles of Alkaloids from Medicinal Plants in the Management of Diabetes Mellitus. In *Journal of Chemistry* (Vol. 2021). Hindawi Limited. https://doi.org/10.1155/2021/2691525

Adil, M., Khan, R. A., Kalam, A., Venkata, S. K., Kandhare, A. D., Ghosh, P., & Sharma, M. (2017). Effect of anti-diabetic drugs on bone metabolism: Evidence from preclinical and clinical studies. *Pharmacological Reports*, *69*(6), 1328–1340. https://doi.org/10.1016/J.PHAREP.2017.05.008

Alexandra, F. D., Frethernety, A., Amiani, W., & Aprelea, R. N. (2023). Uji Aktivitas Antihiperglikemia Ekstrak Batang Bajakah Tampala (Uncaria gambir (W.Hunter) Roxb) pada Tikus Diabetes. *Jurnal Kedokteran Universitas Palangka Raya*, *11*(1). https://doi.org/10.37304/jkupr.v11i1.8577

Al-Ishaq, R. K., Abotaleb, M., Kubatka, P., Kajo, K., & Büsselberg, D. (2019). Flavonoids and their anti-diabetic effects: Cellular mechanisms and effects to improve blood sugar levels. *Biomolecules*, *9*(9). https://doi.org/10.3390/biom9090430

Ardalani, H., Hejazi Amiri, F., Hadipanah, A., & Kongstad, K. T. (2021). Potential antidiabetic phytochemicals in plant roots: a review of in vivo studies. In *Journal of Diabetes and Metabolic Disorders* (Vol. 20, Issue 2, pp. 1837–1854). Springer Science and Business Media Deutschland GmbH. https://doi.org/10.1007/s40200-021-00853-9

Azzahra, A., Farhani, N., Syahfitri, W., & Pasaribu, S. F. (2022). Potensi Kandungan Flavonoid Dalam Kayu Bajakah Sebagai Antidiabetes. *Jurnal Pendidikan Tambusai*, *6*(2), 14345–14350.

Cahyana, Y., & Adiyanti, T. (2021). Review: Flavonoids as antidiabetic agents. *Indonesian Journal of Chemistry*, *21*(2), 512–526. https://doi.org/10.22146/ijc.58439

David, A. V. A., Arulmoli, R., & Parasuraman, S. (2016). Overviews of biological importance of quercetin: a bioactive flavonoid. In *Pharmacognosy Reviews* (Vol. 10, Issue 20, pp. 84–89). Medknow Publications. https://doi.org/10.4103/0973-7847.194044

Dewi, N. L. K. A. A., Prameswari, P. N. D., Cahyaningsih, E., Megawati, F., Agustini, N. P. D., & Juliadi, D. (2022). Review : Pemanfaatan Tanaman Sebagai Fitoterapi pada Diabetes Mellitus. *Jurnal Integrasi Obat Tradisional*, *2*(1), 2963–2161. https://usadha.unmas.ac.id

Faoziyah, A. R., Rahmah, N. N., & Febriani, L. (2019). Pemanfaatan Tanaman Obat Sebagai Obat Tradisional sebagai Alternatif Pengobatan Herbal Pasien Hipertensi dan Diabetes Mellitus. In *Jurnal Pengabdian Masyarakat Al-Irsyad: Vol. I* (Issue 2).

Fisman, E. Z., & Tenenbaum, A. (2015). Antidiabetic treatment with gliptins: Focus on cardiovascular effects and outcomes. In *Cardiovascular Diabetology* (Vol. 14, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s12933-015-0294-0

Flores-Sanchez, I. J., & Ramos-Valdivia, A. C. (2017). A review from patents inspired by two plant genera: Uncaria and Hamelia. *Phytochemistry Reviews*, *16*(4), 693–723. https://doi.org/10.1007/s11101-017-9498-0

Hussain, T., Tan, B., Murtaza, G., Liu, G., Rahu, N., Saleem Kalhoro, M., Hussain Kalhoro, D., Adebowale, T. O., Usman Mazhar, M., Rehman, Z. ur, Martínez, Y., Akber Khan, S., & Yin, Y. (2020). Flavonoids and type 2 diabetes: Evidence of efficacy in clinical and animal studies and delivery strategies to enhance their therapeutic efficacy. *Pharmacological Research*, *152*. https://doi.org/10.1016/j.phrs.2020.104629

Jain, N., Mohan, S. C., & Sumathi, S. (2021). Mechanisms of Action of Flavonoids in the Management of Diabetes mellitus. *Journal of Drug Delivery and Therapeutics*, *11*(5-S), 194–202. https://doi.org/10.22270/jddt.v11i5-s.5101

Kumar, A., Aswal, S., Semwal, R. B., Chauhan, A., Joshi, S. K., & Semwal, D. K. (2019). Role of plant-derived alkaloids against diabetes and diabetes-related complications: a mechanism-based approach. In *Phytochemistry Reviews* (Vol. 18, Issue 5, pp. 1277–1298). Springer. https://doi.org/10.1007/s11101-019-09648-6

Li, J., Bai, L., Li, X., He, L., Zheng, Y., Lu, H., Li, J., Zhong, L., Tong, R., Jiang, Z., & Shi, J. (2019). Antidiabetic potential of flavonoids from traditional Chinese medicine: A review. In *American Journal of Chinese Medicine* (Vol. 47, Issue 5, pp. 933–957). World Scientific Publishing Co. Pte Ltd. https://doi.org/10.1142/S0192415X19500496

Maulina, S., Pratiwi, D. R., & Erwin, E. (2019). Skrining fitokimia dan bioaktivitas ekstrak akar Uncaria nervosa Elmer (bajakah). *Jurnal Atomik*, *4*(2), 100–102.

Muhammad, I., Rahman, N., Gul-E-nayab, Nishan, U., & Shah, M. (2021). Antidiabetic activities of alkaloids isolated from medicinal plants. *Brazilian Journal of Pharmaceutical Sciences*, *57*. https://doi.org/10.1590/s2175-97902020000419130

Mulatsari, E., Mumpuni, E., & Ramadhan, I. (2019). Skrining Virtual dan Elusidasi Moda Ikatan Senyawa dalam Bawang Putih (Allium sativum L.) sebagai Penghambat Reseptor Advanced Glycation End Products (Screening Virtual and Binding Mode Elucidation of Compounds in Garlic (Allium sativum L.) as an Inhibitor Advanced Glycation End Products Receptor). *JURNAL ILMU KEFARMASIAN INDONESIA*, *17*(2), 210–217. http://www.tcd.uni-

Nursyafitri, D., Ferdinan, A., Sri, F., Farmasi, R. A., & Pontianak, Y. (2021). Skrining Fitokimia dan Parameter Non Spesifik Ekstrak Etanol Akar Bajakah (Spatholobus littoralis Hassk.). *Jurnal Farmasi IKIFA*, *1*(1).

Palermo, A., D'Onofrio, L., Eastell, R., Schwartz, A. V., Pozzilli, P., & Napoli, N. (2015). Oral anti-diabetic drugs and fracture risk, cut to the bone: safe or dangerous? A narrative review. In *Osteoporosis International* (Vol. 26, Issue 8, pp. 2073–2089). Springer London. https://doi.org/10.1007/s00198-015-3123-0

Panche, A. N., Diwan, A. D., & Chandra, S. R. (2016). Flavonoids: an overview. *Journal of Nutritional Science*, *5*(c47), 1–15. https://doi.org/10.1017/jns.2016.41

Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI. (2018). *Laporan Riset Kesehatan Dasar*.

Qin, N., Lu, X., Liu, Y., Qiao, Y., Qu, W., Feng, F., & Sun, H. (2020). Recent research progress of Uncaria spp. based on alkaloids: phytochemistry, pharmacology and structural chemistry. *European Journal of Medicinal Chemistry*. https://doi.org/10.1016/j.ejmech.2020.112960

Ravipati, A. S., Reddy, N., & Koyyalamudi, S. R. (2014). Biologically active compounds from the genus Uncaria (Rubiaceae). *Studies in Natural Products Chemistry*, *43*, 381–408. https://doi.org/10.1016/B978-0-444-63430-6.00013-8

Ridho, F. M. (2020). *Kandungan Metabolit Sekunder dari Ekstrak Kayu Bajakah (Uncaria nervosa Elmer) dan Bioaktivitasnya Sebagai Antikanker* [Universitas Airlangga]. http://lib.unair.ac.id

Salehi, B., Ata, A., V. Anil Kumar, N. V. A., Sharopov, F., Ramírez-Alarcón, K., Ruiz-Ortega, A., Abdulmajid Ayatollahi, S. A., Tsouh Fokou, P. V. T., Kobarfard, F., Amiruddin Zakaria, Z. A., Iriti, M., Taheri, Y., Martorell, M., Sureda, A., Setzer, W. N., Durazzo, A., Lucarini, M., Santini, A., Capasso, R., … Sharifi-Rad, J. (2019). Antidiabetic Potential of Medicinal Plants and Their Active Components. *Biomolecules*, *9*(10), 551. https://doi.org/10.3390/biom9100551

Sari, W. P. (2022). Potensial Terapi Antikanker Melalui Senyawa Bioaktif dari Nutrasetikal. *Jurnal Ilmu Medis Indonesia*, *1*(2), 59–70. https://doi.org/10.35912/jimi.v1i2.922

Tjokroprawiro, A., Setiawan, P. B., Effendi, C., Santoso, D., & Soegiarto, G. (2015). *Buku Ajar Ilmu Penyakit Dalam* (2nd ed.). Airlangga University Press.

Veeramuthu, D., Raja, W. R. T., Al-Dhabi, N. A., & Savarimuthu, I. (2017). Flavonoids: Anticancer Properties. In *Flavonoids - From Biosynthesis to Human Health* (pp. 287–303). InTech. https://doi.org/10.5772/68095

Wang, T., Li, Q., & Bi, K. (2018). Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. *Asian Journal of Pharmaceutical Sciences*, *13*(1), 12–23. https://doi.org/10.1016/j.ajps.2017.08.004

World Health Organization. (2023). *Diabetes*. https://www.who.int/health-topics/diabetes#tab=tab_1

Yang, H., & Yang, L. (2016). Targeting cAMP/PKA pathway for glycemic control and type 2 diabetes therapy. In *Journal of Molecular Endocrinology* (Vol. 57, Issue 2, pp. R93–R108). BioScientifica Ltd. https://doi.org/10.1530/JME-15-0316

Zhang, Q., Zhao, J. J., Xu, J., Feng, F., & Qu, W. (2015). Medicinal uses, phytochemistry and pharmacology of the genus Uncaria. *Journal of Ethnopharmacology*, *173*, 48–80. https://doi.org/10.1016/j.jep.2015.06.011