HYDROGEN
JURNAL KEPENDIDIKAN KIMIA
http://ojs.ikipmataram.ac.id/index.php/hydrogen/index

June 2023. 11(3)
e-ISSN: 2656-3061
p-ISSN: 2338-6487
pp. 286-295

Inhibition of α-Glucosidase Enzyme by Ethanol Extract of *Kratom* Leaf Variant (*Mitragyna speciosa* Korth.)

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Article History
Received: 10-05-2023
Revised: 31-05-2023
Published: 15-06-2023

Keywords enzim α-glukosidase, *Mitragyna speciosa* korth., diabetes melitus,ethanol extract

Abstract
Diabetes mellitus characterized by acute hyperglycemia has become a worldwide epidemic. One plant in Indonesia that has empirical potential as an antidiabetic is *kratom* (*Mitragyna speciosa* Korth.). There are 3 types of *kratom* variants that are widely used by the public, namely green, red, and white *kratom* variants. This variant is distinguished by the presence of veins on *kratom* leaves. However, antidiabetic research with the mechanism of inhibition of the enzyme α-glucosidase from *kratom* leaves red, green, and white variants has not been widely studied. This study aims to determine the inhibitory activity of α-glucosidase enzyme by *Kratom* Leaf Ethanol Extract (*Mitragyna speciosa* Korth.) Various variants. Green, red and white variant *kratom* leaf powder macerated with 96% ethanol for 72 hours, and inhibition of α-glucosidase enzyme activity using ethanol extract and akarbose as positive control. In vitro testing was carried out using a microplate reader with a wavelength of 405 nm. Ethanol extract of *kratom* leaf red, green, and white variants of 96% at a concentration of 500 µg/ml can inhibit the activity of α-glucosidase enzymes by 10.57%, 13.06%, and 5.33%, respectively. This shows that the three *kratom* variants have activity as inhibitors of α-glucosidase enzymes but are classified as very weak, with IC50>200 µg / ml. The inhibitory activity of all three extracts differed markedly ($p<0.05$). This difference can be caused by the content of secondary metabolites in each variant of *Kratom*.

How to Cite: Wijayanti, D., Masriani, M., Fadly, D., Muharini, R., & Rasmawan, R. (2023). Inhibition of α-Glucosidase Enzyme by Ethanol Extract of *Kratom* Leaf Variant (*Mitragyna speciosa* Korth.). Hydrogen: Jurnal Kependidikan Kimia, 11(3), 286-295. doi:https://doi.org/10.33394/hjkk.v11i3.7776

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INTRODUCTION

Diabetes mellitus characterized by acute hyperglycemia has become a worldwide epidemic. Indonesia ranks 5th after India, China, America, and Brazil from the number of people with diabetes mellitus (IDF Atlas., 2022). The International Diabetes Federation (IDF) reports that around 537 million people worldwide suffer from diabetes with a mortality rate of 6.7 million each year (WHO, 2022). This figure is expected to increase to 783 million by 2045. Diabetes poses an economic burden of 966 billion USD or about 17% of the total health budget in the world (IDF Atlas., 2022). The total cost incurred by JKN (National Health Insurance) amounted to 6.1 trillion for the treatment of diabetes and its complications. The cost needed by patients without complications is 5.4 million/person/year and for the treatment of complications is 14 million/person/year (Patty, Mufarrihah, and Nita 2021). This data shows the urgent need to implement strategies to overcome and reduce mortality from diabetes mellitus.

The main and effective strategy to improve the condition of diabetes is to control post-prandial hyperglycemia (Nguelefack et al., 2020). α-glucosidase inhibitors as one of the antidiabetes mellitus ingredients that work by inhibiting the enzyme α-glucosidase, the main enzyme responsible for the hydrolysis process of oligosaccharides and disaccharides into monosaccharides (Hamid et al., 2015). Inhibition of α-glucosidase in diabetics lowers post-prandial glucose levels by delaying glucose absorption (Mataputun, Rorong, and Pontoh 2013). α-glucosidase inhibitors such as akarbose, voglibose, miglitol, and nojirimicin have been widely used as antidiabetics and have been shown to be effective in reducing hyperglycemia, but have side effects and increase diabetes complications. Given the side effects caused by oral drugs, natural α-glucosidase inhibitors from plants can be used as an alternative to the pharmacological therapy of diabetes mellitus. Some natural plants have shown activity as α-glucosidase inhibitors such as cat's whiskers (Orthosiphon aristatus) (Yuliana et al., 2016), bungur (Lagerstroemia speciosa (L.) Pers) (Riyanti, MA, and E 2021), okra fruit (Abelmoschus esculentus (L) Moench), Dutch teak leaves (Guazuma ulmifolia), black sticky rice (Oryza sativa Var glutinosa) (Budiman, 2011), and Simpur (Dillenia suffrutticosa) (Elmaniar and Muhtadi 2017; Mahargyani 2019; Masriani, Fadly, and Bohari 2020; Mohamed et al. 2012). One plant that has potential as an inhibitor of α-glucosidase is *kratom*.

Kratom (Mitragyna speciosa Korth.) nicknamed the leaf of paradise from Borneo, is a plant from the Rubiaceae family. This plant is widely found in West Kalimantan, especially in Kapuas Hulu Regency. Based on the color of the leaf veins, *kratom* plants are divided into three variants, namely red *kratom*, green *kratom*, and white *kratom* (Figure 1). The three variants have different activities. The red vein variant tends to be a strong pain reliever, the white vein variant tends to increase endurance, and the green variant tends to increase excitement (Warner, Kaufman, and Grundmann 2015).

(a) (b) (c)

Figure 1. *Kratom* Leaf Pictures (a) White veins, (b) Green veins, (c) Red veins

(personal documentation)

Traditionally *kratom* has been used by the people of Indonesia, Malaysia and Thailand to increase stamina, treat diarrhea, stomach pain, insomnia, cholesterol, gout and diabetes (Prozialeck et al., 2020; Purintrapiban et al., 2011). Several empirical properties have been tested and proven that *kratom* leaves have pharmacological effects including analgesics (Nugraha, Robiyanto, and Luliana, 2018), antinociceptives (Luliana &; Islamy, 2018), antidiarrheal (Suhaimi Dian, 2020), antibacterial (Suhaimi, Puspasari, and Apriani, 2019), antioxidants (Setyawati, 2020), and have cytotoxic effects on breast cancer cells (Ikhwan, Harlia, and Widiyantoro, 2018).

Kratom leaves are known to have 57 compounds dominated by alkaloids and other compounds including flavonoids, phenolics, triterpenoids, and saponins (Meireles et al., 2019). The content of alkaloids, phenolics and flavonoids is known to have the ability to deal with diabetes problems. Alkaloids work as antidiabetics through various mechanisms including signaling pathways, inhibition, stimulation of various systems such as PTP-1B blockade, improving insulin sensitivity, modulating oxidative stress and inhibition of α-glucosidase enzymes (Ajebli, Khan, and Eddouks 2020). In the study of Yin et al (2014) mentioned that alkaloids and phenolics from several types of extractive substances showed inhibitory activity of α-glucosidase. Examples are alkaloid compounds isolated from Adhatoda vasica Nees leaves, deoxynojirimin isolated from adenophores, phagomine alkaloids and cytidine from Orus atropurpurea leaves which show stronger inhibitory potential than akarbose (Zhenhua Yin, Wei Zhang, Fajin Feng, Yong Zhang 2014)

Research on the biological activity of *kratom* leaves has been widely conducted, including as analgesics, antinociceptives, antidiarrheals, antibacterials, and antioxidants (Meireles et al., 2019; Ramanathana et al., 2021). However, research related to activity on three types of *kratom* leaves, namely red, green and white *kratom* as inhibitors of the enzyme α-glucosidase has not existed. Not yet known with certainty the value of inhibition in ethanol extract of *kratom* leaf powder (M. speciosa Korth.) Green, red, and white variants and which extracts have the best potential in inhibiting the enzyme α-glucosidase. Therefore, research was conducted on the inhibitory activity of the three *kratom* variants against the enzyme α-glycosidase.

METHOD

Tools and Materials

The tools used consist of drying cabinets, incubators, analytical balances, vortexes, pH meters, centrifuges, microplate readers, cuvettes, microtubes, micropipettes, freezers, and laboratory glassware. The plant material used in this study was green, red, and white *kratom* leaves (*Mitragyna speciosa* korth.). The chemicals used are 96% ethanol, Na_2CO_3, dimethyl sulfoxide (DMSO), α-glucosidase enzymes, p-Nitrophenyl-α-D'glucopyranoside (p-NPG), akarbase tablets, and aquades.

Extraction

A total of 200 grams of *kratom* leaf powder each (green, red and white powder) was macerated with 96% ethanol solvent at room temperature for 3 days and stirring was done every 1x24 hours then the filtrate was separated from the pulp. Repeated extraction process for 2 times in the same way. The result is an extract which is then concentrated using a waterbath at a temperature of 50 ° C until a concentrated extract is formed. The extract was then used to test the inhibitory activity of the enzyme α-glucosidase (Masriani et al., 2023).

α-Glucosidase Enzyme Activity Test

Testing the activity of α-glucosidase enzyme refers to research (Masriani et al. 2020). A mixture of 150 L samples with a concentration range of 15.625-500 µg/mL; and 100 µL of 0.1 M sodium phosphate buffer (pH = 6.8) containing the enzyme α-glucosidase (0.1 µg/mL) were incubated for 10 min at 37 °C. After pre-incubation, 200 µL of 1 mM solution pNPG was added in 0.1 M sodium phosphate buffer (pH = 6.8). Next, incubated for 30 minutes at 37°C. After pre-incubation, 200 µL of 1 mM solution pNPG was added in 0.1 M sodium phosphate buffer (pH = 6.8). Next, incubated for 30 minutes at 37°C. Then, 1.0 mL of 0.1 M Na2CO3 solution was added. The inhibition activity of the enzyme α-glucosidase was determined by measuring the yellow color of p-nitrophenol released by pNPG at a wavelength of 405 nm (Masriani et al., 2020). Akarbose is used as a positive control. The percentage of inhibition activity of the enzyme α-glucosidase is calculated by the following equation:

$$\%\text{Inhibition} = \frac{\text{control absorbance} - \text{sample absorbance}}{\text{control absorbance}} x100$$

The IC_{50} value of each sample is expressed in a linear regression equation with a y value equal to 50 and the x value to be determined is the value of IC_{50}.

Data Analysis

The data obtained in this study was expressed by averaging ± standard deviations from three tests. Next, it was analyzed using the SPSS program version 21.0 with the ANOVA One Way method and Tukey to determine the average difference among the samples. If a sig value of $p < 0.05$ is obtained, it is stated that there is a significant difference in the sample (Nasution, 2018).

RESULTS AND DISCUSSION

Sample Extraction

The extraction of three dry *kratom* variants powder was carried out by maceration method. This method uses the principle of solubility, namely polar compounds will dissolve in polar solvents, vice versa nonpolar compounds will dissolve in non-polar solvents (Ministry of Health RI, 2005). The solvent used is 96% ethanol because this solvent is able to dissolve polar compounds, volatile, non-toxic, and the work is safer for all secondary metabolites (Mardhiani et al., 2018). The hydroxyl group in ethanol plays a role in dissolving polar ions and molecules, while the alkyl group is responsible for binding non-polar compounds. This characteristic causes ethanol to dissolve polar and nonpolar compounds well (Bayani, 2016).

The extraction results on the three types of *kratom* leaves produce different yields, where in green *kratom* the yield obtained is dark brown with a stickier texture resembling caramel, while in red and white *kratom* the yield obtained is deep brown and has a texture that is not too sticky and less dense (Figure 2.)

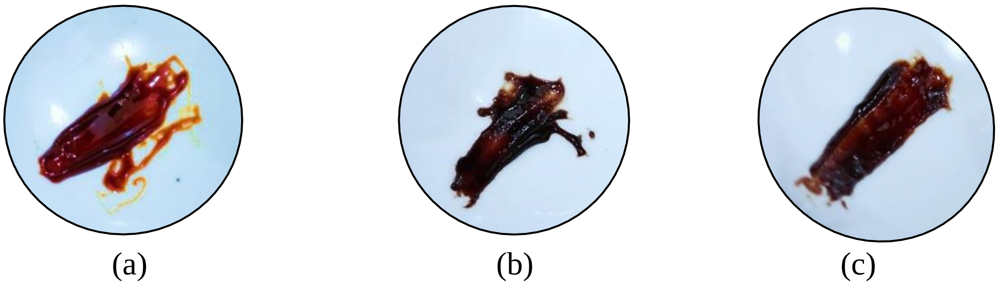

Figure 2. *Kratom* leaf extract (a) green *kratom*, (b) red *kratom*, (c) white *kratom* red *kratom*

α-Glucosidase Enzyme Activity Test

Diabetes mellitus is an endocrine disease characterized by hyperglycemia. There are 2 types of diabetes that are most commonly suffered, namely type 1 and type 2. As many as 9% of deaths are contributed by type 2 diabetes. This indicates that there is an urgent need to find potential therapeutic agent treatment alternatives (Syed Ahsan Elahi Bukhari, Syed Mubashar Sabir, Shabaz Ali, Ali Turaib 2022). Inhibition of α-gklucosidase enzyme aims to delay glucose absorption in the intestine and reduce postprandial hyperglycemia (Rachmatiah, Nurvita, and D 2018). Akarbose is an enzyme inhibitor compound α-glucosidase which is widely used as an oral antidiabetic and clinically proven. However, this drug has side effects such as triggering hypoglycemia and stomach pain so other alternatives are sought such as α-glucosidase inhibitors from natural ingredients, one of which is *kratom* leaves which are traditionally used as antidiabetics (Heri et al., 2020; Ningrum et al., 2021a).

The antidiabetic activity of a plant can be carried out by testing the inhibitory ability of α-glucosidase. In this study, the inhibitory activity of ethanol extract was tested for three *kratom* variants, namely the red, green, and white variants against the enzyme α-glucosidase. The principle of this test is that a substance that acts as an inhibitor will bind to the enzyme α-glucosidase so that the hydrolysis of pNPG substrates (p-nitrophenyl-α-D-glucopyranosida) into p-nitrophenol will be inhibited. The amount of p-nitrophenol formed will be measured for absorbance using a microplate reader at a wavelength of 405 nm. The smaller the absorbance of p-nitrophenol formed, the greater the inhibitory activity (Tran et al., 2021).

The results of testing the inhibitory activity of ethanol extracts of three *kratom* variants against the α-glucosidase enzyme showed that the three *kratom* variants were able to inhibit the activity of the α-glucosidase enzyme. The higher the concentration of the extract, the percentage of inhibition increases. Green *kratom* ethanol extract showed the highest inhibitory activity against the enzyme α-glucosidase (Figure 3). Sequentially, the percentage of inhibition of *kratom* leaf ethanol extract against the enzyme α-glucosidase is green *kratom*>red *kratom*>white *kratom*. The inhibitory effect of α-glucosidase enzymes from the same compound can differ depending on substrate level, temperature conditions, pH, incubation time, and enzyme concentration at the time of the enzymatic reaction (Masriani et al., 2020). The enzyme form is maintained at a certain temperature and pH. Changes in temperature and pH can break the intramolecular bonds of the enzyme, allowing it to change its shape. Optimal enzyme activity usually occurs at temperatures of 30 to 40 °C. In the human body, enzymes have optimal activity at pH 6.5 – 7.4 (Sismindari et al., 2016).

The difference in the ability of the three types of *kratom* variants to inhibit the α-glucosidase enzyme may also be caused by differences in the type and / or concentration of secondary metabolites contained in *kratom* leaves. According to Sinulungga (2020), the inhibitory activity of α-glucosidase can differ depending on the content of secondary metabolites possessed by the extract. Secondary metabolites with a structure that has an affinity resembling a substrate, will easily occupy the active side of the enzyme α-glucosidase and inhibit the work of the enzyme. Thus, the more similar the structure of secondary metabolites to the substrate, the higher the inhibition obtained (Sinulingga, Subandrate, and Safyudin 2020).

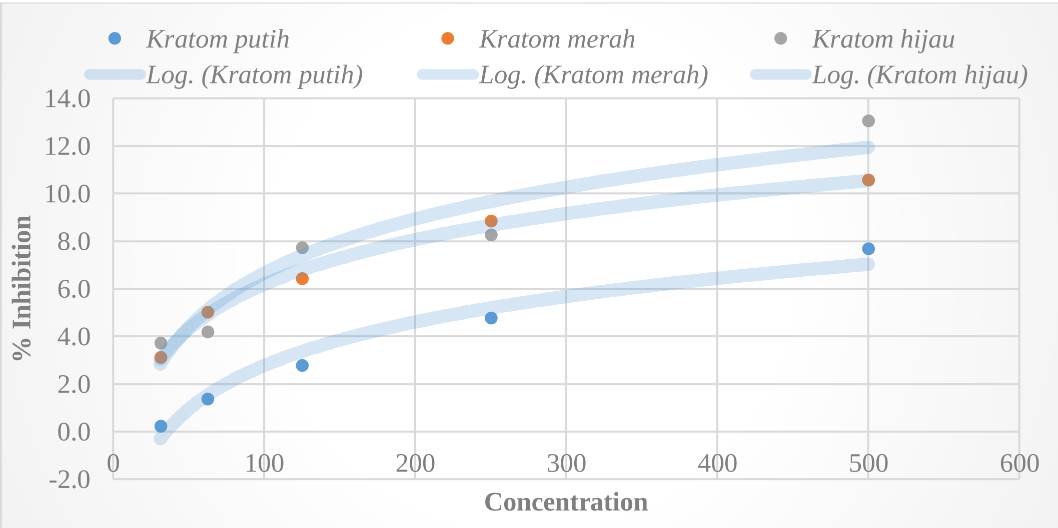

Figure 3. % Inhibition of Ethanol Extract of Three Variants of *Kratom* Leaves against α-glucosidase Enzyme of *Kratom putih* (white veins Kratom), *Kratom merah* (red veins *Kratom*), *Kratom hijau* (green veins *Kratom*),

The inhibitory activity of enzymes shown by *kratom* leaves is inseparable from the content of secondary metabolites contained in it. All three types of *kratom* leaves are known to contain alkaloid compounds, flavonoids, tannins, saponins, phenolics, and triterpenoids (Masriani et al., 2023).

Alkaloids are known to lower blood sugar levels by various mechanisms. Alkaloids can inhibit glucose absorption in the intestine, improve glucose transport in the blood, inhibit blood glucose absorption through inhibition of α-glucosidase, glucose-6-phosphatase, fructose-1,6-

bisphosphatase, and enzymes that play a role in gluconeogenesis (Fatmawati, Susilawati, Liniyanti D Oswari, Fadiya 2021). Looking at the weak inhibitory activity, it is suspected that the empirically proven antidiabetic activity of the three *kratom* variants is not through the mechanism of inhibition of the α-glucosidase enzyme but from various other mechanisms (Sari sasi gendro, 2022).

In addition to alkaloids, the content of secondary metabolites such as tannins, saponins, triterpenoids, fllavonoids and phenolics also plays a role in the inhibitory activity shown. Tannins are predators of free radicals and antidiabetic agents with a mechanism of lowering glucose levels in the blood of insulin mediator action (Kumari &; Jain, 2012). Flavonoids and phenolics are compounds rich in hydroxyl groups (Wibawa, 2021). The antidiabetic mechanism by this compound occurs through hydroxylation and substitution bonds in β-pancreatic installments (Pratiwi et al., 2021). Oxygen bound to the hydroxyl group can bind to hydrogen from the active side of the enzyme α-glucosidase so that there is an inhibition of glucose production in the blood (Herdien et al., 2020).

When referring to IC_{50} values (Table 1), all *kratom* variants show very weak inhibitory activity of α-glucosidase. According to Riyanti et al (2019) the inhibitory activity of a sample is categorized into 5, namely >200 µg/ml (very weak), 150-200 µg/ml (weak), 100-150 µg/ml (medium), 50-100 µg/ml (strong) and <50 µg/ml is very strong. Based on these criteria, the inhibitory activity of red, green, and white *kratom* leaf ethanol extract against α-glucosidase enzymes is very weak because of the IC_{50}>200 µg/mL value (Riyanti et al., 2019). Akarbose as a comparison showed very strong inhibitory activity and much higher than sample extracts (Table 1). In this study, IC50 akarbose amounted to 0.2058 µg / ml.

The inhibitory activity of the enzyme α-glucosidase *kratom* leaf extract is much lower than that of akarbose because akarbose is a pure compound, while *kratom* extract is still a crude extract where the compound content in this extract is still mixed with compounds that may work antagonistically in inhibiting α-glucosidase enzymes (Nguelefack et al., 2020). The low activity of an extract can also be caused by several things such as modifications in testing and the concentration of active compounds contained in the sample (Suprihatin et al., 2020).

Table 1. IC_{50} Value of Inhibition Activity of α-Glucosidase Enzyme by *Kratom* Leaf Ethanol Extract (M.Speciosa Korth)

Sample	**Line Equation**	**IC_{50} (µg/mL)**
Red *Kratom*	$y = 2{,}7064\ln(x) - 6{,}2778$ $R^2 = 0{,}9949$	>200
Green *Kratom*	$y = 3{,}2841\ln(x) - 8{,}4683$ $R^2 = 0{,}9126$	>200
White *Kratom*	$y = 2{,}6438\ln(x) - 9{,}4031$ $R^2 = 0{,}964$	>200
Akarbose	$y = 13{,}05\ln(x) + 70{,}627$ $R^2 = 0{,}9982$	0,20587

Kratom has 57 compounds that are dominated by achaloid compounds. The main compounds are indole alkaloids mitragynine (66%) and 7-hydroxy-mitragynine (2%) (Kamble et al., 2021). The results of the study (Purnama Melania, Masriani 2023), the total phenolic levels of green, red, and white *kratom* were 6.11 mg GAE/g, 8.67 mg GAE/g, and 9.09 mg GAE/g, while flavonoid levels were 0.086 mg GAE/g, 0.68 mg GAE/g, and 1.13 mg GAE/g, respectively. It can be seen that compounds that are thought to play an important role in the inhibitory activity of α-glucosidase, namely flavonoids and phenolics are minor compounds in *kratom* leaves and are suspected to be the cause of low inhibitory activity against α-glucosidase. In addition, it is suspected that the mechanism of antidiabetic activity possessed by *kratom* leaf extract is not through inhibition of the enzyme α-glucosidase, but through other mechanisms. Although empirically *kratom* leaves are beneficial for the treatment of diabetes, based on these findings, it is necessary to test other antidiabetic mechanisms of *kratom* leaves (Ningrum et al., 2021b).

CONCLUSION

From the results of the study it was concluded that red, green and white *kratom* leaves have activity as inhibitors of α-glucosidase enzymes. Of the three *kratom*s, green *kratom* has the strongest inhibitory activity compared to red and white *kratom*, but its inhibitory properties are still very weak, because of the IC_{50}>200 μg / ml value. The results of this study add new information about the inhibitory activity of the α-glucosidase enzyme owned by the three variants of *kratom* leaves. Based on these findings, it is hoped that it can be a reference for future research to explore the potential of *kratom* leaves as an antidiabetic.

RECOMMENDATIONS

Based on the results of this study, it is recommended that future studies can test other antidiabetic mechanisms of *kratom* leaves both in *vivo* and *in vitro.*

ACKNOWLEDGMENT

The author would like to thank the Faculty of Teacher Training and Education (FKIP) Tanjungpura University (UNTAN), for providing PNBP FKIP DIPA 2022 funding assistance Number: SP DIPA-023.17.2.677517/2022 and PT. Natural Creations of Borneo West Kalimantan which has provided *kratom* samples.

BIBLIOGRAPHY

Ajebli, M., Khan, H., & Eddouks, M. (2020). Natural Alkaloids and Diabetes Mellitus: A Review. *Endocrine, Metabolic & Immune Disorders - Drug Targets, 21*(1). https://doi.org/10.2174/1871530320666200821124817

Bayani, F. (2016). Analisis Fenol Total dan Uji Aktivitas Antioksidan dari Ekstrak Buah Sentul (Sandoricum koetjape Merr). *Hydrogen: Jurnal Kependidikan Kimia, 4(1)*.

Budiman, A. (2011). Isolasi Enzim Alfa Glukosidase dari Gabah (Oryza sativa var. Ciiherang). *Skripsi*.

Depkes RI. (2005). *Pharmaceutical Care Untuk Penyakit Diabetes Mellitus.* Departemen Kesehatan Republik Indonesia.

Elmaniar, R., & Muhtadi. (2017). Aktivitas Penghambatan Enzim a-Glukosidase oleh Ekstrak Etanol Umbi Ubi Jalar Ungu (Ipomea batatas L.). *The 5th Urecol Proceeding, February*.

Fatmawati, Susilawati, Liniyanti D Oswari, Fadiya, N. (2021). Uji Aktivitas Penghambatan Enzim Alfa-Glukosidase Ekstrak Air dan Ekstrak Etanol Kayu Kuning (Arcangelisia flava). *Jurnal Kedokteran Dan Kesehatan, 8*(1).

Hamid, H. A., Yusoff, M. M., Liu, M., & Karim, M. R. (2015). α-Glucosidase and α-amylase inhibitory constituents of Tinospora crispa: Isolation and chemical profile confirmation by ultra-high performance liquid chromatography-quadrupole time-of-flight/mass spectrometry. *Journal of Functional Foods*, *16*, 74–80. https://doi.org/10.1016/j.jff.2015.04.011

Herdien, D. R., Rahmadhani, C. A., Nurmala, S., & Yanuar, A. (2020). Anti-Diabetes Mellitus Potential Compounds Of Flavonoid Citrus Peel: A Review On Mechanism. *Berkala Ilmiah Mahasiswa Farmasi Indonesia (BIMFI)*, *7*(2). https://doi.org/10.48177/bimfi.v7i2.48

Heri, W., Siti, J., Achmad, K. A., Henny, N., & Sandeep, P. (2020). Determination of phenolic and flavonoid levels and antioxidant activity test from ethanol extract of biak-leaves (*Mitragyna speciosa*) with ABTS method [2,2-azinobis- (3-ethylbenzotiazolin) -6-sulfonic acid]. *Research Journal of Chemistry and Environment*, *24*(5).

IDF Atlas., I. D. F. (2022). *Diabetes Atlas. 10th Edition*. Brussels.

Ikhwan, D., Harlia, & Widiyantoro, A. (2018). Karakterisasi Senyawa Sitotoksik Dari Fraksi Etil Asetat Daun *Kratom* (*Mitragyna speciosa* Korth.) dan Aktivitasnya Terhadap Sel Kanker Payudara T47D. *Jurnal Kimia Khatulistiwa*, *7*(2), 18–24.

Kamble, S. H., Berthold, E. C., King, T. I., Raju Kanumuri, S. R., Popa, R., Herting, J. R., León, F., Sharma, A., McMahon, L. R., Avery, B. A., & McCurdy, C. R. (2021). Pharmacokinetics of Eleven *Kratom* Alkaloids following an Oral Dose of Either Traditional or Commercial *Kratom* Products in Rats. In *Journal of Natural Products* (Vol. 84, Issue 4). https://doi.org/10.1021/acs.jnatprod.0c01163

Kumari, M., & Jain, S. (2012). Tannins: An Antinutrient with Positive Effect to Manage Diabetes. *Research Journal of Recent Sciences*, *1*(12).

Luliana, S., & Islamy, M. R. (2018). Aktivitas Antinosiseptif Fraksi Diklorometana Daun *Kratom* (*Mitragyna speciosa* Korth.) Rute Oral Pada Mencit Jantan Swiss. *Pharmaceutical Sciences and Research*, *5*(2), 58–64. https://doi.org/10.7454/psr.v5i2.3895

Mahargyani, W. (2019). Uji Aktivitas Antidiabetes Ekstrak n-Heksan Kulit Buah Naga Merah (Hylocereus polyrhyzus). *EduChemia (Jurnal Kimia Dan Pendidikan)*, *4*(1). https://doi.org/10.30870/educhemia.v4i1.3958

Mardhiani, Y. D., Yulianti, H., Azhary, DenyP., & Rusdiana, T. (2018). Forulasi dan Stabiltas Sediaan Serum dari Ekstrak Kopi Hijau (Coffe Canephora). *Indones Nat Res Pharm J*, *2*(2).

Masriani, Fadly, D., & Bohari. (2020). α-glucosidase inhibitory activity of ethanol extract obtained from dillenia suffruticosa and pycnarrhena cauliflora. *Journal of Global Pharma Technology*, *12*(2).

Masriani, M., Muharini, R., Wijayanti, D., Melanie, P., & Widiansari, M. (2023). *Phytochemical Screening of Ethanol Extracts from Three Variants of Kratom Leaves (Mitragyna speciosa Korth*. *11*(2), 192–201. https://doi.org/10.33394/hjkk.v11i2.7122

Mataputun, S. P., Rorong, J. A., & Pontoh, J. (2013). Aktivitas Inhibitor α-Glukosidase Ekstrak Kulit Batang Matoa (Pometia pinnata. Spp.) sebagai Agen Antihiperglikemik. *Jurnal MIPA*, *2*(2), 119. https://doi.org/10.35799/jm.2.2.2013.3030

Meireles, V., Rosado, T., Barroso, M., Soares, S., Gonçalves, J., Luís, Â., Caramelo, D., Simão, A., Fernández, N., Duarte, A., & Gallardo, E. (2019). *Mitragyna speciosa*: Clinical, Toxicological Aspects and Analysis in Biological and Non-Biological Samples. *Medicines*, *6*(1), 35. https://doi.org/10.3390/medicines6010035

Mohamed, E. A. H., Siddiqui, M. J. A., Ang, L. F., Sadikun, A., Chan, S. H., Tan, S. C., Asmawi, M. Z., & Yam, M. F. (2012). Potent α-glucosidase and α-amylase inhibitory activities of standardized 50% ethanolic extracts and sinensetin from Orthosiphon stamineus Benth as anti-diabetic mechanism. *BMC Complementary and Alternative Medicine*, *12*. https://doi.org/10.1186/1472-6882-12-176

Nasution, S. M. (2018). *AKTIVITAS PENGHAMBATAN ENZIM α -GLUKOSIDASE EKSTRAK ETANOL DAUN PIRDOT (Saurauia vulcani Korth.) SECARA IN VITRO*.

Nguelefack, T. B., Fofie, C. K., Nguelefack-Mbuyo, E. P., & Wuyt, A. K. (2020). Multimodal α-Glucosidase and α-Amylase Inhibition and Antioxidant Effect of the Aqueous and Methanol Extracts from the Trunk Bark of Ceiba pentandra. *BioMed Research International*, *2020*, 3063674. https://doi.org/10.1155/2020/3063674

Ningrum, A. M., Christina, M., Putri, T. R., & Simamora, C. J. K. (2021a). Probability Induction of *Kratom* Plant Bioactive Components in Antidiabetic and Antiobesity Studies. *BIOEDUSCIENCE*, *5*(3). https://doi.org/10.22236/j.bes/536900

Ningrum, A. M., Christina, M., Putri, T. R., & Simamora, C. J. K. (2021b). Probability Induction of *Kratom* Plant Bioactive Components in Antidiabetic and Antiobesity Studies. *BIOEDUSCIENCE*, *5*(3), 234–240. https://doi.org/10.22236/j.bes/536900

Nugraha, W. I., Robiyanto, R., & Luliana, S. (2018). Antinociceptive Activity of Aqueous Fraction of *Kratom* Leaves *Mitragyna speciosa* Korth.) on Male Swiss Albino Mice. *Majalah Obat Tradisional*, *23*(2). https://doi.org/10.22146/mot.32085

Patty, Y. F. P. P., Mufarrihah, & Nita, Y. (2021). Cost of illness of diabetes mellitus in Indonesia: A systematic review. In *Journal of Basic and Clinical Physiology and Pharmacology* (Vol. 32, Issue 4). https://doi.org/10.1515/jbcpp-2020-0502

Pratiwi, A., Datau, W. A., Alamri, Y. B. A., & Kandowangko, N. Y. (2021). PELUANG PEMANFAATAN TUMBUHAN PEPEROMIA PELLUCIDA (L.) KUNTH SEBAGAI TEH HERBAL ANTIDIABETES. *Jambura Journal of Health Sciences and Research*, *3*(1). https://doi.org/10.35971/jjhsr.v3i1.7593

Prozialeck, W. C., Edwards, J. R., Lamar, P. C., Plotkin, B. J., Sigar, I. M., Grundmann, O., & Veltri, C. A. (2020). Evaluation of the mitragynine content, levels of toxic metals and the presence of microbes in *kratom* products purchased in the Western Suburbs of Chicago. *International Journal of Environmental Research and Public Health*, *17*(15). https://doi.org/10.3390/ijerph17155512

Purintrapiban, J., Keawpradub, N., Kansenalak, S., Chittrakarn, S., Janchawee, B., & Sawangjaroen, K. (2011). Study on glucose transport in muscle cells by extracts from *Mitragyna speciosa* (Korth) and mitragynine. *Natural Product Research*, *25*(15), 1379–1387. https://doi.org/10.1080/14786410802267627

Purnama Melania, Masriani, R. M. (2023). Korelasi Kadar Fenolik Total dan Flavonoid dengan Antioksidan Tiga Varian Daun *Kratom* (*Mitragyna speciosa* Korth.). *Jurnal Sains Farmasi Dan Kllinis*.

Rachmatiah, T., Nurvita, H., & D, R. T. (2018). Potensi Antidiabetes Pada Tumbuhan Petai Cina (Leucaena leucocephala (Lam).De Wit). *Sainstech: Jurnal Penelitian Dan Pengkajian Sains Dan Teknologi*, *25*(1). https://doi.org/10.37277/stch.v25i1.146

Ramanathana, S., Leo, F., Cheara, N. J. Y., Yusofa, S. R., Murugaiyahc, V., Mcmahond, L. R., & Mccurdyb, C. R. (2021). *Kratom (Mitragyna speciosa Korth .): Deskripsi tentang etnobotani , alkaloid kimia , dan* (Vol. 69).

Riyanti, S., MA, S., & E, K. (2021). Potensi Daun Bungur (Lagerstroemia loudonii Teijsm. & Binn.) Yang Gugur Sebagai Penghambat Alfa-Glukosidase. *Jurnal Farmasi Udayana*. https://doi.org/10.24843/jfu.2021.v10.i01.p04

Riyanti, S., Ratnawati, J., & Aprilianti, S. (2019). Potensi buah okra (Abelmoschus esculentus (L.) Moench) sebagai inhibitor alfa-glukosidase. *Kartika : Jurnal Ilmiah Farmasi*, *6*(1). https://doi.org/10.26874/kjif.v6i1.122

Sari sasi gendro, dea aulya. (2022). Uji Aktivitas Antidiabetes Ekstrak Daun Senggani (Melastoma Malabathricum L.) Secara In Vitro Dengan Metode Penghambatan A - Glukosidase. *Lp2m Ust Jogja*, *3*(2).

Setyawati, H. (2020). Uji Aktivitas Antioksidan Ekstrak etanol Daun *Kratom* (*Mitragyna speciosa*) Dengan Metode 1, 1 Difenil-2-Pikrihidrazil (DPPH). *Jurnal Farmasi Udayana*. https://doi.org/10.24843/jfu.2020.v09.i03.p09

Sinulingga, S., Subandrate, S., & Safyudin, S. (2020). Uji Fitokimia dan Potensi Antidiabetes Fraksi Etanol Air Benalu Kersen (Dendrophtoe petandra (L) Miq). *Jurnal Kedokteran Dan Kesehatan*, *16*(1). https://doi.org/10.24853/jkk.16.1.76-83

Suhaimi Dian, S. K. (2020). Uji Antidiare Granul Dari Ekstrak Etanol Daun *Kratom* (Mytragina Specioca Korth) Terhadap Mencit Putih Jantan (Mus Musculus L). *Jurnal Ilmu Kefarmasian Indonesia*, *18*(Vol 18 No 1 (2020): JIFI).

Suhaimi, Puspasari, H., & Apriani, M. (2019). Aktivitas Antibakteri Ekstrak Daun *Kratom* (*Mitragyna speciosa* Korth) Terhadap Bakteri Propionibacterium acnes Sebagai Penyebab Jerawat. *Open Journal Systems STF Muhammadiyah Cirebon :*, *4*(1).

Suprihatin, T., Rahayu, S., Rifa'i, M., & Widyarti, S. (2020). Senyawa pada Serbuk Rimpang Kunyit (Curcuma longa L.) yang Berpotensi sebagai Antioksidan. *Buletin Anatomi Dan Fisiologi*, *5*(1), 35–42. https://doi.org/10.14710/baf.5.1.2020.35-42

Syed Ahsan Elahi Bukhari, Syed Mubashar Sabir, Shabaz Ali, Ali Turaib, S. X. (2022). Antioxidant and Enzyme inhibitory activities of Zizypusjujuba, Adhatoda vasica and beeberis lycium from hilly areas. *Journal of King Saud University*, *1*, 1–6.

Tran, C. L., Dao, T. B. N., Tran, T. N., Mai, D. T., Tran, T. M. D., Tran, N. M. A., Dang, V. S., Vo, T. X., Duong, T. H., & Sichaem, J. (2021). Alpha-glucosidase inhibitory diterpenes from euphorbia antiquorum growing in Vietnam. *Molecules*, *26*(8). https://doi.org/10.3390/molecules26082257

Warner, M. L., Kaufman, N. C., & Grundmann, O. (2015). *The pharmacology and toxicology of kratom : from traditional herb to drug of abuse*. https://doi.org/10.1007/s00414-015-1279-y

WHO, W. H. O. (2022). *Global Report on Diabetes France*.

Wibawa, A. A. C. (2021). Kapasitas Total Antioksidan Ekstrak Metanol Biji Kakao (Theobroma cacao. L) Dengan Metode Spektrofotometri Uv-Vis. *Hydrogen: Jurnal Kependidikan Kimia*, *9(1)*.

Yuliana, N. D., Budijanto, S., Wijaya, C. H., & Khatib, A. (2016). *[α -Glucosidase Inhibitor and Antioxidant Compounds from Orthosiphon stamineus Benth Using FTIR Based Metabolomics]*. *27*(1), 17–30. https://doi.org/10.6066/jtip.2016.27.1.17

Zhenhua Yin, Wei Zhang, Fajin Feng, Yong Zhang, W. K. (2014). alpha Glucosidase Inhibitors Isolated From Medicinal Plants. *Food Science and Human Wellness*, *3*(3–4), 136–174.