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The potency of selected ethnomedicinal plants from East Kalimantan, Indonesia as antidiabetic agents and free-radical scavengers

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Abstract. *Ramadhan R, Phuwapraisirisan P, Amirta R, Darmawan MFB, Ul-Haq K, Kusuma IW, Suwito H, Abdulgani N, Mukhdlor A, Saparwadi. 2022. The potency of selected ethnomedicinal plants from East Kalimantan, Indonesia as antidiabetic agents and free-radical scavengers. Biodiversitas 23: 2225-2230.* Ten ethnomedicinal plant extracts from East Kalimantan flora, traditionally used to treat blood sugar levels and other diabetes-related diseases, were examined *in vitro* for their antidiabetic and free radical scavenging activities by inhibiting rat alpha-glucosidase and several free radicals such as DPPH, ABTS, and Nitric oxide respectively. Out of the ten plant species investigated for their antidiabetic activity against maltase and sucrase rat alpha-glucosidase, three exhibited the strongest α-glucosidase inhibitory activity with maltose as a substrate, namely extracts of *Garcinia nervosa*, *Syzygium caudatilimbum*, and *Shorea balangeran* with IC_{50} values of 0.046; 0.037; 0.045 mg/mL. Meanwhile, quercetin as a positive control appeared to have a comparable IC_{50} value. Furthermore, among the ten extracts, *Syzygium caudatilimbum*, *Shorea balangeran*, and *Ixora javanica* showed good inhibition against sucrase rat alpha-glucosidase. Moreover, the antioxidant test showed that the ten methanol extracts of plants from East Kalimantan have an antioxidant activity indicated by IC_{50} values. The present study confirms that the ethnopharmacological use of selected plants from East Kalimantan might have potential as an antidiabetic and natural antioxidant.

Keywords: Antidiabetic, antioxidant, biodiversity, ethnomedicinal plants, free radicals

INTRODUCTION

Historically, medicinal plants have been the main source of treasure in tropical countries. Medicinal plants, a non-timber forest product (NTFP), are a significant constituent of livelihood (Salhi et al. 2019). Human cultures have utilized plants not only for staple food but also for therapy against diseases dan illnesses (Shaw et al. 2010). The use of medicinal plants for disease prevention and treatment has been well established globally for more than a few decades (Mudau et al. 2022). In East Kalimantan, ethnomedicinal plants are the most accessible form of health care resource, particularly to local people living far from the capital city. The local people of East Kalimantan (Dayak tribes) pass down significant information on potential plants in the forest for traditional ceremonies and medicines from generation to generation (Joshi et al. 2004). This traditional knowledge can be considered as scientific evidence practiced by local people who actually apply medicinal plants as particular remedies. Medicinal plants contain many secondary metabolites (phytochemicals), such as polyphenols, coumarins, alkaloids, triterpenes, and other metabolites, that exhibit biological activities including antibacterial, antifungal, anti-inflammatory, antioxidant, antidiabetes, and antiplasmodial (Maroyi 2017; Onyango et al. 2019) that may create their therapeutic properties.

Type-2 diabetes mellitus (T2DM) is one of the most chronic diseases characterized by hyperglycemia. Sustained diabetes mellitus progresses to various complications, such as vascular disease, eye disease, kidney illness, diabetic foot, and others (Duarte et al. 2020). Excessive glucose in diabetes patients can be degraded into a potential precursor of overproduction of free radicals and—sooner or later—oxidative stress, which contributes to the aforementioned complications (Ji et al. 2021). Presently, oral synthetic diabetic agents such as acarbose, voglibose, and miglitol are used to treat type-2 DM that regrettably cause side effects, including flatulence, diarrhea, and abdominal disorder (Wang et al. 2022). Inhibition of α-glucosidase is

one of the approaches to treating T2DM (Kim et al. 2022). Accordingly, recent updates on lower blood glucose level treatment showed a trend of consuming medicinal plants due to their ability. These plants have been used traditionally to treat diabetes and its complications (Hossai et al. 2020). Although East Kalimantan medicinal plants have long been used in traditional medicine to treat different illnesses including diabetes, there is a lack of scientific information on their antidiabetic and antioxidant activities. Information about traditional uses of ethnomedicinal plants in East Kalimantan is passed down from generation to generation. Therefore, in this study, the authors investigated ten ethnomedicinal plants to evaluate their potency as antidiabetic agents and free radical scavengers as well as to provide a scientific background to their traditional uses as ethnomedicinal plants. Moreover, to the best of the author's knowledge, this study is the first to report antidiabetic agents and free radical scavengers in ethnomedicinal plants from East Kalimantan.

MATERIALS AND METHODS

Plant collection and identification

The fresh parts of ten ethnomedicinal plants were collected in Kutai Kartanegara District, East Kalimantan. Voucher specimens for each ethnomedicinal plant were prepared and deposited in the Laboratory of Forest Products Chemistry and Renewable Energy, Faculty of Forestry, Mulawarman University. Ten ethnomedicinal plants in this study are listed in Table 1.

Chemical reagents

The organic chemicals, namely methanol and dimethyl sulfoxide (DMSO), were obtained from Merck (Darmstadt, Germany). The three free radical sources (DPPH, ABTS, and Nitric Oxide) were procured from Sigma Chemical Co. The rat intestinal acetone powder was purchased from Sigma Aldrich. Other chemicals of analytical grade were procured from Tokyo Chemical Industry (TCI) Co. Ltd.

Extraction of ethnomedicinal plants

The extraction of ten ethnomedicinal plants from East Kalimantan was performed according to the methods of Ramadhan et al. (2019). In order to prepare crude methanol extract, a dried powder sample from ten ethnomedicinal plants was treated three times with methanol at room temperature for two days. After the extraction was complete, all ten extracts were filtrated and evaporated at 50°C using vacuo (BUCHI Rotavapor® R-100). All the methanol extracts were stored in a refrigerator at -20°C for further use in the bioassay test.

Antidiabetic activity

Rat α-glucosidase inhibitory activity

In vitro rat α-glucosidase inhibition was assessed based on the previously described method by Ramadhan et al. (2019) with minor modifications. The subsequent enzyme reactions were carried out in a buffer phosphate system, then all extracts were equipped and individually dissolved in DMSO (Dimethyl sulfoxide) with various final concentrations (0.0025-0.0625 mg/mL). After adding 20 µL of rat α-glucosidase solution to various concentrations of the sample following glucose kit solution, the mixture was incubated for 10 minutes (maltose substrate) and 40 minutes (sucrose substrate) at 37°C, respectively. The absorbance was measured using the microplate reader BIOCROM EZ Read 2000 at 503 nm. Quercetin was used as a positive control of natural products. The inhibitory rate of test samples against rat α-glucosidase was calculated as follows: inhibition rate (%) = $(A_{control}-A_{sample})/A_{control}$ x 100. The samples' half inhibitory concentration (IC_{50}) describes that the samples' concentration causes 50% of enzyme inhibition.

Antioxidant activities

DPPH radical inhibitory activity

The free radical scavenging activity of ten ethnomedicinal plants and ascorbic acid were measured by the stable DPPH method as described previously (Casado et al. 2010). This assay was carried out using microplate reader BIOCROM EZ Read 2000. The DPPH solution was prepared by dissolving the powder in 100 mL of methanol. Volumes of samples (20 µL; extracts and ascorbic acid, respectively) at serial concentrations (0.004-1 mg/mL) were mixed with 0.01 M DPPH solution. The reaction mixture was left at room temperature. The discoloration was measured at 517 nm after a 30-minute incubation. The radical scavenging activity was calculated using the equation of scavenging activity (%): $(A_{control}-A_{sample})/A_{control}$ x 100.

Table 1. Selected ethnomedicinal plants from East Kalimantan, Indonesia

Ethnomedicinal plants	Part used	Local names	Voucher specimens
Garcinia nervosa Miq.	Stem	Manggis Hutan	LBTI-R-12
Mimosa pigra L.	Stem	Malu-malu	LBTI-R-26
Pterospermum javanicum Jungh.	Branch & Twig	Bayur	LBTI-P-42
Ixora javanica (Blume) DC.	Stem	Ketumba	LBTI-S-14
Syzygium caudatilimbum (Merr.) Merr. & L.M.Perry	Stem	Beluma	LBTI-R-39
Ficus hispida	Stem	Kebolo	LBTI-S-17
Gluta velutina Blume	Twig	Serengat	LBTI-S-09
Lepisanthes amoena (Hassk.) Leenh.	Stem	Bengalon	LBTI-T-31
Artocarpus longifolius Becc.	Stem	Terap hutan	LBTI-S-06
Shorea balangeran Burck	Stem	Kahoi	LBTI-R-30

ABTS radical inhibitory activity

The $ABTS^{\bullet+}$ scavenging activity of the ten ethnomedicinal extracts was determined based on the method developed by Ramadhan et al. (2018) with some modifications. The free radical ABTS was generated by the reaction between ABTS in water and 2.45 mM potassium persulfate, and it was stored in a dark room for 12 hours. As for the assessment of the ten ethnomedicinal plant extracts' radical scavenging activity, various concentrations of extracts and ascorbic acid (0.04-1 mg/mL) were individually added to 100 µL of $ABTS^{\bullet+}$ solution. After a 60-minute incubation, absorbance was determined with microplate reader BIOCROM EZ Read 2000 at 750 nm. The percentage of $ABTS^{\bullet+}$ inhibition was calculated using the following formula: scavenging activity (%): $(A_{control}-A_{sample})/A_{control}$ x 100.

Nitric oxide radical inhibitory activity

The nitric oxide inhibitory activity was determined by the Griess reaction. The method of Njoya et al. (2017) was implemented to assess the scavenging activity of ten ethnomedicinal plant extracts and ascorbic acid (standard) against nitric oxide free radical. In short, 20 µL of serial concentration of extracts was added with 30 µL of sodium nitroprusside. After incubation for 60 minutes, 100 µL of Griess reagent was added to the mixture, then the pink chromophore was measured spectrophotometrically at 540 nm. The scavenging activity of nitric oxide (%) was calculated with the following formula: $(A_{control}-A_{sample})/A_{control}$ x 100.

Data analysis

The assessment results are expressed as mean±SD and all analyses were run in triplicate. The quantitative data obtained were analyzed descriptively.

RESULTS AND DISCUSSION

Antidiabetes activity

In order to investigate the inhibitory effect of ten ethnomedicinal plants from East Kalimantan on rat intestinal α-glucosidase, the authors performed *in vitro* using both maltose and sucrose substrates as described in the materials and methods section above. α-Glucosidase is a crucial enzyme that hydrolyzes carbohydrates and plays a major role in controlling digestion and absorption of glucose in the small intestine. At present, one of the potential approaches to delicacy diabetes treatment is to inhibit carbolytic enzymes such α-glucosidase for lowering blood glucose levels in metabolism (Ji et al. 2021; Nipun et al. 2021).

The antidiabetic activity of ten ethnomedicinal plant extracts is shown in Table 2. From this preliminary study, extracts of *Garcinia nervosa*, *Syzygium caudatilimbum*, and *Shorea balangeran* exhibited the strongest α-glucosidase inhibitory activity with maltose as a substrate and IC_{50} values of 0.046 mg/mL, 0.037 mg/mL, and 0.045 mg/mL respectively. It was significantly comparable to the quercetin as a positive control with IC_{50} value of 0.040 mg/mL. According to previous studies by Li et al. (2009) and Indrianingsih et al. (2015), quercetin can be used as a positive control because it has a stronger inhibitory effect on α-glucosidase and it is a natural inhibitor that is more potent than synthetic inhibitors in controlling blood sugar level. In this study, extract of *G. nervosa* had a good inhibitory activity with an IC_{50} value that was quite similar to that of the positive control. Based on the results in Table 2, the lowest IC_{50} values indicated a higher α-glucosidase inhibitory activity of ten ethnomedicinal plant extracts as an antidiabetic agent by inhibiting maltase α-glucosidase in the subsequent order: *Ficus hispida* > *Ixora javanica* > *Gluta velutina* > *Pterospermum javanicum* > *Lepisanthes amoena* > *Artocarpus longifolius* > *Garcinia nervosa* > *Shorea balangeran* > *Syzygium caudatilimbum*. Based on a previous report, genus *Garcinia* contains several important secondary metabolites, such as xanthones, biflavonoids, flavonoids, and coumarins (Jabit et al. 2009). Parveen et al. (2004) and Wong et al. (2017) found that *G. nervosa* leaves and barks contain such biflavonoids and pyranoxanthones that are rich in hydroxyl groups. According to some literature, it is proof that hydroxyl groups are present in the aromatic moieties that can form hydrogen bonds with the polar group of enzymes, and hydrophobic association can contribute to inhibiting α-glucosidase (Asgar 2013). Regarding the results found, extracts of *S. caudatilimbum*, and *S. balangeran* also presented comparable IC_{50} values to quercetin. This finding is in line with that of Shinde et al. (2008) who reported that *Syzygium cumini* had antidiabetic activity by inhibiting maltase and sucrase α-glucosidase. Furthermore, Manarahan et al. (2012) and Arumugam et al. (2016) reported that phytochemicals of *Syzygium malaccense* and *Syzygium aqueum,* such as myricitrin, myricetin-3-*O*-rhamnoside, and europtin-3-*O*-rhamnoside, had the potency to inhibit α-glucosidase. In addition, Kissinger et al. (2016) stated that methanol extract of stem bark from *S. balangeran*, whose species contains oligostilbenoids group as the major phytochemical, showed antidiabetic activity by inhibiting baker's yeast α-glucosidase with an IC_{50} value of 0.816 ppm (Tukiran et al. 2005).

Among the ten extracts tested, the extract of *S. caudatilimbum* exhibited the greatest inhibitory effect against sucrase α-glucosidase (IC_{50} 0.070 mg/mL), followed by the extracts of *S. balangeran* and *Ixora javanica* compared to quercetin as a positive control. On the other hand, as shown in Table 2, other ethnomedicinal extracts had no inhibition activity against sucrase α-glucosidase. In another study, Oktaviyanti et al. (2020) evaluated the total flavonoids from *I. javanica* whose phytochemicals, such as flavonoid glycosides and triterpenoids, have been isolated from *I. javanica* (Dontha et al. 2015). In addition, several previous studies reported bioactivities of genus *Ixora*, such as anti-inflammatory, antimicrobial, antidiabetic, antiplatelet, antidiarrhea, and wound-healing potency (Maniyar et al. 2010; Anila and Hashim 2019; Ragasa et al. 2004). However, antidiabetic activities of methanol extracts from *G. nervosa*, *S. caudatilimbum*, *S. balangeran*, and *I. javanica* have not been reported before. Therefore, to the best of the authors'

3owledge, there is no report on antidiabetic screening using rat intestinal α-glucosidase, maltose and sucrose as substrates, and the aforementioned ethnomedicinal plants from East Kalimantan, except the one presented in this study. Accordingly, this study encourages further studies to isolate and identify particularly bioactive compounds from extracts that may cause antidiabetic activity.

Tabel 2. The IC_{50} values of α-glucosidase inhibitory effect of selected ethnomedicinal plants

Ethnomedicinal plants	IC_{50} (mg/mL)	
	Maltase	Sucrase
Garcinia nervosa Miq.	0.046 ± 0.01	NI
Mimosa pigra L.	NI[b]	NI
Pterospermum javanicum Jungh.	0.117 ± 0.02	NI
Ixora javanica (Blume) DC.	0.195 ± 0.04	0.096 ± 0.02
Syzygium caudatilimbum (Merr.) Merr. & L.M.Perry	0.037 ± 0.01	0.070 ± 0.02
Ficus hispida	0.282 ± 0.12	NI
Gluta velutina Blume	0.170 ± 0.09	NI
Lepisanthes amoena (Hassk.) Leenh.	0.115 ± 0.02	NI
Artocarpus longifolius Becc.	0.094 ± 0.01	NI
Shorea balangeran Burck	0.045 ± 0.02	0.071 ± 0.01
Quercetin[a]	0.040 ± 0.01	0.030 ± 0.02

Note: [a]Positive control, [b]No inhibition, inhibitory effects less than 30% at 0.0625 mg/mL (final concentration). Each value represents the mean ± S.D (n=3)

Tabel 3. Antioxidant activity of ethnomedicinal plants against free radicals

Ethnomedicinal plants	IC_{50} (mg/mL)		
	DPPH	ABTS	Nitric oxide
Garcinia nervosa Miq.	0.13 ± 0.02	0.26 ± 0.18	0.24 ± 0.05
Mimosa pigra L.	NI[b]	NI	0.68 ± 0.30
Pterospermum javanicum Jungh.	0.46 ± 0.02	0.24 ± 0.16	0.16 ± 0.02
Ixora javanica (Blume) DC.	0.39 ± 0.01	0.35 ± 0.08	0.81 ± 0.20
Syzygium caudatilimbum (Merr.) Merr. & L.M.Perry	0.10 ± 0.02	0.07 ± 0.01	0.07 ± 0.02
Ficus hispida L.f.	NI	0.27 ± 0.08	NI
Gluta velutina Blume	0.44 ± 0.01	0.51 ± 0.07	0.15 ± 0.04
Lepisanthes amoena (Hassk.) Leenh.	0.83 ± 0.37	0.98 ± 0.44	0.98 ± 0.42
Artocarpus longifolius Becc.	0.98 ± 0.45	0.28 ± 0.11	NI
Shorea balangeran Burck	0.04 ± 0.01	0.06 ± 0.01	0.11 ± 0.04
Ascorbic acid[a]	0.05 ± 0.01	0.12 ± 0.01	0.05 ± 0.02

Note: [a]Positive control, [b]No inhibition, inhibitory effects less than 45% at 1 mg/mL. Each value represents the mean ± S.D (n=3)

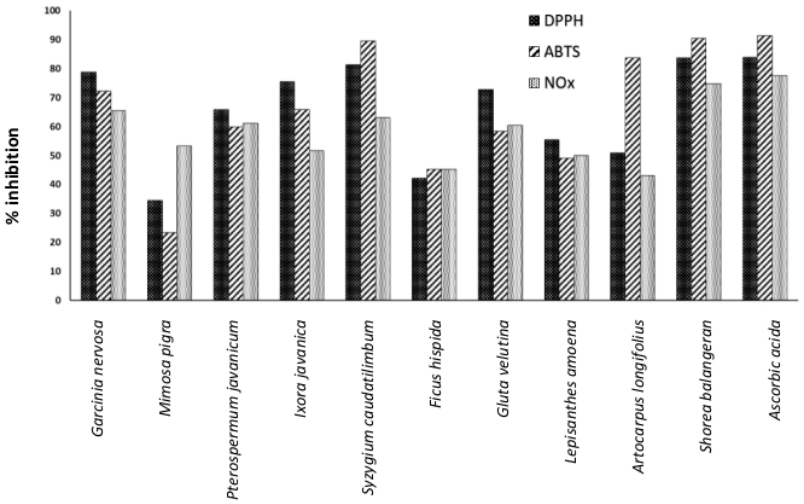

Figure 1. Inhibition percentage of ethnomedicinal plants against free radicals (at 1 mg/mL)

Antioxidant properties

In the present work, three different approaches were successfully employed to evaluate the antioxidant capacity of the ethnomedicinal plant extracts, such as DPPH, ABTS, and Nitric oxide free radical scavenging activities. The results were compared with ascorbic acid as a positive control. The free radical scavenging properties of ten ethnomedicinal plants from East Kalimantan are presented in Table 3. Among the ethnomedicinal plant extracts, *S. balangeran* showed a good inhibition percentage with 83.78% at 1 mg/mL (Figure 1) with a very strong IC_{50} value (0.04 mg/mL) that is similar to the IC_{50} value of ascorbic acid (0.05 mg/mL) as a positive control. The highest antioxidant activity of plant extracts is indicated by the lowest IC_{50} value in the assessment against free radicals. As stated by Marjoni and Zulfisa (2017), IC_{50} values of 0.05-0.1 mg/mL show strong antioxidant activity, whereas IC_{50} values <0.05 mg/mL demonstrate very strong antioxidant activity. Some reports of free radical scavenger activity of numerous ethnomedicinal plant species in this present work have been stated. The results of this study are in agreement with those of Subramanian et al. (2013) who reported the antioxidant activity of stem bark extract of *S. roxburghii* against DPPH free radicals. Thus, the findings in this study also demonstrated that *S. caudatilimbum* and *G. nervosa* extracts had IC_{50} values of 0.10 mg/mL and 0.13 mg/mL respectively, categorized as strong antioxidant activity. This finding is in line with that of See et al. (2016) who found that a stem bark from other species, such as *Garcinia benthamiana*, had antioxidant activity due to the presence of phytochemicals, including phloroglucinols. Meanwhile, Walean et al. (2020) reported that ethyl acetate extract of *Syzygium luzonense* stem bark had antioxidant activity against DPPH free radical with 85.07% inhibition at 250 ppm. However, the results above pointed out that several ethnomedicinal plant species from East Kalimantan showed antioxidant activity.

The free radical scavenging activity of ethnomedicinal plant extracts was also assessed using ABTS free radicals. ABTS free radicals are generated by an oxidation reaction with potassium persulfate ($K_2S_2O_8$) and they are converted into a non-radical form in a reaction with plant extracts (Hilla et al. 2013). The inhibition percentage (%) and IC_{50} value of ten extracts against ABTS free radicals are shown in Figure 1 and Table 3 respectively. A higher inhibition percentage (%) indicates higher free radical scavenging potential. The order of ten extracts' IC_{50} values of antioxidant activity against ABTS free radical from the lowest to the highest is as follows: *S. balangeran* < *S. caudatilimbum* < *P. javanicum* < *G. nervosa* < *F. hispida* < *A. longifolius* < *I. javanica* < *G. velutina* < *L. amoena* < *M. pigra*. Based on the aforementioned results, *S. balangeran* and *S. caudatilimbum* exhibited very strong antioxidant activity against ABTS free radicals with IC_{50} values of 0.06 mg/mL and 0.07 mg/ml respectively, which were more potent than that of ascorbic acid as a positive standard. Meanwhile, *P. javanicum*, *G. nervosa* and *A. longifolius* showed moderate antioxidant activity based on antioxidant categories of Marjoni and Zulfisa (2017). On the other hand, the researchers observed that methanol extract of *S. Roxburghii* stem bark exhibited strong antioxidant activity against ABTS free radical (Subramanian et al. 2013). These results are in line with the presence of phenolic compounds. Another study by Metasari et al. (2020) found that phytochemicals from *S. samarangense*, including quercetin and gallic acid, had antioxidant activity. Pieme et al. (2014) also discovered that the antioxidant activity of *S. guineense* was attributed to the presence of phenolic compounds. However, this study demonstrated that several ethnomedicinal plants from East Kalimantan have strong potential as sources of natural antioxidants. Furthermore, according to the author's knowledge, this study is the first to show antioxidant activity of ethnomedicinal plants from East Kalimantan.

The investigated antioxidant activity of ten ethnomedicinal plants was further determined by nitric oxide inhibitory activity. Nitric oxide (NO) is a proinflammatory mediator that can lead to tissue damage as well as activation of acute and chronic inflammation when it is overproduced (Njoya et al. 2017). Nitric oxide is a free radical since it has an unpaired electron and it displays important reactivity with other free radicals, such as superoxide, further forming the reactive peroxynitrite anion ($ONOO^-$) (Habu and Ibeh 2015; Hazra et al. 2008). Habu and Ibeh (2015) mentioned that plant extracts inhibited by scavenging nitric formation in peroxynitrite form a straight line competing through oxygen in the reaction system. As reported in Table 3, *S. caudatilimbum* showed the strongest antioxidant activity against nitric oxide radical with IC_{50} value of 0.07 mg/mL, followed by *S. balangeran* Burck, *G. velutina* Blume, and *P. javanicum* Jungh with IC_{50} values of 0.11 mg/mL, 0.15 mg/mL, and 0.16 mg/mL respectively. In accordance with the aforementioned antioxidant activity results, ten selected ethnomedicinal plants from East Kalimantan can serve as potential sources of natural antioxidants against free radicals often associated with neurogenerative diseases.

In conclusion, this study is the first to reveal antidiabetic activities in ten selected ethnomedicinal plants from East Kalimantan by inhibiting rat intestinal α-glucosidase and antioxidants by scavenging several free radicals, such DPPH, ABTS, and Nitric oxide. Furthermore, this study justified the therapeutic uses of these plants in ethnomedicine by providing scientific evidence. This study also suggested a broad spectrum of actions in selected plants for treating diabetes and its complications caused by free radicals. With the information reported in this study, ethnomedicinal plant extracts with excellent bioactivities need to be further investigated by isolating bioactive components, which may confirm their benefits for diabetes therapy.

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