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Original Article

Phytochemical Constituents, and *In vitro* Antidiabetic and Antioxidant Properties of Various Extracts of Kenikir (*Cosmos caudatus*) Leaves

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is one of the most common degenerative disorders. For therapeutic use, herbs are commonly used in Indonesia for T2DM treatment, one of them is (*Cosmos caudatus*) *kenikir's* leaves. In previous studies, *kenikir's* leaves have high antidiabetic and antioxidant activity. However, a comparison of antidiabetic activity from many extracts of *kenikir's* leave is remain unclear. This study will compare the antidiabetic and antioxidant properties of various *kenikir's* leave extract. *Kenikir's* leaves are extracted by maceration methods for three days using three different solvents: boiling water, 50% ethanol, dan ethanol 100%. Then, phenolic and flavonoid content will be measured, as well as antioxidant properties by DPPH radical scavenging activity assay, and antidiabetic properties by α-glucosidase inhibition assay, also LCMS/MS will be used to predict the compound from each extract. The result shows that 50% ethanol extract has highest phenolic and flavonoid content than others. It also has significantly higher antioxidant ($p<0.05$) and antidiabetic ($p<0.05$) properties than others. Meanwhile, LCMS/MS result of 50% ethanol extract predicts 6 chemical component, that quercetin is the most dominant compound. 50% ethanol extract of *kenikir's* leaves is superior from other extracts on phenolic and flavonoid content, antioxidant properties, and antidiabetic properties.

Key words: α-Glucosidase.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent metabolic disorders that characterize by chronic hyperglykemia.[1] This condition leads to an increase in many adverse effects on glucose biochemistry pathway, including glucose oxidation, the formation of advanced glycation end-products (AGE), and activation of polyol pathway. Consequently, that will give rise to free radical formation that will damage many organs and cause microvascular and microvascular complications, such as cardiomyopathy, retinopathy, neuropathy, and nephropathy.[2] Antioxidant is one of the agents that can prevent T2DM complications by transfer its electron, thus free radicals become more stable and less toxic to the body.[2,3] It is well known that herbs have abundant antioxidant components in it, thus have been widely used to treat many disorders including T2DM[4], one of them is *kenikir* (*Cosmos caudatus*).[5]

Just like any other herbs, *Kenikir* has abundant organic compounds in it, especially polyphenol that often be linked with antidiabetic activity.[2,6] Previous studies have demonstrated that *kenikir* contains many active substances, such as flavonoid, saponin, alkaloid, tannin, and polyphenol.[6] Other studies explained that *C. caudatus* water extract has a very high phenolic compound.[7] A very high antioxidant activity was also detected in methanol and ethanol extract of kenikir.[5] Moreover, n-hexane and ethanol extract have direct antidiabetic activity by inhibition of α-glucosidase and α-amylase enzyme that has a role in glucose absorption in the human body.[5,7,8] Those extracts were known to have antidiabetic activity because have catechin, α-D-glucopyranoside, and α-tocopherol in it.[7] Furthermore, dichloromethane extract also had an antihypertensive effect.[7]

Even though therapeutic effects of this plant as antioxidant and antidiabetic have been explained, the effect of solvent that is used for the extraction process towards antidiabetic activity has not been explained properly. Therefore, this study will compare antioxidant and antidiabetic activity of different extraction solvents from *kenikir's* leaves by *in vitro* study using DPPH radical scavenging assay and α-glucosidase inhibition assay.

METHODS

Plant material

Plant materials of *Cosmos caudatus* leaves were collected from PUSPITEK LIPI Serpong, South Tangerang. Then, it was cleaned from foreign material and dried using vacuum oven at 50^{0}C. Dried sample was mashed and sieved to be uniform powder.

Extraction process

14 g sample were extracted using maceration methods by 3 different solvents: warm water, 50% ethanol, and 96% ethanol, 15 mL each for three days. Next, it was filtered by filtration paper, then concentrated by rotary evaporator at 50^{0}C, 150 rpm.

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Phytochemistry screening

Alkaloids test

5 mg extract, 0.1 mL HCl 2N and 0.9 ml aquadest were added to the tube, then heat, filtered, and divided into 2 test tubes. Each tube was treated with Bouchardat's reagent and Mayer's reagent respectively. Formation of reddish brown and white color respectively indicated the presence of alkaloid.[9,10]

Flavonoid test

4 mg extract was dissolved by 3 mL ethanol and added to the tube. Added 0.1 mg magnesium and 10 drops of concentrated HCl. Formation of pink color indicated the presence of flavonoid.[11]

Tannin test

Next, few drops of $FeCl_3$ were added. The presence of tannin is indicated by formation of dark blue or greenish black color.[12]

Saponin test

5 mg extract and 10 mL boiling water were added to the tube, then shook it for 10 seconds. After that, added 10 drops of HCl 2 N to the tube. Appearance of the foam showed the presence of saponin.[11]

Terpenoid test

5 mg extract was dissolved with 3 mL dichloromethane, then steamed it. After that, 6 drops of acetic acid and 3 drops of sulfuric acid were added to the tube. Blue-green color formation indicated the presence of terpenoid.[13]

Total phenolic and flavonoid compounds

Total phenolic concentration was measured by Folin-Ciocalteu methods with gallic acid as a standard. Meanwhile, total flavonoid was determined by aluminium chloride colorimetric assay with quercetin as a standard.[3]

Antioxidant activity test: DPPH radical scavenging assay

Antioxidant activity test is measured by *DPPH-radical scavenging activity.* 5 µL of extract dissolved in 155 µL ethanol, then mixed with 40 µL DPPH and incubate for 30 minutes in dark room with room temperature. After that, read with microplate reader at 515 nm wavelength. Percentage of inhibition is measured by following formula:

$$\% \text{ Inhibition} = \frac{(\text{Abs}_{\text{blank}} - \text{Abs}_{\text{extract}})}{\text{Abs}_{\text{blank}}} \times 100\%$$

Next, the test was re-performed with different extract concentration, including 100, 50, 25, 12,5, and 6.25 ppm. The result would form a graph, that will be used to determine IC50 by linear regression methods.

Antidiabetic activity test: α-glucosidase inhibition assay

Antidiabetic activity test is measured by *α-glucosidase inhibition assay.* 5 µL of extract was mixed with 5 µL DMSO and 45 µL buffer phosphate. Then, added 25 µL substrate and 25 µL α-glucosidase enzyme, and incubated for 15 minutes. Next, added 95 µL sodium bicarbonate 0.2 M to terminate enzymatic activity. After that, read with microplate reader at 400 nm wavelength. Percentage of inhibition is measured by calculate extract (s_1), background extract (s_0), blank (b_1), and background blank (b_0) by following formula:

$$\% \text{ Inhibition} = \frac{[(A_{b1} - A_{b0}) - (A_{s1} - A_{s0})]}{(A_{b1} - A_{b0})} \times 100\%$$

Next, the test was re-performed with different extract concentration, including 200, 150, 100, 50, and 25 ppm. The result would form a graph, that will be used to determine IC50 of antidiabetic activity by linear regression methods.

LCMS/MS analysis

LCMS/MS analysis will be performed using *Waters Corporation* Systems, where Liquid Chromatography (LC) specification is *UPLC I-Class Plus System*, while Mass Spectrometry (MS) specification is *Xevo G2-Xs QTof Quadrupole Time-of-Flight Mass Spectrometry*. LC condition including: using *separation column*; solvents is using 0.1% formic acid/water and acetonitrile + 0.1 formic acid; 1 µL injection volume; 0.3 mL/min flow rate; and column temperature is 40°C. Meanwhile, MS condition including: ESI ionization; positive polarity; 30 V Cone Voltage; 6.00 eV and 10.00 eV Collition energy; and precursor ion 100-1200 m/z. *UNIFI Scientific Information System* will be used to analyse the results.

RESULTS

Phytochemical screening

The results of phytochemical screening are shown that 96% ethanol extract has more diverse metabolite compounds than others. Those compounds are alkaloid, tannin, saponin, and terpenoid as shown in **Table 1.** However, flavonoid was detected only in 50% ethanol extract.

Total phenolic and flavonoid compounds

The concentration results in 1,000 µg/ml extracts are shown as gallic acid equivalent for phenolic compound and quercetin equivalent for flavonoid compound. All of the extracts are contain both phenolic and flavonoid content that 50% ethanol extract is the highest one as shown in Figure 1.

Antioxidant activity

All of *kenikir's* leaves extracts demonstrated the capacity of DPPH free radical scavenging activity, with 50% ethanol extract exhibit the strongest antioxidant activity compared to other extracts. The mean inhibition activity of 50% ethanol extract was 84.036% (Figure 2a), that statistically significant compare to others ($p < 0.05$). However, the difference between 96% ethanol and water extract was not statistically

Table 1: Phytochemical screening of kenikir.

	Water	50% ethanol	96% ethanol
Bouchardat Test	+	-	-
Mayer Test	-	+	+
Flavonoid Test	-	+	-
Tannin Test	+	+	++
Saponin Test	-	-	+
Terpenoid Test	-	-	+

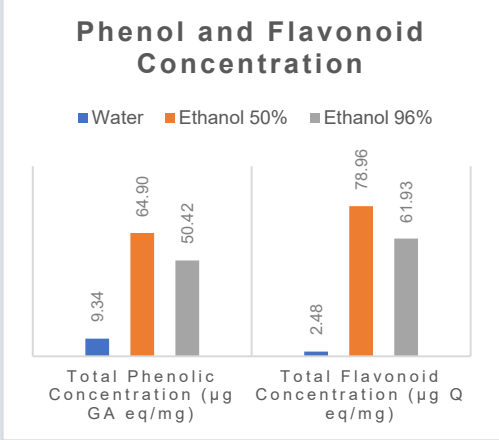

Figure 1: Total phenolic dan flavonoid of *kenikir* extract.

significant ($p > 0.05$). The 50% ethanol extract had IC50 about 59,99 ± 4,49 µg/ml, that still significantly weaker than quercetin as a control ($p < 0.05$), that had IC50 around 5,976 ± 0,08 µg/ml (Figure 2b).

Antidiabetic activity

All of *kenikir's* leaves extracts possessed the capacity of inhibiting the α-glucosidase enzyme, with 50% ethanol extract had the strongest inhibiting activity compare to other extracts. The mean inhibition of 50% ethanol extract was 61,8% (Figure 3a), that statistically significant compare to others ($p < 0.05$). However, 96% ethanol extract was not significantly stronger than water extract ($p > 0.05$). The 50% ethanol extract had IC50 about 77,17 ± 37,08 µg/ml, that still significantly weaker than quercetin ($p < 0.05$), that had IC50 about 1,38 ± 0,433 µg/ml (Figure 3b).

LCMS/MS analysis

18 bioactive components were found in the LCMS/MS analysis results of 50% ethanol, 96% ethanol, and water extracts as seen in chromatograms (Figure 4). As shown in Table 2, 50% ethanol and 96% ethanol extract had similar bioactive component, while water extract was different.

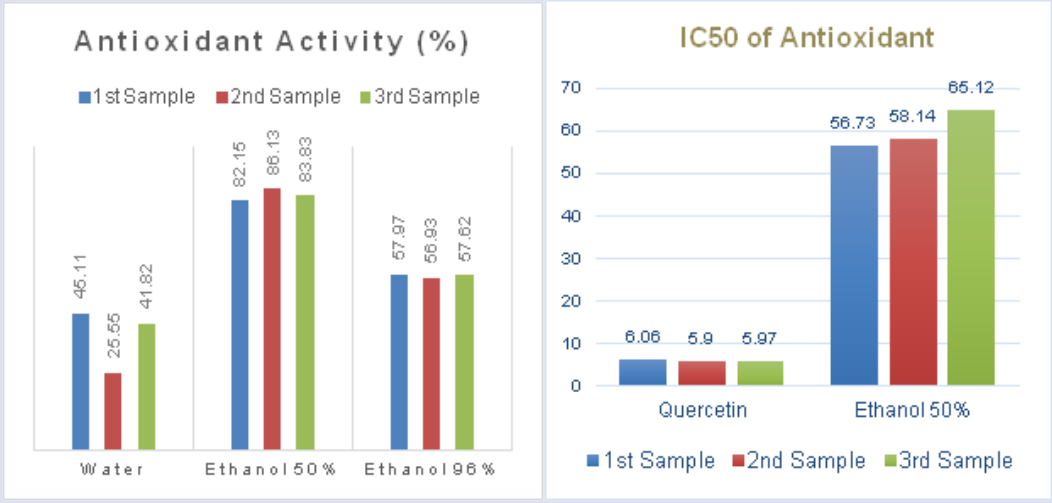

Figure 2: Presentation of inhibition (a) and IC50 (b) of antioxidant activity.

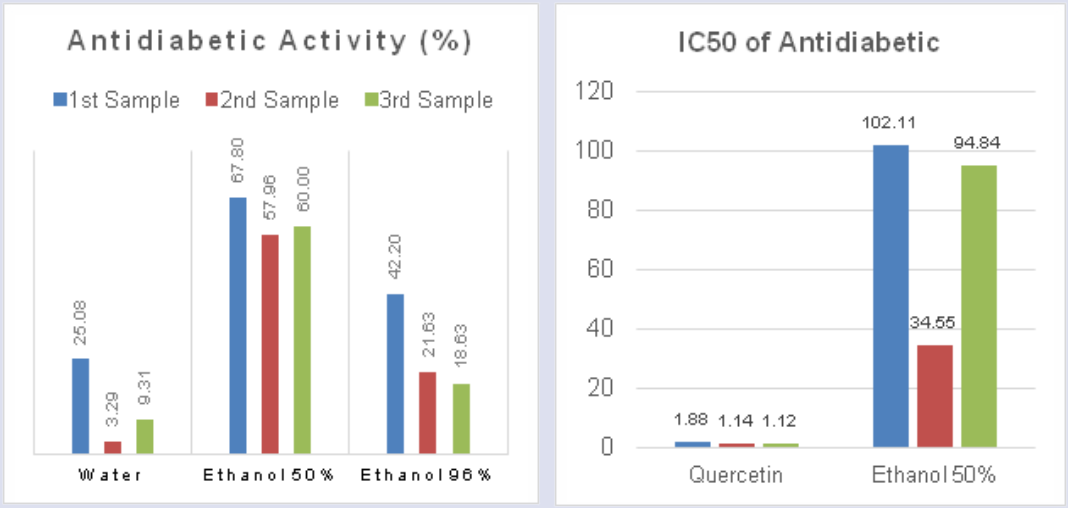

Figure 3: Presentation of inhibition (a) and IC50 (b) of antidiabetic activity.

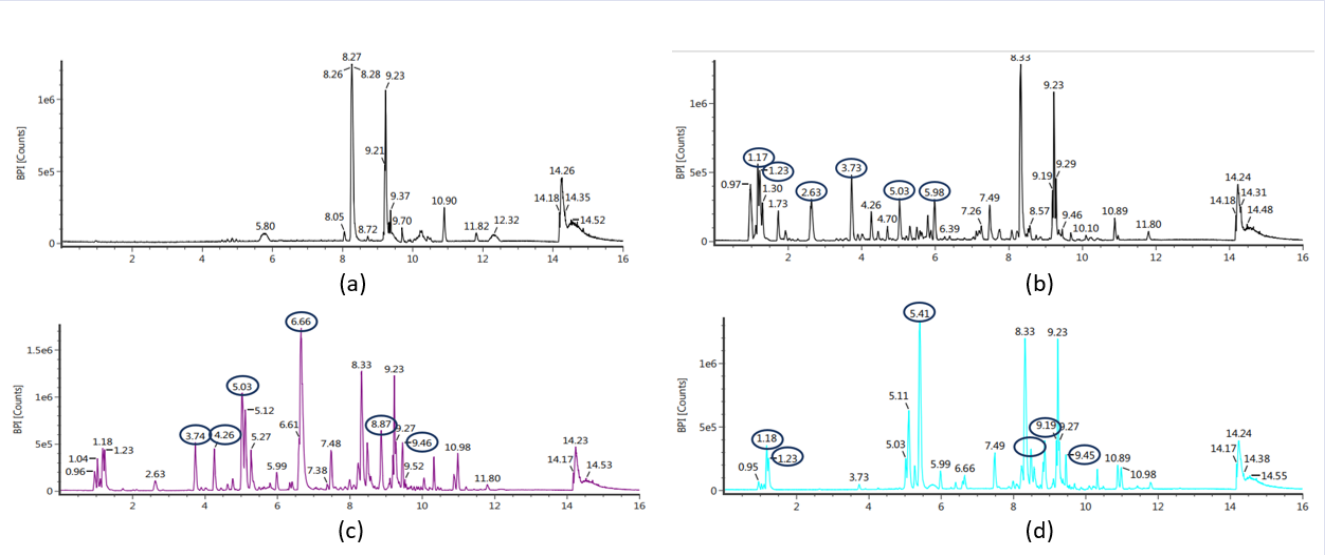

Figure 4: Cromatogram result of blank (a), water extract (b), 50% ethanol extract (c), and 96% ethanol extract (d).

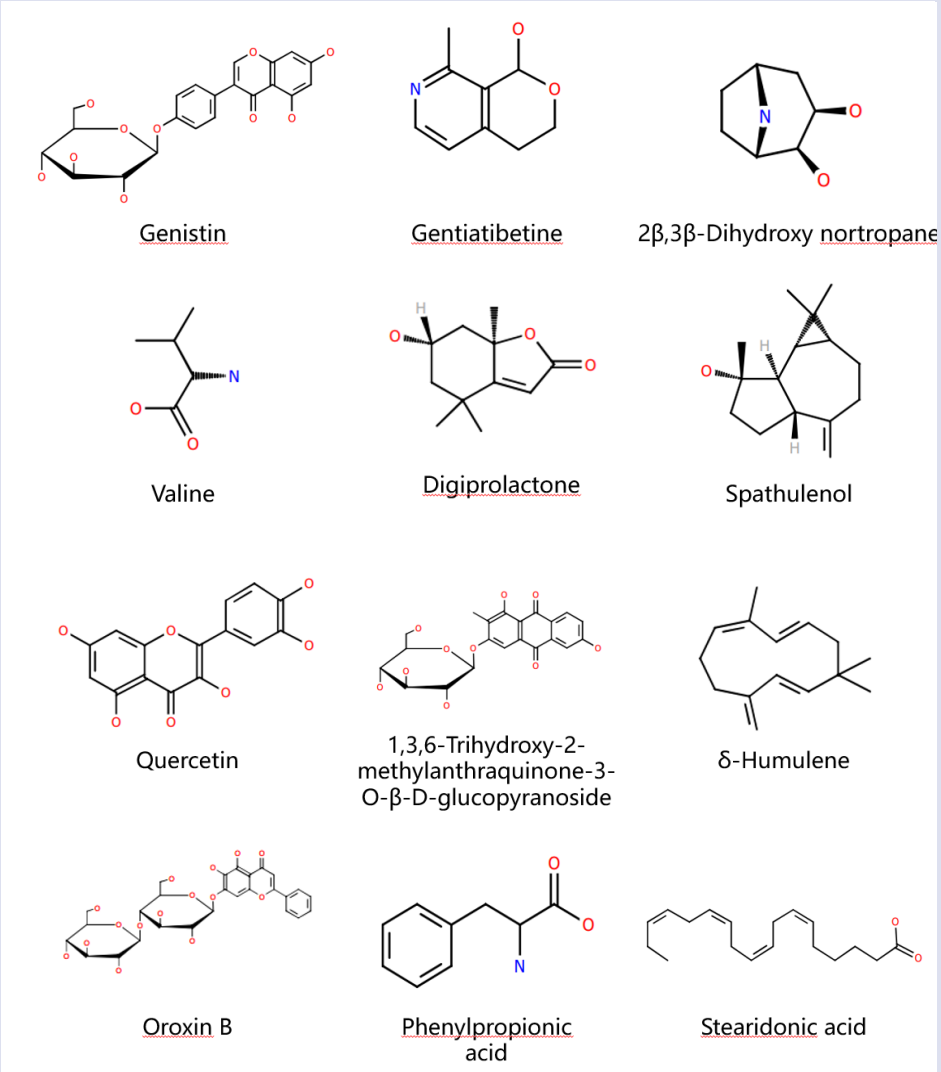

Figure 5: Chemical structure of bioactive compounds that have been revealed in kenikir extracts using LCMS/MS.

DISCUSSION

The kenikir's leaves were extracted using different solvents to analyze the effect to its antioxidant and antidiabetic activity. This study used ethanol as a solvent for extracting samples because of its semipolar characteristic while warm water is a polar solvent.[9] It is also one of the safe solvents that are allowed to be used in food ingredients together with ethyl acetate and acetone.[3] Warm water was used because high temperatures will increase cell wall permeability and facilitate the extraction process.[9] Combination of those solvents (50% ethanol) is used to affect certain compounds that less soluble in 96% ethanol.

Phytochemical screening results showed kenikir's leaves bioactive components are alkaloids, flavonoids, saponin, tannin, and terpenoids that is parallel with previous studies.[6,7] Those bioactive components are known to have medicinal properties, especially as the antioxidant and antidiabetic agents. Alkaloids are had antioxidant activity and play a role as the antidiabetic agent by down-regulating gluconeogenesis activity.[5,14] Flavonoids can inhibit the formation of reactive oxygen species (ROS) and induce beta cell regeneration so can prevent T2DM complications.[15] Saponin has antioxidant activity both *in vitro* and in vivo studies and also can reduce blood glucose level by inhibits glucose transportation in gastrointestinal tract.[5,16] Tannin is also antidiabetic agent that can increase glycogenesis and decrease glucose absorption.[5] Lastly, terpenoids are used for antidiabetic medication in various country.[17] These screening results were not in parallel with quantitative test that more reliable. It might be due to many factors, including human error.

The results of total phenolic and flavonoid content were not in line with the previous study. Rahman et al demonstrated that ethanol extract had higher phenolic and flavonoid contents than 50% ethanol extract.[18] That study also found that ethanol extract had stronger antioxidant activity.[18] According to previous studies, antioxidant activity is often linked with phenolic compounds, that also include flavonoids.[6] These unparalleled results with the previous study might occur because of many differences, such as harvesting periods, environmental and weather conditions, and environmental temperatures.[19] In this study, 50% ethanol extract, that is semipolar extract, was more powerful in both total phenolic, total flavonoids, and antioxidant activity than any other extracts. Its IC50 of antioxidant activity was also classified as a strong antioxidant based on Fidrianny I.[20] This biological property is beneficial for preventing T2DM complications.[2]

Antidiabetic activity results of kenikir extracts as α-glucosidase inhibitor showed similar result, where 50% ethanol extract had the greatest inhibition percentage. The IC50 of antidiabetic activity was 77,17 ± 37,08 µg/ml, that is still lower than quercetin as the positive control but parallel with Chan ECW that got the IC50 of α-glucosidase inhibition around 58 ppm for ethanol extract.[5] This results might indicate that antidiabetic components from kenikir extract are more likely to dissolve in 50% ethanol solvent.

The LCMS/MS analysis profiling analysis of 3 different *kenikir's* leaves extracts revealed 12 bioactive compounds that are predominantly secondary metabolites. The compounds were found to have various biological properties, especially antioxidant and antidiabetic activity (Table 3). Water extract was revealed 2 compounds, that is genistin and gentiatibetine. Both of them had weak antioxidant activity[21], while only genistin had antidiabetic property.[22,23] 50% ethanol extract had 6 compounds that have more diverse biological potency. Quercetin is one of the compounds that are a strong antioxidant agent and also have stronger antidiabetic activity than acarbose.[24–27] This compound is the main component of ethanol extracts according to detector response in Table 2 that correlated with its high antioxidant and antidiabetic activity. Other compounds are: oroxin B, that have weak antioxidant activity[28]; Stearidonic acid and Phenylpropionic acid that have antidiabetic activity[29–31]; and 1,3,6-Trihydroxy-2-methylanthraquinone-3-O-β-D-glucopyranoside, a novel compound that its biological properties have not been explained clearly and might be a potential compound because its *glucopyranoside* group that has antidiabetic activity.[7] Meanwhile, 96% ethanol extract had similar compounds with 50% ethanol extract, except *spathulenol* that have antidiabetic activity greater than acarbose.[32]

Table 3: Bioactive components in kenikir extract and its beneficial potency.

No.	Compound	Chemical Group	Biological Properties	Studies
			Water Extract	
1	Genistin	Isoflavone	Anticancer, antioxidant, and antidiabetic agent Antioxidant agent (IC50 =180 ppm) Antidiabetic agent (Ki = 5,7 x 10-5 µg/ml)	Moseti D, *et al*[23] Ruslan K, *et al*[22] Moseti D, *et al*[23]
2	Gentiatibetine	Alkaloid	Anticancer, antibacterial, and antioxidant agent	Bayliak, *et al*[21]
			50% ethanol Extract	
1	Quercetin	Flavonols	Anticancer and antioxidant agent Therapeutic Agent for CVD and degenerative disorders α-glucosidase inhibitor greater than acarbose Antioxidant agent by inhibits polyol pathway Antilipidemic agent	Lesjak, *et al*[24] Serban, *et al*[25] Soltesova, *et al*[26] Soltesova, *et al*[26] Srinivasana P, *et al*[27]
2	1,3,6-Trihydroxy-2-methylanthraquinone-3-O-β-D-glucopyranoside	Methyl-Glycoside	Have not studied yet	
3	Oroxin B	Flavonoid	Antidiabetic in *O. indicum* Its isomer (Oroxin D and C) are antidiabetic compound Weak antioxidant activity	Dong Y, *et al*[28] Li G, *et al*[33] Dong Y, *et al*[28]
4	δ-Humulene	Terpenoid	Its isomer (α-humulene) is anticancer agent	Chen H, *et al*[34]
5	Stearidonic acid	Omega-3 PUFA	Antidiabetic agent Antitumor agent and lipid regulator Anti-inflammation agent	Gao YX, *et al*[29] Yan Li, *et al*[35] Sung J *et al*
6	Phenylpropionic acid	Carboxylic Acid	Antidiabetic dan antithrombotic agent (agonist GPR40)	Kuranov SO, *et al*[30]dan Li Z, *et al*[31]
			96% ethanol Extract	
1	Spathulenol	Tricyclic Alcohol	Dominant compound (87%) in *Psidium gineense* α-glucosidase inhibitor (IC50 = 1,18 µg/ml) greater than acarbose	Bahadori, *et al*[32]

CONCLUSION

The use of different solvents in the extraction process will affect the antioxidant and antidiabetic activity of the extract. In this study, 50% ethanol extract of kenikir's leaves is the best solvent that has the highest total phenolic and flavonoid concentration, antioxidant activity, and antidiabetic activity than 96% ethanol and water extract. LCMS/MS analysis of 50% ethanol extract shown high amount of quercetin that had been demonstrated as a potent antioxidant and antidiabetic agent.

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