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Synthesis of Cr(III)-Aspartate and Cu(II)-Aspartate Complexes as Antidiabetic Compound

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ABSTRACT

The synthesis of Cr(III)-Aspartate and Cu(II)-Aspartate complexes has been successfully conducted by reacting $CrCl_3 \cdot 6H_2O$ and $CuCl_2 \cdot 2H_2O$ metals with aspartic acid. Therefore, this study aimed to synthesize $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ as well as test their antidiabetic effects. The synthesis results of $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ in the form of light purple and blue solids were 0.3001 g and 0.3095 g with a yield of 95.14% and 95.02%, respectively. Furthermore, the antidiabetic test used 27 male mice (*Mus musculus*) with nine treatments for 21 days. The data obtained were analyzed statistically using analysis of variance, and the antidiabetic activity was expressed in percent glucose lowering. The result showed a decrease in blood glucose levels in mice after alloxan induction, with percent glucose lowering (%GL) values of 74.1874% for $Cr(Asp)_2Cl_2$ and 76.1337% for $Cu(Asp)Cl_2$ compounds. Therefore, the $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ compounds can be used as antidiabetic in mice which are also potentially used as metal-based drugs for the treatment of Diabetes mellitus (DM).

Keywords: antidiabetic, Cr(III)-aspartate, Cu(II)-aspartate, mice

INTRODUCTION

Diabetes mellitus (DM), one of the top ten causes of death worldwide, is a disease caused by high blood sugar. It has caused the deaths of 1.6 million people in 2016 of which 90% had type 2 diabetes (WHO, 2018). Type 2 DM is caused by an inactive insulin receptor, which results in insulin not working optimally (DeFronzo *et al*., 2015). Type 2 DM is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world (Olokaba *et al.,* 2012).

Many inorganic compounds have been used and tested their biological activities as antimalarial (Hadi *et al.*, 2018; Hansch and Verma, 2009), anticancer and antitumor (Gielen, 2003; Rehman *et al.* 2009; Hadi *et al.*, 2010; Hadi *et al*., 2012), antifungal (Joshi *et al*., 2020), antibacterial (Annissa *et al.*, 2017, Hadi *et al.*, 2021; Samsuar *et al.*, 2021), inhibitor corrosion (Hadi *et al.*, 2015; Kurniasih *et al.*, 2015; Hazani *et al*., 2019). The study on various metal complexes have also shown very interesting antidiabetic activities, the metals include chromium, manganese, molybdenum, copper, cobalt, zinc, tungsten and vanadium (Thompson *et al.,* 2004; Budiasih *et al.,* 2013b; Sundaramurthy *et al.,* 2016).

One of the transition metals used for the treatment of DM is chromium(III), which plays a role in increasing the sensitivity of insulin receptors to interact with insulin (Cefalu and Hu, 2004; Lewicki *et al.,* 2014). These receptors can activate glucose transport to enter the cell membrane, and also to enhance the distribution and energy converting functions (Krejpcio, 2001; Lewicki *et al.,* 2014). In addition, the Cr(III) is a glucose tolerance factor (GTF), which functions to activate insulin receptors to increase the activity of glucose metabolism into energy and the effectiveness of insulin (Anderson, 2000).

The use of Cr(III) with amino acids in the form of new compounds is a potential opportunity for antidiabetic applications, and in this study, aspartic acid contained in GTF was used. Besides chromium, copper (II) metal can also act as an antidiabetic Cu metal with a Schiff base, which is synthesized and tested as an antidiabetic with a glucosidase inhibition value of 0.40% (4 µg/mL) in complex 1 (N-(salicylidene)-L-valine) and 2 (N-(3,5-dichlorosalicyliden)-L-valine) of 0.05% (0.5 µg/mL). Therefore, Cu metal with a Schiff base has diabetes inhibitory activity (Sundaramurthy *et al.,* 2016). Cr(III) and Cu(II) metal complex

compounds were synthesized with aspartic acid; the compounds formed were tested on male mice to determine the activity of antidiabetic compounds.

MATERIALS AND METHODS

Materials and Instrumentation

The materials used include $CrCl_3 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, amino acid aspartic acid, sodium hydroxide solution (1 M NaOH), alloxan, 5 mg glibenclamide, 0.9% NaCl, distilled water, double distilled water, aluminum foil, sugar strips, feed mice in the form of pellets, alcohol swab, and instrumentation: UV-Vis spectra were obtained using UV-Vis spectrophotometer Hitachi U-2010, the IR spectra were measured using FT-IR Bruker VERTEX 70 spectrophotometer, and SEM-EDX analysis was conducted using Scanning Electron Microscope (SEM-EDX) ZEISS EVO® MA 10.

Synthesis and Characterization of $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$

The synthesis of $CrCl_3 \cdot 6H_2O$ with aspartic acid was conducted at a ratio of 1:3 mmol using the procedure reported by Budiasih *et al.* (2013a). The $CrCl_3 \cdot 6H_2O$ solution was prepared by dissolving 0.26 g (1 mmol) $CrCl_3 \cdot 6H_2O$ in 25 mL distilled water. Meanwhile, the aspartic acid solution was prepared by dissolving 0.39 g (3 mmol) aspartic acid in 25 mL distilled water. The two were mixed and added with 0.1 M NaOH solution at varying pH (2, 4, 5, 6, and 7), refluxed at 60°C with time variations (1, 2, 3, and 4 h), and frozen dry for 48 h (Yang *et al.,* 2005). Furthermore, the synthesis of $CuCl_2 \cdot 2H_2O$ with aspartic acid was conducted at a ratio of 1:2 mmol in line with the previously performed procedure. The $CuCl_2 \cdot 2H_2O$ and aspartic acid sample solutions were prepared by dissolving 0.17 g (1 mmol) $CuCl_2 \cdot 2H_2O$ and 0.26 g (2 mmol) aspartic acid in 25 mL distilled water respectively. Thereafter, the next treatment conducted was similar to the synthesis of $Cr(Asp)_2Cl_2$.

The characterization of $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ complex compounds was conducted using a UV-Vis spectrophotometer at a wave length of 300–1000 nm. Furthermore, IR was conducted to identify the functional groups present in the $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ complex compounds at wavenumbers 4000–400 cm^{-1}.

Antidiabetic Test

The antidiabetic test was conducted based on the reported procedure available in the literature (Sharma *et al.*, 2011; Budiasih *et al.,* 2013b; Ariastuti *et al.,* 2020) and as following: male mice (*Mus musculus*) between 3-4 months old and weighing 30-40 g, as many as 27 were used. Before treatment, 27 mice were acclimatized for 7 days in order to get adapted to the new environment and minimize the effects of stress that can affect their metabolism. During the acclimatization process, they were given food and water ad libitum until they were satisfied. All treatment groups were induced by alloxan by injecting the solution subcutaneously at the nape of the neck using 150 mg/kgbw. It aimed to make the mice to become diabetic. Based on the American Diabetes Association, the criteria for diabetes diagnosis are an increase in blood glucose levels (hyperglycemia) ≥126 mg/dL.

RESULTS AND DISCUSSION

The Synthesis of $Cr(Asp)_2Cl_2$

The synthesis results of $Cr(Asp)_2Cl_2$ were obtained in the form of light and blackish purple solids. In the complex without the addition of NaOH, it was obtained that a solid of 0.3543 g was blackish purple. However, at pH 4 and 5, it had a light purple color of 0.4001 and 0.2645 g, respectively; and at pH 6, it was 0.2432 g in the form of blackish purple (Figure 1). The characterization using a UV-Vis spectrophotometer shows the shift in wavelengths after reacting $CrCl_3 \cdot 6H_2O$ with aspartic acid (Figure 2).

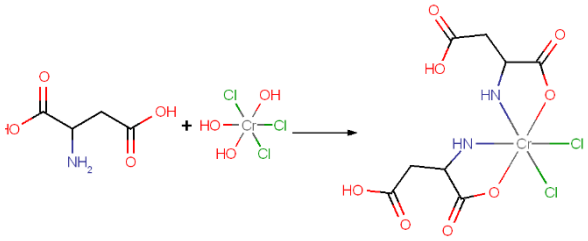


Figure 1. The reaction between Cr(III) and aspartic acid.

The maximum wavelength (λ_{max}) of $CrCl_3 \cdot 6H_2O$ metal (439 and 630 nm), toward a smaller one in the $Cr(Asp)_2Cl_2$ complex at pH 2 (408 and 599 nm) and at pH 4 (383 and 538 nm) (Figure 2 (a)). This shows that there has been a reaction between $CrCl_3 \cdot 6H_2O$ and aspartic acid.

The shifting toward a smaller wavelength is called a blue shift (hypsochromic) and it occurs when the increase in the solvation of the electron pair results in a decrease in the n orbital energy.

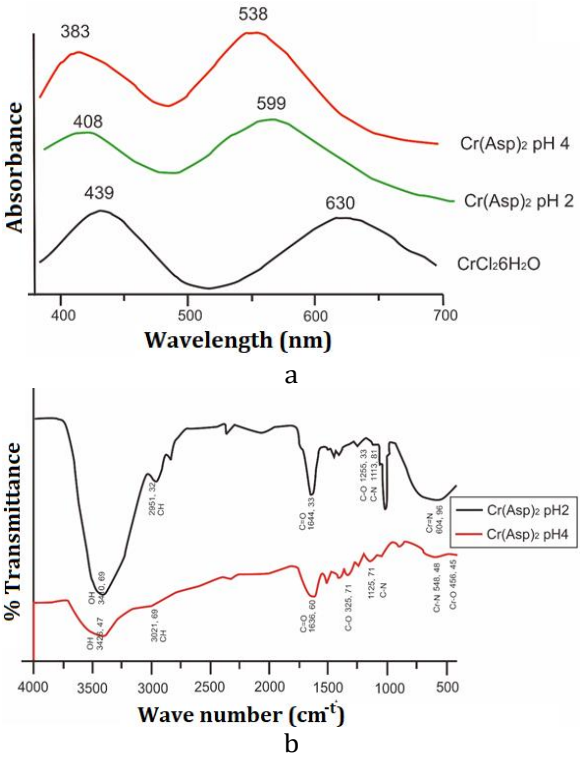


Figure 2. The spectra of (a) Uv-Vis; (b) FT-IR of the $Cr(Asp)_2Cl_2$ compound

At pH 2, there is OH absorption at 3410.69 cm^{-1}, CH stretching vibrations at 2951.32 cm^{-1}, C=O absorption at 1644.33 cm^{-1}, C–O and C–N stretch are visible at 1255.33 and 1113.81 cm^{-1} (Figure 2 (b)). Furthermore, the Cr–N absorption is in the area of 604.96 cm^{-1} indicating that there is a bond between the Cr and the N atoms. On the contrary, at pH 4, there is OH absorption at 3426 and 47 cm^{-1}, the stretching vibration of CH at 3021.69 cm^{-1}, C=O absorption at 1636.60 cm^{-1}, C–O and C–N stretch were seen at 325.71 and 1156.34 cm^{-1}. The Cr–N and Cr–O absorption was found in 548.48 and 456.45 cm^{-1}, these values are in agreement to the data reported by Mangamma *et al.* (2007). Meanwhile, the coordinate covalent bond between metal and ligands can be seen at the wavenumber below 625 cm^{-1}. Based on the IR spectra in Figures 2 (a) and (b), the synthesized compound used for the antidiabetic test is $Cr(Asp)_2Cl_2$. It was obtained as the result of synthesis at pH 4, which indicates the formation of Cr–N and Cr–O bonds from aspartic acid. The SEM/EDX measurement results for the $Cr(Asp)_2Cl_2$ complex show that there are still Cl ligands. Therefore, the aspartate ligand does not completely replace the water molecule and the Cl atom (Figure 3 and Table I).

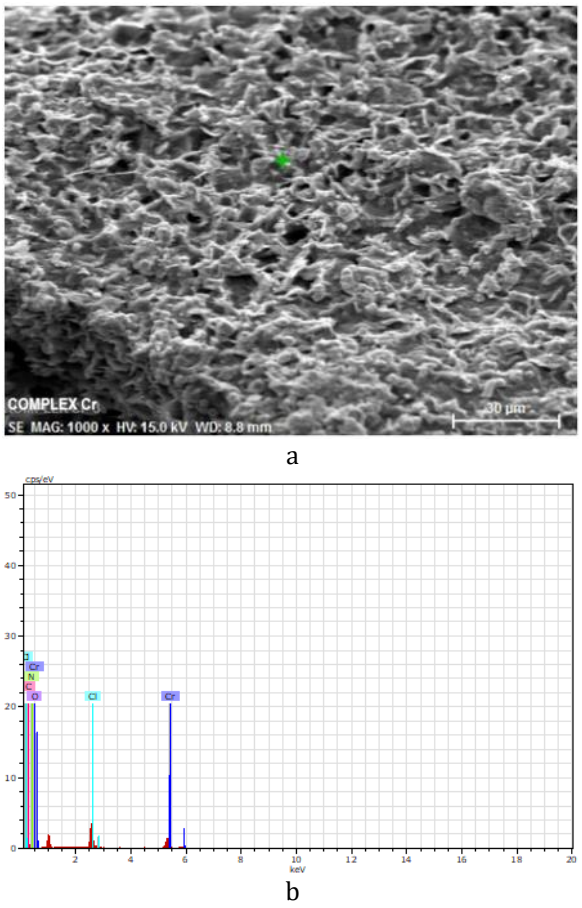


Figure 3. (a) SEM image; (b) EDX spectra of the $Cr(Asp)_2Cl_2$ compound

The Synthesis of $Cu(Asp)Cl_2$

The synthesis results of $Cu(Asp)Cl_2$ at pH 7 in the form of a blue solid at 1 h are 0.2083 g; 2 h, 0.2258 g; 3 h, 0.2967 g; and 4 h, and 0.2110 g; and most solids are found in the time of 3 h. The synthesis at pH 2 obtained a green solid as much as 0.2935 g, pH 4, 5, and 6 having a weight of 0.3095, 0.2712, and 0.2876 g, respectively. The molecular structure formed from the reaction between $CuCl_2 \cdot 2H_2O$ and aspartic acid in distilled water is $Cu(Asp)Cl_2$ compound (Figure 4).

Table I. The composition of metal element in $Cr(Asp)_2Cl_2$ measured with EDX

EI	AN	Series	C. Norm [wt. %]	C. Atom [wt. %]	C. Error [at. %]	(1 sigma) [wt. %]
O	8	K-Series	35.25	39.84	37.29	5.54
C	6	K-Series	30.71	34.64	43.20	4.94
N	7	K-Series	12.88	14.52	15.53	3.05
Cl	17	K-Series	5.33	6.02	2.54	0.22
Cr	24	K-Series	4.42	4.98	1.44	0.17
		Total	88.65	100.00	100.00	

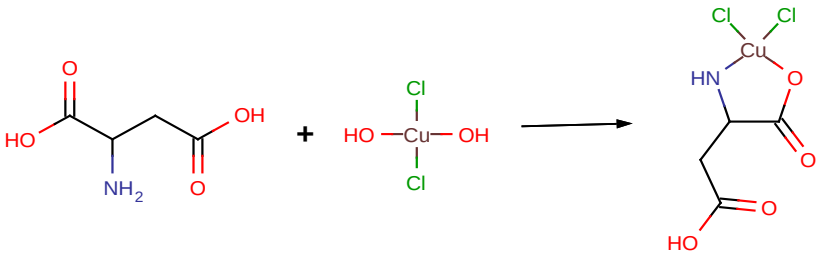


Figure 4. The reaction between Cu(II) and aspartic acid

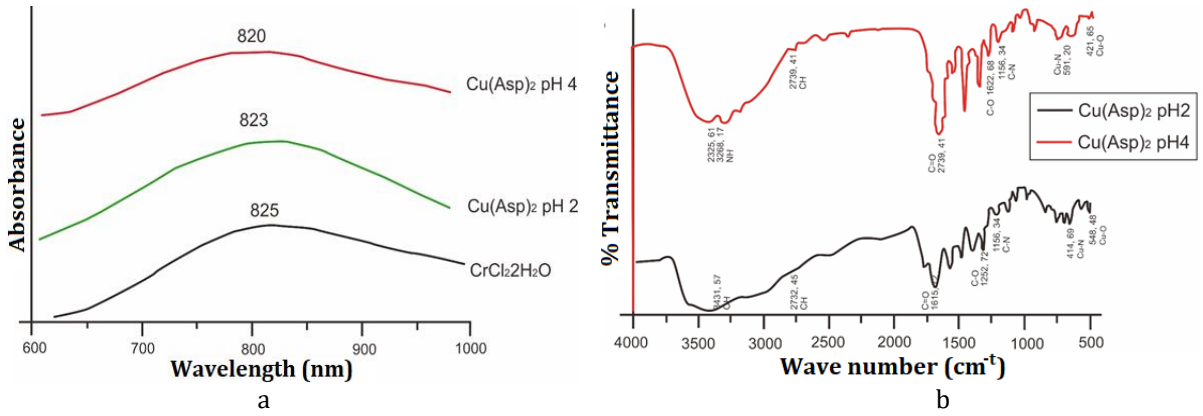


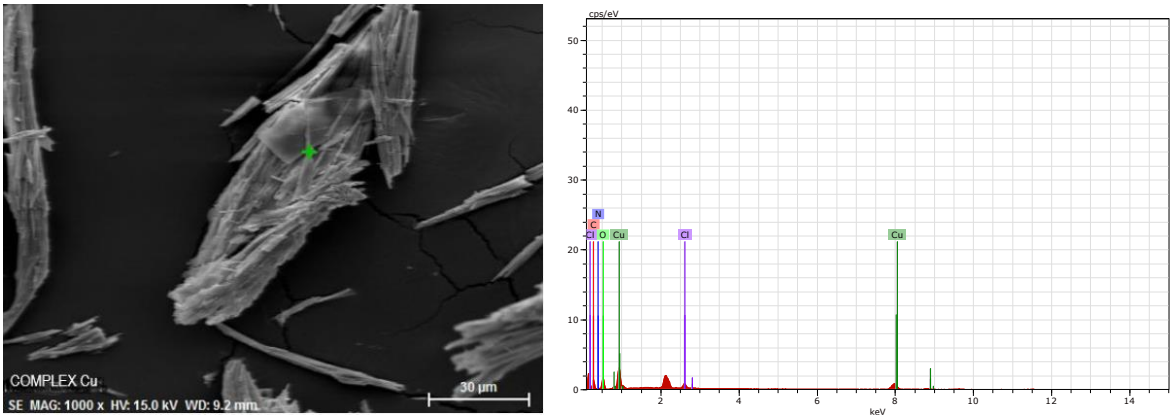
Figure 5. The spectra of (a) Uv-Vis; (b) FT-IR of the $Cu(Asp)Cl_2$ compound

$CuCl_2{\cdot}2H_2O$ metal has a maximum wavelength (λ_{max}) at 825nm (Figure 5.a). Meanwhile, in the complex compounds formed, $Cu(Asp)Cl_2$ pH 2 is absorbed at a wavelength of 823 nm and $Cu(Asp)Cl_2$ pH 4 is at 820 nm. This causes a shift to a smaller λ_{max} due to the reaction between $CuCl_2{\cdot}2H_2O$ and aspartate. Therefore, the $CuCl_2{\cdot}2H_2O$ complex changes into a new Cu(II); H_2O and Cl ligands are replaced by aspartate as a new ligand that binds coordination with Cu(II) to form the $Cu(Asp)Cl_2$ complex.

At pH 2, there is OH absorption at 3431.57 cm^{-1}, CH stretching vibration at 2732.45 cm^{-1}, C=O absorption at 1615.72cm^{-1}, CO and CN stretch at 1252.72 and 1156.34cm^{-1}, and the Cr–N and Cr–O absorption were 548.48 and 414.69 cm^{-1} (Figure 5.b). At pH 4, there is no OH absorption, and NH absorption appears at 3325.61–3268.17 cm^{-1}, CH stretching vibration is at 2739.41 cm^{-1}, C=O absorption at 1622.68 cm^{-1}, CO and CN peaks were observed at 1234.45 and 1156.34 cm^{-1} (Figure 5.b). Also, Cu–N and Cu–O absorption was found at 591.20 and 421.65 cm^{-1}, these values are close the reported values reported by Al-Jeboori and Al-Shimiesawi (2013) and the coordinate covalent bond between metal and ligands can be seen at the wavenumber below 625 cm^{-1}. The elements in the $Cu(Asp)Cl_2$ complex characterization using SEM/EDX (Figure 6 and Table II).

Table II. The composition of metal element of $Cu(Asp)Cl_2$ using EDX measurement

EI	AN	Series	C. Norm [wt. %]	C. Atom [wt. %]	C. Error [at. %]	(1 sigma) [wt. %]
Cu	29	K-Series	24.98	51.32	19.03	1.00
C	6	K-Series	11.21	23.04	45.19	2.24
O	8	K-Series	8.29	17.04	23.09	1.54
N	7	K-Series	2.38	4.88	8.22	0.83
Cl	17	K-Series	1.81	3.72	2.47	0.11
		Total	48.68	100.00	100.00	



a b

Figure 6. (a) SEM image; (b) EDX spectra of the $Cu(Asp)Cl_2$ compound

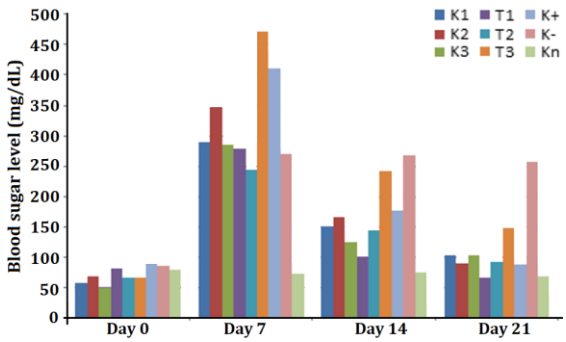


Figure 7. The changes in blood glucose levels in mice

The SEM/EDX measurement results for $Cu(Asp)Cl_2$, indicating that the complex formed contains a Cl atom (Figure 6). Therefore, only one molecular aspartate ligand is attached to the Cu atom since the complex formed is $Cu(Asp)Cl_2$.

Antidiabetic Test

Results of observations regarding the effect of the complex compounds $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ on the decrease in total blood glucose levels of alloxan-induced mice (Figure 7).

The blood glucose levels of the mice were measured on day 0 and for each mouse, it ranged from 57.67 to 89.33 mg/dL. Subcutaneous alloxan induction treatment was given at a dose of 150 mg/kgbw to put them in an antidiabetic condition. Alloxan was chosen as a diabetogenic agent because of its ability to display the antidiabetic effects within 2–3 days of treatment (Lelono and Tachibana, 2013). The induction causes blood glucose levels of mice to fluctuate for 8–48 h, which includes the phases of hyperglycemia and hypoglycemia that occur alternately before the occurrence of permanent

Table III. Percentage of blood glucose in mice

Group	**$Cr(Asp)_2Cl_2$**			**$Cu(Asp)Cl_2$**			**Control**		
Treatment	K1	K2	K3	T1	T2	T3	K+	K-	Kn
%GL	64.4419	74.1874	63.6257	76.1337	61.8852	68.5734	78.3455	4.44444	4.62963

Table IV. The average of blood glucose levels in mice after given $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ compounds

Treatment $Cr(Asp)_2Cl_2$	**Mean Blood Glucose Levels of Mice (Mean ± Std. Deviation)**	**Treatment $Cu(Asp)Cl_2$**	**Mean Blood Glucose Levels of Mice (Mean ± Std. Deviation)**
K1	103.00±30.61[a]	T1	66.67±17.15[a]
K2	90.00±36.59[a]	T2	93.00±61.02[a]
K3	103.67±18.50[a]	T3	148.33±25,54[b]
K(+)	89.00±4.00[a]	K(+)	89.00±4.00[a]
K(-)	224.67±16.50[b]	K(-)	224.67±16,50[c]
K(n)	68.67±9.60[a]	K(n)	68.67±9.60[a]

Note: Figures followed by a different superscript show a significant difference based on the 5% LSD test

hyperglycemia (Lenzen, 2008). In addition, the results on the seventh day showed an increase in blood glucose levels in mice. The increase was quite diverse, because the response of the body of each mouse to alloxan was different, resulting in a different increase in blood glucose levels. This is due to the damage in the β cells of the pancreas, which is a site for the secretion of the hormone insulin. The mechanism of action of alloxan in damaging pancreatic β cells occurs through the formation of reactive oxygen compounds that form superoxide radicals from redox reactions. Through the redox cycle, a highly reactive hydroxyl is formed and it caused rapid damage to pancreatic β cells.

Blood glucose levels of mice increased between 244 and 472 mg/dL and those with diabetes in the K1, K2, K3, T1, T2, T3, K(+), and K(−) treatment groups experienced polyuria (increased urine volume), as shown in the damp and smelly cage conditions. For 14 days, $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ were given to mice in the K1, K2, K3, T1, T2, and T3 treatment groups, and glibenclamide compound was orally administered in the K(+) treatment group. The results of measuring blood glucose levels in the K1, K2, K3, T1, T2, T3, and K(+) on the 14th and 21st days showed a gradual decrease in blood glucose levels. Also, the effect of the treatment can be observed from the percent glucose lowering (%GL), which is the percentage reduction in blood sugar levels (Sharma *et al.,* 2011; Pelin *et al.,* 2017). The %GL is the difference between the sugar content (average) of the diabetes mice group before and after treatment.

The percent results of blood glucose in mice, and in the $Cr(Asp)_2Cl_2$ group, K2 treatment had the highest %GL value, accounting for 74.1874% (Table III). Meanwhile, in the $Cu(Asp)Cl_2$ control group, T1 treatment had the highest %GL, that is, 76.1337%. The K2 and T1 treatment groups had %GL values that were close to the positive control (glibenclamide) of 78.3455%. Therefore, $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ groups have almost a similar level of effectiveness as glibenclamide.

The results of one-way analysis of variance test on grade values blood glucose in each treatment group show that $Cr(Asp)_2Cl_2$ has a significant effect ($p < 0.05$). After administering $Cr(Asp)_2Cl_2$ compound, the blood glucose increased. The following table shows the mean blood sugar of mice after giving $Cr(Asp)_2Cl_2$ compound on the 21st day.

The results of the smallest significant difference measurement of the mean blood sugar levels against the $Cr(Asp)_2Cl_2$ compound administered (Table IV). There was a significant difference between K(−) and K1, K2, K3, K(+), and K(n) treatments. On the contrary, there was no significant difference between K(n), K2, K3, K(+), and K1 treatments.

Therefore, K1, K2, K3, and K(+) treatments have a value that is almost similar to K(n) and very different from K(−) treatment.

As shown by the results of measuring blood glucose levels in mice by giving Cu(Asp)Cl2 compounds in Table 2, there was a significant difference between K(−) and T1, T2, K(+), and K(n) treatments. Furthermore, there was a significant difference between T3 and T1, T2, K(+), and K(n) treatments. In contrast, there was no significant difference between K(n) and T1, T2, and K(+) treatments. These results are similar to those of previous studies using $Cr(Ala)_3$ and $Cu(Ala)_2$ complexes to reduce glucose levels in mice (Ambarwati *et al.,* 2020).

Based on the study that has been conducted, the compounds synthesized, $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$, can reduce blood glucose levels in mice.

CONCLUSIONS

The synthesis of $CrCl_3{\cdot}6H_2O$ compound with aspartic acid obtained maximum results at pH 4 with a synthesis time of 4 h resulting in a light purple solid with a yield of 95.14%. The synthesis of $CuCl_2{\cdot}2H_2O$ compounds with aspartic acid obtained a maximum result at pH 4 with a time of 3 h, and resulted in blue solid with a yield of 95.02%. The *in vivo* antidiabetic test showed that the $Cr(Asp)_2Cl_2$ and $Cu(Asp)Cl_2$ complex compounds possessed an effect on reducing blood glucose levels after alloxan induction. This was proven with %GL value of 74.1874% for $Cr(Asp)_2Cl_2$ at dose II and 76.1337% for $Cu(Asp)Cl_2$ at dose I.

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