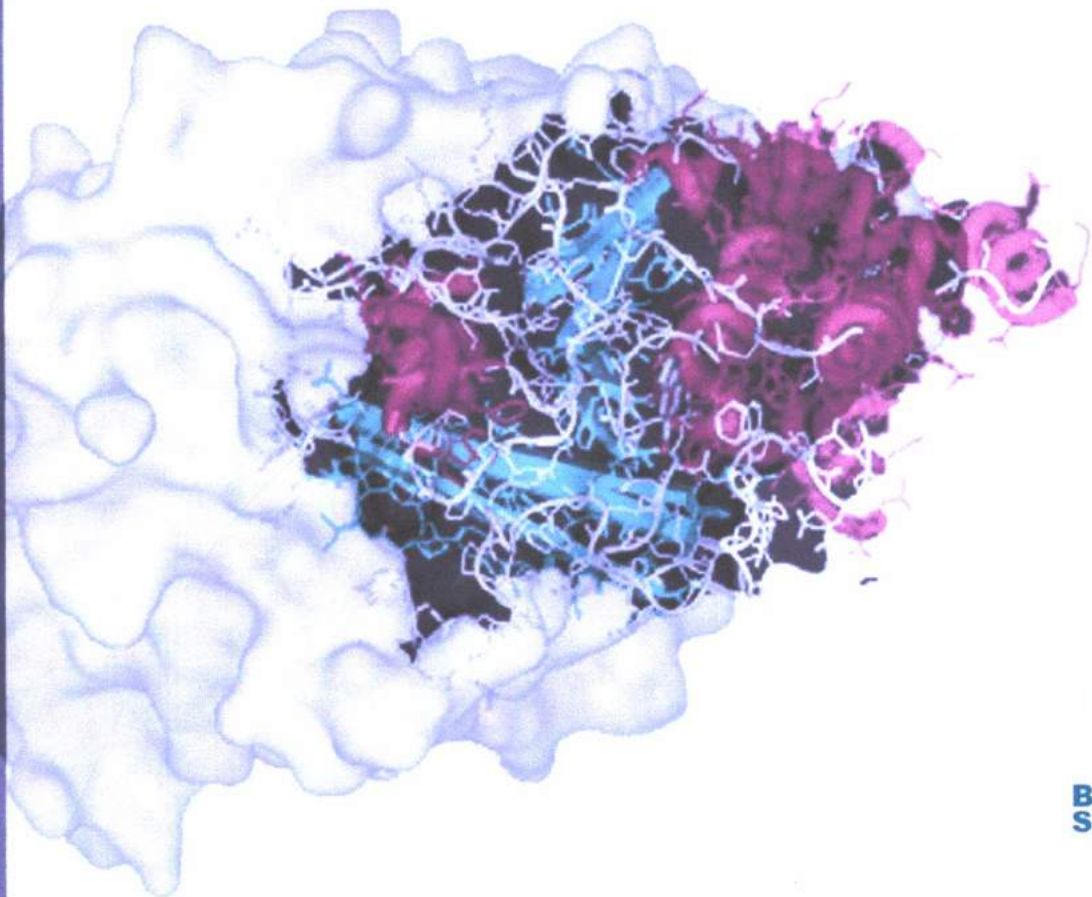


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Study Of *Coleus Amboinicus* Extract in Increasing of Transforming Growth Factor- β 1 (TGF- β 1) Concentration and Docking Prediction Quercetin Derivatives in 4X0M Receptor on Uric Acid-Induced in Rats

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Abstract: Background: *Coleus amboinicus* extracts are known to have anti-oxidant activity, anti-platelet aggregations, anti-bacterial, anticancer and anti-inflammation.

Objective: To evaluate *Coleus amboinicus* (CA) extracts in increasing of transforming growth factor- β 1 concentration and molecular docking prediction of quercetin on receptor 4X0M (TGF- β 1), measuring the levels of BUN, serum creatinine and Glutathione Peroxidase (GPx) on uric acid-induced rats.

Method: Forty-two male Wistar rats (*Rattus norvegicus*), 3 months, 150-200 g were allocated into 3 groups (n=14). The control group received placebo (U-0), treatment group were administered orally with uric acid 1,5% and oxonic acid 2% (U-1) and received 500 mg/kg bw of the CA extracts (U-2) respectively for 30 days. Blood serums collected for analysis of creatinine and BUN concentrations. All groups were sacrificed to collect kidney for measuring of GPx activity and TGF- β 1 concentration was conducted by avidin-horseradish peroxidase (HRP) sandwich-Elisa. Kidney organ was collected to histopathological analyzed by HE and PAS staining.

Results: CA extract analyzed by TLC has a relative fraction of flavonoids, terpenes, saponins, polyphenols and alkaloids. Induction with uric acid has proven to causes acute renal failure with indicated of elevated BUN, serum creatinine concentration and necrotic lesions of tubular membrane in treatment groups. Treatment of CA extract at a dose of 500 mg/kg bw could increase of GPx and of TGF- β 1 concentration significantly ($p \leq 0.05$). Quercetin as a marker compound of CA extract has stronger bind to the TGF- β 1 receptor (PDB code: 4X0M) than its of 3WA_601 ligand by in silico.

Conclusion: CA extract is proven to inhibit acute renal failure by increasing of TGF- β 1 concentration and has strong binding of its receptor.

Keywords: *Coleus Amboinicus*, Transforming Growth Factor- β 1 (TGF- β 1), Glutathione Peroxidase (GPx), Quercetin, Uric Acid

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1. INTRODUCTION

Uric acid is the final product of purine metabolism with the role of the enzyme xanthine oxidase. In some mammals, uric acid is broken down into allantoin compounds that are soluble by using uricase enzymes in the liver. Meanwhile, human liver genes have mutations that do not produce the uricase enzyme, which causes uric acid could not be broken down into allantoin and trigger high uric acid levels in the blood [1]. Oxonic acid is a compound that is antagonistic to urate oxidation [2]. According to previous studies, hyperuricemia affects chronic kidney disease in patients, so control of blood uric acid levels is important for the treatment of chronic kidney failure [3-4]. Giving oxonic acid with uric acid in Wistar rats aims to inhibit the metabolism of uric acid to become an allantoin (uricase enzyme inhibitor) so that the level of uric acid in the blood will be increased [5-6]. Uric acid is insoluble in the distal part of the nephron, so that uric acid is deposited into the tubules causing intrarenal precipitation, tubulointerstitial inflammation and glomerulosclerosis.

Uric acid oxygenates low density lipoprotein (LDL) through the activity of the enzyme NADPH oxidase, producing free radicals (ROS). The increasing in free radicals will cause the formation of arteriosclerosis, tubular atrophy and fibrosis in kidney interstitial tissue, infiltration of inflammatory cells in the glomeruli and interstitial of kidney tissue [7]. Conditions of oxidative stress in the kidneys by uric radicals can inhibit the enzymatic activity of free radical inhibitors such as the intracellular enzymes glutathione peroxidase (GPx) and super oxide dismutase (SOD) and damage to the enzymatic activity of endothelial nitric oxide synthase (eNOS). Tubulointerstitial damage by urate crystals is followed by inflammatory reactions that trigger expression of proinflammatory cytokines such as interleukin-2 (IL-2), macrophage migration inhibitory factors (MIF), and tissue macrophage monocytes [7]. Induction of uric acid in rat shows inflammation and fibrosis of tubular epithelial cells by increasing the expression of transforming growth factor- β 1 (TGF- β 1) and interleukin-1 β expression [8]. The deposition of urate crystals in the epithelial tubules causes the accumulation of macrophages and the expression of monocyte chemoattractant protein-1 (MCP-1) accompanied by an increase in free radicals, cyclooxygenase-2 (COX-2), MIF expression, lymphocyte cell infiltration, expression of interleukin-2R (IL-2R) and expression of MHC-II [5,9].

Treatment related to the condition of high uric acid levels (hyperuricemia) in general using anti-inflammatory drugs, such as non-steroid anti-inflammatory drugs (NSAIDs), uric lowering drugs (xanthine oxidase enzyme inhibitors and antagonists angiotensin converting enzyme (ACE), and uricosuric drugs [10-11]. The use of those drugs has not been effective for patients even the use of NSAIDs and anti-hyperuricemia drugs (allopurinol or probenecid) in the long term cause side effects kidney, hepatotoxic and allergic [12-13]. The development of anti-inflammatory drugs with hyperuricemia is aimed at inhibiting IL-1 β and TNF- α expression, in order to have a more effective therapeutic effect than symptomatic drugs [10,14,15].

Coleus amboinicus are known to have been used as traditionally drug for coughs, bronchitis, laryngitis, diarrhea-dysentery and some food supplements some people in Africa, Asia, Australia and South America [16]. Genetically *coleus amboinicus* plants consist of 62 species and the types of plants examined as medicinal ingredients are *Coleus* or *Plectranthus amboinicus* species. The content of active compounds both from the leaves and stems of *Coleus* plants include monoterpenoids, sesquiterpenoids, diterpenoids, phenolics, squalene, carioophylline, phytol, alkaloids, glycosids, flavonoids, quinones, tannins, and terpenoids [17-20].

Coleus amboinicus contains flavonoid compounds, which become marker compounds, and rosmarinic acid. These two compounds are reported to be able to inhibit the expression of Interleukin and Tumor Necrosis Factor- α in acute inflammation of Wistar rats [21-22] and diuretic activity on induction of Wistar rat nephrolithiasis [20,23]. *Coleus amboinicus* extract can also reduce serum urea, creatinine, and uric acid levels and increase neutrophil, granulocyte and platelet activity, antioxidant activity, anti-platelet aggregation, antibacterial and antiproliferative activity against cancer cells in vitro [24], is anti-inflammatory in rheumatic induction of arthritis of Wistar rats [25] anticonvulsants [26], anti-inflammatory and antitumor in vitro [27].

Characterization and cytokine receptors are grouped in supramolecular cytokine receptors. The mechanism of intracellular signaling begins cytokine binding to the receptor depending on the nature of the receptor. A number of epidermal growth factor cytokines (EGF) or platelet origin growth factors (PDGF) have receptors derived from the tyrosine kinase domain while the transforming growth factor- β 1 (TGF- β 1) receptors in the serine/threonine kinase domain [28]. The activity of flavonoid ligands of *coleus amboinicus* extract on transforming growth factor- β 1 receptor (TGF- β 1) can be analyzed by comparing its receptor with the ligand activity of comparative drug compounds. In silico analysis is a method to find out the image of compounds interacting with receptors, predicting biological activity, and the strength of their bonds with a receptor.

Measurement of ligand-receptor interaction is used to predict the potential activity of active compound. Flavonoid (quercetin) contained in the *coleus amboinicus* is used as marker compounds, against TGF- β 1 receptors [29]. The purpose of this study was to evaluate of *Coleus amboinicus* (CA) extracts in increasing of transforming growth factor- β 1 concentration and molecular docking prediction of flavonoid quercetin on 4X0M (TGF- β 1) receptor, measuring the levels of BUN, serum creatinine and glutathione peroxidase (GPx) activity on uric acid-induced in Wistar rats.

2. MATERIALS AND METHOD

2.1. Material

The research used forty-two Wistar rats (*Rattus norvegicus*), 2-3 months old, were allocated into three treatment groups: the control group U-0 (n=14), had not received of CMC-Na solution at 0.1% after being fasted for 12 hour and were euthanized at

the end of research; Group U-1(n=14) and group U-2 (n=14), after being fasted for 12 hour, was treated with uric acid 500 mg/kg bw and oxonic acid 750 mg/kg bw to induce acute renal failure [3] and the group U-2 received 500 mg/kg bw of coleus amboinicus extracts for 30 days.

2.2. Method

At day 31th all groups were scarified by euthanized and tissue collected. Half a kidney was stored in 10 % formalin for histopathological examination with haematoxylin-eosin (HE). Blood was taken via intra cardial for analysis of serum creatinine (SC) and blood urea nitrogen (BUN) concentration was performed using by the colorimetric method (Creatinine and Blood Urea Nitrogen kit DiaSys Diagnostic Sys GmbH, Germany). Identification of transforming growth factor- β 1(TGF- β 1) and glutathione peroxidase (GPx) concentration was performed using by TGF- β 1 quantikine assay kit Elisa (R&D,USA) and Glutathione Peroxidase Assay & Parameter Total Rat (Biostar). This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for transforming growth factor- β 1 (TGF- β 1) has been pre-coated onto a micro plate, an enzyme-linked monoclonal antibody specific for TGF- β 1, a substrate with color development is measured of absorbance at 450 nm. Measurement of GPx activity indirectly with the enzymatic reaction pair glutathione reductase (GR) and NADPH in the hydroperoxide reduction reaction which produces oxidized glutathione (GSSG) and NADP⁺ a substrate with color development is measured of absorbance at 340 nm.

Kidney tissue sections were examined in areas containing alteration in necrotic and thickening of renal tubules under 400 x magnifications by Olympus light microscope. The percentage of tissue area with alteration were scored: 0 (no alteration or the cells were normal), 1 (1-30% necrotic cells), 2 (31-50% necrotic cells), and 3 (has 51-100% necrotic cells).

2.3. Analysis in silico

In silico analysis is used to predict the potential activity of flavonoids (quercetin) contained in coleus amboinicus and used as marker compounds, against TGF- β 1 receptors by making 2-dimensional (2-D) and 3-dimensional (3-D) structures of 4-amino-8H-pyrido [2, 3-D] pyrimidine-5-one ligands and quercetin ligands from Protein Data Bank (PDB). The receptors downloaded must contain the ligand 3WA_601 as a basic structure similar to quercetin, a marker compound contained in coleus amboinicus. Detecting the cavity in the receptor structure where the ligand will be bound (interacting) by attaching three atoms of the compound to the same three atoms in the ligand in the receptor and docking compounds at the receptor. The parameters measured in the docking process are the energy values involved, in the form of moldock score, rerank score, and hydrogen bonds, as well as the Root Mean Square Deviation (RMSD) value. The lower the docking energy value obtained, the more stable the strength of the drug-receptor binding, and it can be used to predict the activity of a compound [29-30].

2.4. Data Analysis

All the statistical analyses were processed using SPSS for windows, version 22.0. Values of the measured parameters were expressed as mean value \pm SD and the difference between the two groups was determined using unpaired student's t-test, and the significance was considered ($p < 0.05$).

3. RESULTS AND DISCUSSION

3.1. Identification of coleus amboinicus

The results of the identification of Coleus amboinicus extract obtained the relative fraction of coleus amboinicus contents by thin layer chromatography (TLC) method. One of the compounds from the flavonoid group is quercetin, which in this study is used as a marker compound from coleus amboinicus extract. The quercetin content in the coleus amboinicus extract was determined by the TLC-densitometry method and it was found that the extract contained quercetin < 16.9 mg/kg. (Table 1.)

Table 1. Results of the qualitative analysis of coleus amboinicus extracts using the thin layer chromatography (TLC)

Compound	Comparison	Phase Movement	Results
Flavonoid	Routine	Etil asetat:asam formiat: asam asetat glasial:air (100:11:11:27)	Positive (+)
Terpene	Timole	n-Heksan:etil asetat (93:7)	Positive (+)
Alkaloid	Kuinine	Toluen:etil asetat:dietilamin (7:2:1)	Positive (+)
Polifenol	Galat acid	Etil asetat:metanol:air (100:13,5:10)	Positive (+)
Saponine	Saponine	Kloroform:metanol:air (64:50:10)	Positive (+)

The results of the analysis and TLC identification found that amboinicus extract contained flavonoids, terpenes (essential oils), polyphenols, saponins and alkaloids (Figure 1). According to the study of Lukhoba et al [17] and Rice et al [16] coleus

amboinicus plants are geographically spread almost all over the world, especially those found in the continents of Africa, Australia and Asia, consisting of 62 species of plants which are distinguished based on DNA sequence data into two groups, Clade 1 and Clade 2.

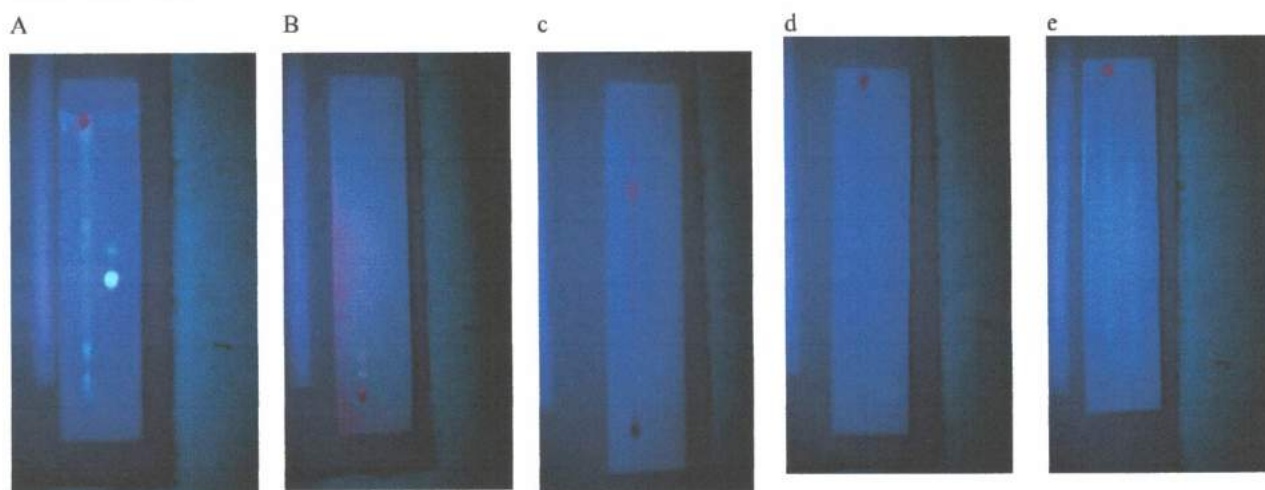


Figure 1. The results of running thin layer chromatography (TLC) from coleus amboinicus extracts which showed positive for flavonoids (a), terpen (b), alkaloids (c), polyphenols (d), and saponins (e).

The content of active compounds both from the leaves and stems of Coleus plants include monoterpenoids, sesquiterpenoids, diterpenoids, phenolics, squalene, carioophyline, phytol, alkaloids, glycosids, flavonoids, quinones, tannins, and terpenoids [16-18]

According to Materska [31] that flavonoids in natural plants have antioxidant content that has the potential as a natural preservative that can prevent allergies, are non-toxic and are anti-carcinogenic by increasing apoptosis of cancer cells. Flavonoids have a basic structure similar to tocopherol (vitamin E) which has antioxidant and antiproliferation activity by inhibiting mast cell secretion [32]. These results are consistent with Soni and Akhlesh [18] which analyzed phytopharmacologically the coleus amboinicus has a very varied content with dominant compounds such as flavonoids, essential oils, polyphenols and glycosides, and contains proteins, carbohydrates, amino acids, quinones, tannins and terpenoids [20-21].

According to Mazzali [33], induction of uric acid can cause renal damage characterized by elevated urea levels. Increased levels of urea in the treated are probably due to hypovolemic and dehydration as the early post-intra renal uric acid depositions response. The mean of serum creatinine levels in Group U1 showed increased with an average of 0.69 mg/dL, which is a significant increase when compared with the controls group. Serum creatinine levels in rats can increase after received with 500 mg/kg bw uric acid and oxonic 750 mg/kg bw, while level of serum creatinine group U2 also increase significantly with average SC of 0.59 mg/dL (Table 2).

3.2. Biochemical blood samples and serology

The mean levels of blood urea nitrogen (BUN) concentration in the control rats (U0) ranged from 28.65 mg/dL post treatment which are still within normal limits (10–58 mg/dL). The group U1 showed significantly increased levels of BUN 41.22 mg/dl as long as groups U2 at 31.25 mg/dl after uric acid induction, compared with control rats ($p < 0.05$).

Table 2. Comparison of blood urea nitrogen (BUN), serum creatinine (SC), transforming growth factor- β 1 (TGF- β 1) and glutathione peroxidase (GPx) on uric acid-induced in various group

Group	BUN (mg/dl)	Serum Creatinine (mg/dl)	TGF- β 1 (pg/ml)	GPx (mU/mL)
Control (U-0) (n=14)	28.65 ^a \pm 2.39	0.517 ^a \pm 0.023	55.28 ^a \pm 31.38	0.29 ^a \pm 0.117
Uric-induced (U-1)	41.22 ^b \pm 3.30	0.694 ^b \pm 0.051	119.19 ^b \pm 23.33	0.48 ^b \pm 0.230

(n=14)				
Uric+CA extract (U-2)	31.25 ^c ± 2.64	0.599 ^c ± 0.315	181.83 ^c ± 30.90	0.39 ^b ± 0.161
(n=14)				

Superscript in the same column indicate a significant difference of $p \leq 0.05$

The concentration of transforming growth factor- β 1 (TGF- β 1) in the control rat group given placebo (U0) was 55.28 pg/mL, the group given uric acid-induced (U1) showed an average increase of 119.19 pg/mL, the U2 group = 181.83 pg/mL, which is significantly different ($p < 0.05$) when compared to U-0. The expression of transforming growth factor- β 1 (TGF- β 1) in the U2 group showed a significant increase ($p < 0.05$) compared to the U1 group. The results showed that administration of coelus amboinicus extract (U2 group) showed a significant increasing in TGF- β 1 concentration ($p < 0.05$).

Meanwhile, Glutathione peroxidase (GPx) level in the control rat group (U0) was 0.29 mU/mL. In the treatment group given induction of uric acid (U1) showed an average increase of 0.48 mU/mL and the U2 group = 0.39 mU/mL, The value was significantly different when compared with the U0 group ($p < 0.05$). In the U1 group showed no significant differences with the U2 ($p > 0.05$). Glutathione peroxidase (GPx) activity in the U-1 and U-2 treatment groups showed no significant difference ($p > 0.05$), which means that there was no effect of coelus amboinicus extract in treatment group (Table 2).

3.3. Morphohistology of renal

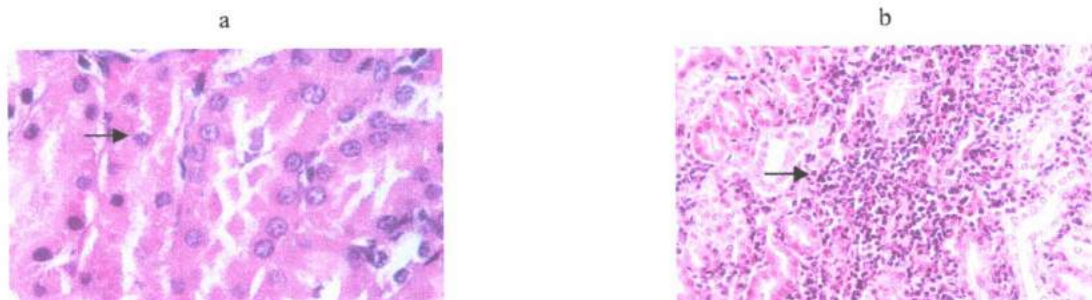
Scoring method based from previously study [34], the histopathology scores for the U1 group (which received CMC-Na) were 1.64 for necrosis, scores 2.17 for MT thickening and 3.20 for CB thickening. These scores were significantly greater ($p \leq 0.05$) than the necrosis and thickening of MT and CB score for the U-2 groups. The scores for necrosis were significantly different ($p \leq 0.05$) between treatment groups, with scores of 0.0 for U-0 and scores 1.0 for U1 groups, respectively. The thickening MT scores and thickening CB score were significantly different ($p \leq 0.05$) between treatment groups, with scores of 1.55 and 2.40 for U-0, scores 2.61 and 4.75 in U-2 groups, respectively (Table 3).

Table 3. Distribution of histopatological scoring in necrotic membrane tubules (MT) tickening and capsula bowman (CB) thickening in variuos group

Group	Necrotic	MT thickening	CB thickening
Control (U-0) (n=14)	0.00	1.55 ^a ± 0.42	2.40 ^a ± 0.63
Uric-induced (U-1) (n=14)	1.64	2.17 ^b ± 0.41	3.20 ^b ± 0.75
Uric+CA extract (U-2) (n=14)	1.00	2.61 ^c ± 0.76	4.75 ^c ± 1.06

Superscript in the same column indicate a significant difference of $p \leq 0.05$

The administration of Coleus amboinicus extracts to Wistar rats can reduce kidney cell damage (necrosis and thickened) due to uric acid induction and show the process of kidney tissue repair (Figure 2).



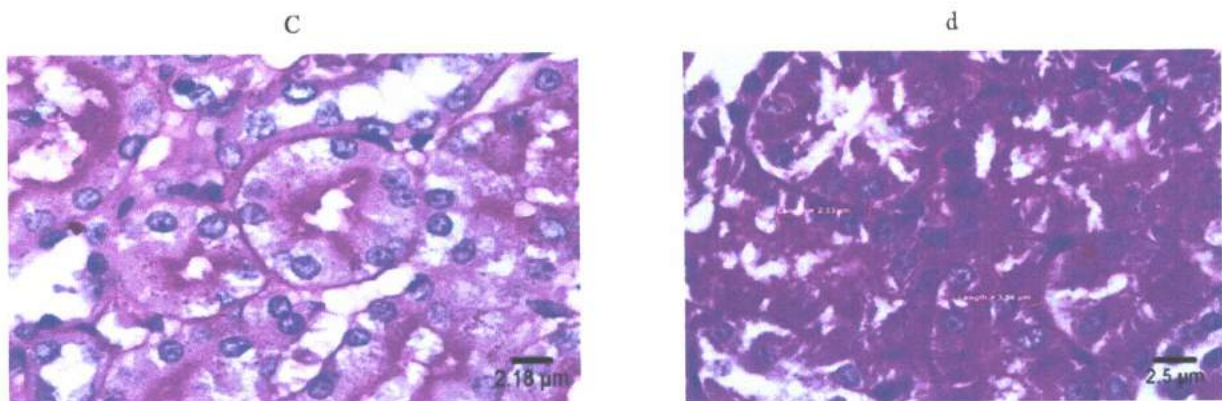


Figure 2. Histopathological change of the control group showing normal cell structure in the glomerulus and tubules (a) and uric acid induction group showing infiltration of neutrophil inflammatory cells in the necrotic interstitial region (b) (HE, 100x). Histopathological of the control group showing cell structure in glomerulus and tubules no change (c) and uric acid-induced group which shows thickening of the basement membrane tubules (d) (PAS, 1000x).

3.4. Docking molecule of quercetin

By in silico analysis of quercetin marker compounds at the transforming growth factor- β 1 (TGF- β 1) receptor by making 2-dimensional and 3-dimensional structure of 4-amino-8H-pyrido ligand molecule [2,3-D] pyrimidin-5-one (3WA_601) and quercetin ligand. The secondary structure of the TGF- β 1 receptor (PDB code: 4X0M) that binds to the 3WA_601 ligand and quercetin. Molecular docking results of 3WA_601 ligands and quercetin of TGF- β 1 receptors showed the average value of 3WA_601 ligand score was -63.460 ± 0.3574 , and the flavonoid ligand was -101.444 ± 0.6462 (Table 4).

Table 4. Mean of *Re-rank score* ligands bind to 4X0M (TGF- β 1) receptor (kcal/mol)

Ligand	Rerank score 1	Rerank score 2	Rerank score 3	Mean \pm SD
3WA_601	-63.31	-63.87	-63.20	-63.46 \pm 0.35
Quercetin	-100.69	-101.78	-101.85	-101.44 \pm 0.64

Quercetin ligand has lower score than 3WA_601 ligands scores so that the energy needed to form bonds between receptors and flavonoid ligand is lower that it imply more stable bonds and stronger compound activity. From the analysis of hydrogen bonds and amino acids involved in the process of ligand-receptor interaction, it was found that ligand 3WA_601 binds to 2 amino acids (Asp 281 and His 283), while ligand of flavonoids can bind 4 amino acids (Asp 281, His 283, Gly 261, and Ser 280). The results of molecular docking are in accordance with the results of administration of *colus amboinicus* extracts containing quercetin flavonoids (U2) increased level of TGF- β 1 concentration (Figure 3).

The role of uric acid is paradoxical in mammals, one role can function as an antioxidant in extracellular tissue by activating peroxynitrite (ONOO⁻) as results of NO reaction with superoxide (O₂⁻). Meanwhile uric acid is prooxidant in intra-cellular by diverting L-arginine to produce urea, reacting with NO to produce nitrosated uric acid into glutathione (GSH) and 6-aminouracil and it activating NADPH oxidation to produce free radicals [9].

According to Huang et al. [35] TGF- β 1 expression is an anti-inflammatory cytokine, works autocrine or paracrine which acts to regulate cell proliferation, apoptosis, chemotaxis, immunity, and inflammatory response, and tissue repair (fibrosis) of kidney tissue. TGF- β 1 expression is a major factor in the process of fibrosis through the expression of SMAD-2 and SMAD-3 proteins which stimulate the ECM fibrogenic gene and protein mitogen kinase (MAPKs).

Increasing TGF- β 1 expression is an indicator of decreased renal cell damage (necrosis) due to uric acid induction, and shows the process of renal tissue repair in Wistar rats that are necrotic due to uric acid induction. According to the research of Xie et al. [36] TGF- β 1 expression plays a role in regulating mesangial cell proliferation and extracellular matrix secretion in nephropathy-diabetic.

TGF- β 1 expression in vivo affects the expression of collagen genes and the synthesis of mesangial extracellular matrix (ECM) in glomerular mesangium. ECM accumulation can cause tubulointerstitial fibrosis, thickening of the glomerular basement

membrane and glomerular sclerosis. According to Liu et al. [37] TGF- β 1 expression can induce profibrogenic independently through activation of EGF receptors and activation of angiotensin II, endothelin 1 and oxidative stress conditions in the process of renal fibrogenesis. According to Kim et al. [6] TGF- β 1 expression in tubular cells has a role in tubulointerstitial fibrosis caused by uric acid.

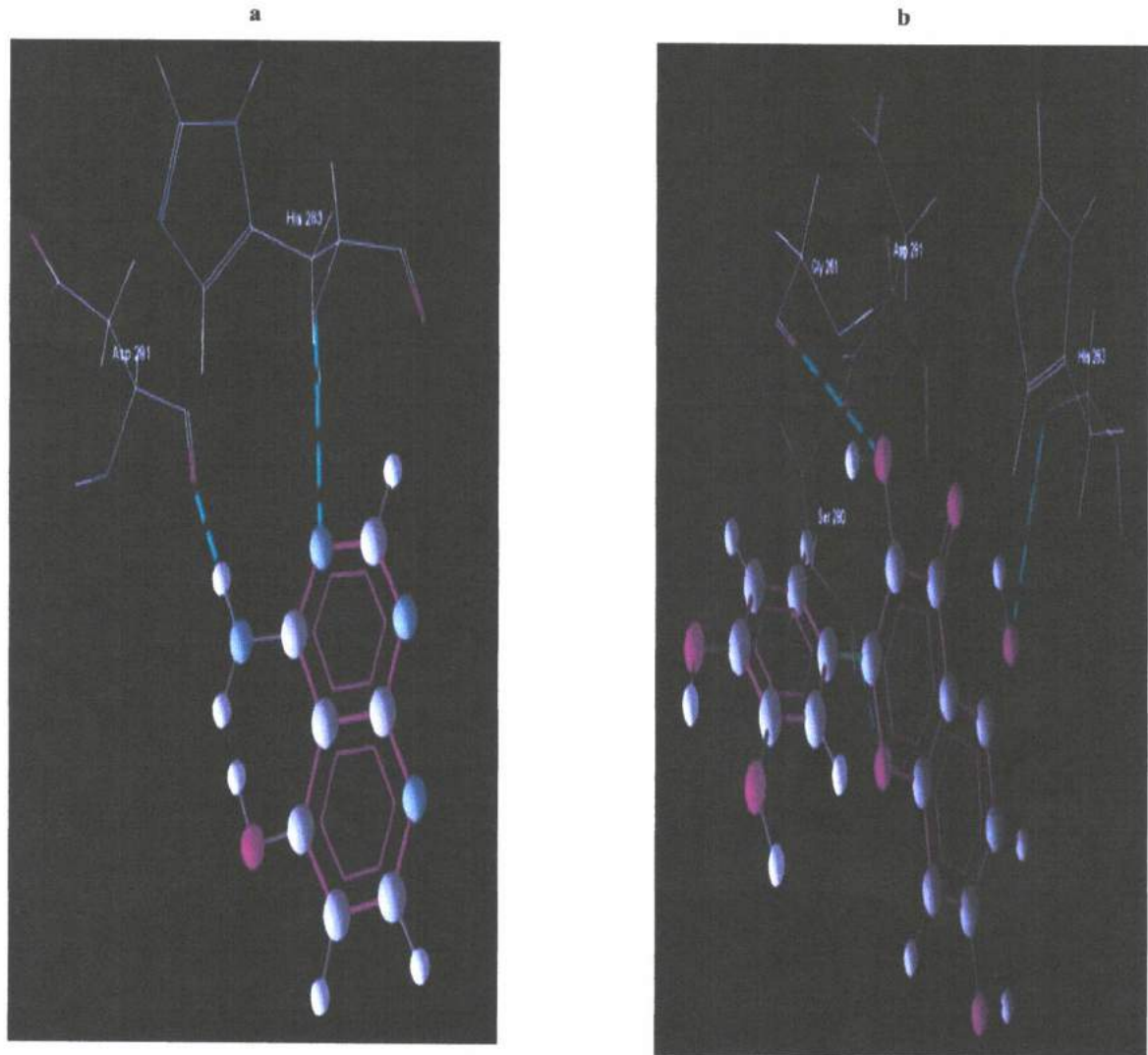


Figure 3. Three-dimensional structure of amino acids at TGF- β 1 receptor bound by ligand 3WA_601 that binds 2 amino acids Asp 281 and His 283 (a), and amino acids at TGF- β 1 receptor bound by quercetin which binds 4 amino acids Asp 281, His 283, Gly 261, and Ser 280(b).

Glutathione peroxidase (GPx) level in the control rat group (U0) was 0.29 mU/mL. In the treatment group given induction of uric acid (U1) showed an average increase of 0.48 mU/mL and the U2 group = 0.39 mU/mL, The value was significantly different when compared with the U0 group ($p < 0.05$). In the U1 group showed no significant differences with the U2 ($p > 0.05$, Table 3). Glutathione peroxidase (GPx) activity in the U-1 and U-2 treatment groups showed no significant difference ($p > 0.05$), which means that there was no effect of coelus amboinicus extract. This shows that the mechanism of action of the extract of coelus amboinicus does not go through the activity of decreasing the enzyme glutathione peroxidase (GPx).

CONCLUSION

Induction of uric acid and oxonic acid had effect on the formation of acute renal failure lesions in rats. The administration of Coelus amboinicus is proven to inhibit renal acute failure on uric acid-induced by increasing level of TGF- β 1 concentration and its quercetin has strong binding to TGF- β 1receptor by in silico analyzed. Subsequent research on the identification of the Coelus amboinicus molecule that affects kidney cell repair in experimental animals

LIST OF ABBREVIATIONS

ACE	=	Angiotensin Converting Enzyme
AINS	=	Anti Inflamasi Non Steroid
CA	=	Coleus amboinicus
C3	=	Complement 3
COX-2	=	Cyclooxygenase-2
EGF	=	Epidermal Growth Factor
GA	=	Gout Arthritis
GPx	=	Glutathione Peroxidase
GLUT	=	Glucose Transporter
IL-1 β	=	Interleukin -1 β
ICAM-1	=	Intercellular Adhesion Molecule 1
LD	=	Lethal Dose
MCP-1	=	Macrophage Chemoattractant Protein-1
MIF	=	Macrophage Migration Inhibitory Factor
MSU	=	Monosodium Urea
NOS	=	Nitric Oxide Synthase
OAT	=	Organic Anion Transporter
OA	=	Oxonic Acid
PDGF	=	Platelet-Derived Growth Factor
RAS	=	Renin Angiotensin System
ROS	=	Reactive Oxygen Species
TLR	=	Toll-Like Receptor
TGF- β	=	Transforming Growth Factor- β
TNF- α	=	Tumor Necrosis Factor- α
URAT-1	=	Urate Transporters-1
UA	=	Uric Acid
VCAM-1	=	Vascular Cell Adhesion Molecule 1
XO	=	Xanthin Oxidase

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research complies with the ethical clearance with the registration number No.518-KE from Animal Care and Use Committee (ACUC) Faculty of Veterinary Medicine Universitas Airlangga, Surabaya, Indonesia

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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