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Hepatoprotective Activity and Nephroprotective Activity of Peel Extract from Three Varieties of the Passion Fruit (*Passiflora Sp.*) in the Albino Rat

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Abstract

BACKGROUND: The Passion Fruit (Passiflora sp.) that grows in the Indonesian region generally has three varieties, namely purple passion fruit (Passiflora edulis Sims.), red passion fruit (Passiflora ligularis Juss.), and yellow passion fruit (Passiflora verrucifera Lindl.). The passion fruit peel which is an economic waste that has not been utilised optimally, but has many efficacious phytochemical contents.

AIM: The objectives of this research are to examine scientifically hepatoprotective activity (with paracetamol-induced hepatotoxic) and nephroprotective activity (with gentamicin-induced nephrotoxic) from three varieties of the passion fruit (purple passion fruit peel extract, red passion fruit peel extract and yellow passion fruit peel extract) in the albino rat (Rattus norvegicus).

METHODS: Three varieties of passion fruit peels were extracted by maceration method. The experimental animals used were the albino rat (Rattus norvegicus). Hepatoprotective activity was done by the liver biochemical (alanine transaminase and aspartate transaminase) analysis with paracetamol (hepatotoxic compound) induced after 10 days of treatment with extract. Nephroprotective activity was done by the kidney biochemical (urea and creatinine) analysis with gentamicin (nephrotoxic compound) induced after 10 days of treatment with extract.

RESULTS: The hepatoprotective activity for positive control was similar to the 250 mg of purple passion fruit peel extract per kg of body weight, 250 mg of red passion fruit peel extract per kg of body weight, and 500 mg of yellow passion fruit peel extract per kg of body weight. The nephroprotective activity for positive control (50 mg of silymarin per kg of body weight) was similar to the 250 mg of purple passion fruit peel extract per kg of body weight, 500 mg of red passion fruit peel extract per kg of body weight, and 500 mg of yellow passion fruit peel extract per kg of body weight.

CONCLUSIONS: The extracts were shown hepatoprotective activity and nephroprotective activity with a dose-dependent activity. The hepatoprotective activity and nephroprotective activity of purple passion fruit peel extract were the best compared to red passion fruit peel extract and yellow passion fruit peel extract.

Introduction

The liver is an important organ in the body that has an important function, which is: bile secretion, bilirubin metabolism, nutritional metabolism, producing immune agents to control infections, and metabolism of foreign molecules (exogenous chemical and endogenous chemical). The liver is the metabolic centre in the body, especially those given orally. Drug metabolism in the liver occurs in microsome cells through an enzyme system that is very complex through two phases. The first phase includes oxidation reactions, reduction reactions, and hydrolysis reactions. The second phase includes conjugation reactions. Liver damage can be caused by a viral of hepatitis or cirrhosis; drugs can cause toxic effects on the liver resulting in liver damage [1].

The kidney is an important organ that has an important role in the body for blood filtration to excrete waste products, balance electrolytes in the body, control blood pressure, stimulate the production of red blood cells, and regulate the balance of water and

metabolites in the body and maintain acid-base balance in the blood. Drugs and metabolic results of drugs that are in the blood and are no longer used in the body will be excreted by the kidneys through urine. Urine will leave the kidneys to the urinary tract to be removed from the body. Most drugs are excreted by the kidneys, so the use of drugs that exceed the therapeutic dosage can damage the kidneys [2].

Paracetamol is a drug with analgesic and antipyretic effects that is widely used by the wider community. Paracetamol is an over the counter class drug that can be traded freely without supervision, but this drug causes liver damage in the use of high doses. Paracetamol is predicted to be a major factor in the cause of acute liver damage [3], [4]. Gentamicin is an antibiotic derived from aminoglycosides, which is generally an option in the treatment of infections that are needed immediately if a condition that can endanger life is found. Gentamicin is a broad-spectrum antibiotic that has bactericidal activity against gram-positive bacteria and gram-negative bacteria. Gentamicin can cause kidney damage because it rapidly induces extensive renal cortical necrosis with renal dysfunction [5], [6].

The passion fruit is a plant that originates from Brazil and spreads to all countries of the world. The passion fruit can grow in subtropical regions or highland in tropical regions [7]. The passion fruit can be found in several regions in Indonesia; one region in Indonesia that can cultivate the passion fruit is North Sumatera region (Karo district, Simalungun district, Dairi district, and North Tapanuli district). The passion fruit has many varieties that cultivate in all countries of the world, but the passion fruit that grows and develops in Indonesia are three varieties, namely: purple passion fruit, red passion fruit, and yellow passion fruit [8], [9]. Figure 1 shows the physical appearance of purple passion fruit, red passion fruit, and yellow passion fruit.

Figure 1: Physical appearance of purple passion fruit, red passion fruit, and yellow passion fruit

The passion fruit is generally consumed on the inside of the fruit, because the inside of the fruit is the edible portion, and the skin is a waste that has not been utilised optimally [10]. The passion fruit peel has many different phytochemical contents, including alkaloids, flavonoids, steroids, triterpenoids, saponins, tannins, glycosides, and phenolic [11], [12], [13]. The passion fruit peel has also been tested for pharmacological activity as an antioxidant [12], [14], [15], [16], an antimicrobial [13], [15], [16], a neuroprotective [15], [17], a cardioprotective [18], a gastroprotective [19], an analgesic [20], an anti-inflammation [21], an antihypertriglyceridemic [21], and an antihyperglycemic [21], [22].

The hepatoprotective activity and nephroprotective activity of the passion fruit peel extract have never been reported in the research article. But with the abundance of phytochemical content found in the passion fruit peel extract, an extract that is likely to provide hepatoprotective activity [23] and nephroprotective activity [24].

This study aims to examine scientifically hepatoprotective activity (with paracetamol-induced hepatotoxic) and nephroprotective activity (with gentamicin-induced nephrotoxic) from three varieties of the passion fruit (*Passiflora sp.*) (purple passion fruit peel extract, red passion fruit peel extract and yellow passion fruit peel extract) in the albino rat (*Rattus norvegicus*).

Methods

Research

This research was conducted by experimental research. The independent variables were type of the extract (purple passion fruit peel extract, red passion fruit peel extract, and yellow passion fruit peel extract) and dose of the extract (100 mg extract per kg of body weight, 200 mg extract per kg of body weight, and 400 mg extract per kg of body weight). The dependent variables were level of the hepatotoxic or hepatoprotective biochemical marker (alanine transaminase and aspartate transaminase) in the serum and nephrotoxic or nephroprotective biochemical marker (urea and creatinine) in the serum. These research samples were purple passion fruit peel and yellow passion fruit peel obtained from the passion fruit farmer. The passion fruit growth in Gundaling, Berastagi, Karo, Sumatera Utara, 22152, Indonesia. The growth condition was a suitable condition for the passion fruit growth with 1,375 meters above sea level for the average altitude, 16°C to 26°C for the temperature, 60% to 100% for the relative humidity, 2100 mm to 3200 mm for the rainfall, 5 to 6 for the soil pH, 1009 HPa to 1015 HPa for the atmospheric pressure, 4 km/hr to 11 km/hr for the wind speed. Harvest of purple passion fruit, red passion fruit, and yellow passion fruit was done in 85th days to 90th days after the flowers bloom.

Materials and Tools

The materials used in this research were

purple passion fruit peel, red passion fruit peel, yellow passion fruit peel, ethanol (E-Merck), ethylene diamine tetraacetic acid (E-Merck), alanine transaminase activity assay kit (Sigma Aldrich), aspartate transaminase activity assay kit (Sigma Aldrich), urea assay kit (Sigma Aldrich), creatinine assay kit (Sigma Aldrich), sodium carboxymethyl cellulose (Tokyo Chemical Industry), and demineralized water (Brataco).

The tools used in this research were cutter (Kenko), drying cabinet (Alumex), blender (Miyako), balance (Mettler Toledo), analytical balance (Mettler Toledo), filter paper (Whatman), dropper (Iwaki), evaporating dish (Iwaki), maceration vessel (Iwaki), beaker glass (Iwaki), measuring glass (Iwaki), volumetric flask (Iwaki), test tube (Iwaki), hot plate stirrer (Thermo), water bath (Memmert), incubator (Memmert), rotary evaporator (Buchi), thermometer (Lutron), test sieve 10 (Retsch), stopwatch (Casio), spectrophotometer (Agilent).

Samples Identification and Samples Extraction

Samples used in this research were collected and identified at Herbarium Medanense (MEDA), Faculty of Mathematics and Natural Sciences, University of Sumatera Utara, Padang Bulan, Medan Baru, Medan, Sumatera Utara, 20155, Indonesia. The extraction process was based on a modification of the maceration method from Irawan et al., 2018 and Zhang et al., 2018. The passion fruit peel is washed, cut, dried, and powdered. One kilogram of dried passion fruit peel powder was weighed, soaked with 10 L ethanol for 5 days (stirred every day), and filtered. The residue was squeezed, soaked with 5 L ethanol for 3 days (stirred every day), and filtered (the maceration procedure was repeated several times until clear extract was obtained). The aqueous extract was collected and evaporated with a rotary evaporator until a viscous extract was obtained [25], [26]. The extracts obtained were used for hepatoprotective activity test and nephroprotective activity test.

Hepatoprotective Activity Test and Nephroprotective Activity Test

The method used for nephroprotective activity and hepatoprotective activity is a modification of the method from Abel-Hady et al., 2018; Fatima and Sultana, 2018; Tung et al., 2017; Okokon et al., 2017; and Thuwaini et al., 2016. The animals used were the Albino Rat (*Rattus norvegicus*) with Wistar strain which was 8 weeks old-12 weeks and weighed 250 g ± 10 g. The animals were kept for 5 days before the experiments. The animals were kept in standard conditions (12 hours light and 12 hours dark cycle), with temperatures of 23°C ± 2°C, and with relative humidity 50% ± 10%. Experimental animals were divided into 12 groups for testing hepatoprotective activity and 12 groups for testing nephroprotective activity with each group consisting of 10 animals. Table 1 shows the treatment given to each group of experimental animals for 10 days and after 10 days [27], [28], [29], [30], [31].

Table 1: Treatment given to each group of experimental animals for 10 days and after 10 days

Number	Given	Group											
		1	2	3	4	5	6	7	8	9	10	11	12
1	Protection with Standard Protector for 10 Days (mg of Curcumin or mg of Silymarin per kg of body weight) by Oral	-	-	✓	-	-	-	-	-	-	-	-	-
2	Purple Passion Fruit Peel Extract for 10 Days (mg of Purple Passion Fruit Peel Extract per kg of body weight) by Oral	-	-	-	✓	✓	✓	-	-	-	-	-	-
3	Red Passion Fruit Peel Extract for 10 Days (mg of Red Passion Fruit Peel Extract per kg of body weight) by Oral	-	-	-	-	-	-	✓	✓	✓	-	-	-
4	Yellow Passion Fruit Peel Extract for 10 Days (mg of Yellow Passion Fruit Peel Extract per kg of body weight) by Oral	-	-	-	-	-	-	-	-	-	✓	✓	✓
5	Induction with Toxic Inducer after 10 Days (mg of Paracetamol or mg of Gentamicin per kg of body weight) by Intraperitoneal	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

All groups (group 1 to group 12) were given food and drink ad libitum. The protector used were 250 mg of curcumin per kg of body weight (for hepatoprotective activity) and 50 mg of silymarin per kg of body weight (for nephroprotective activity). The inducer used were 500 mg of paracetamol per kg of body weight (for hepatotoxic activity) and 125 mg of gentamicin per kg of body weight (for nephrotoxic activity). The samples used were purple passion fruit peel extract, red passion fruit peel extract and yellow passion fruit peel extract. Each extract was used with various concentrations (125 mg of extract per kg of body weight, 250 mg of extract per kg of body weight, and 500 mg of extract per kg of body weight). The animals from all groups were sacrificed under diethyl ether anaesthesia, and then the blood samples were collected after 24-hour induction with toxic inducer by cardiac puncture by using 21 gauge needles mounted on a 5 ml syringe into ethylene diamine tetraacetic acid.

The blood samples obtained were centrifuged at 3000 rotations per minute for 15 minutes. Serum obtained were used for the biochemical analysis with hepatoprotective activity parameters (alanine transaminase and aspartate transaminase) and nephroprotective activity parameters (urea and creatinine) [27], [28], [29], [30], [31]. The biochemical analysis of hepatoprotective activity parameters (alanine transaminase and aspartate transaminase) and the biochemical analysis of nephroprotective activity parameters (urea and creatinine) were carried out by the standard method from Sigma Aldrich.

Results

Increasing the dose of administration will increase the hepatoprotective activity and the nephroprotective activity. This can be seen from the results that increase treatment dose will improve the liver function through a decrease in the alanine transaminase value and aspartate transaminase value and improve the kidney function through a decrease in the urea value and creatinine value so that it can be seen that purple passion fruit peel extract, red passion fruit peel extract, and yellow passion fruit peel extract have a dose-dependent hepatoprotective activity and dose-dependent nephroprotective activity. Table 2 shows the results of treatment of hepatoprotective activity test (alanine transaminase and aspartate transaminase) and treatment of nephroprotective activity test (urea and creatinine).

Table 2: Results of treatment of hepatoprotective activity test (alanine transaminase and aspartate transaminase) and treatment of nephroprotective activity test (urea and creatinine)

Number	Treatment		Alanine Transaminase (IU/L)	Aspartate Transaminase (IU/L)	Urea (mg/dL)	Creatinine (mg/dL)
1	Control	Normal	27.45 ± 2.84 $^{\#\dagger}$	33.19 ± 3.11 $^{\#\dagger}$	13.12 ± 1.51 $^{\#\dagger}$	0.441 ± 0.024 $^{\#\dagger}$
2		Negative	95.84 ± 9.87 *‡	116.17 ± 10.94 *‡	77.64 ± 9.12 *‡	7.419 ± 0.409 *‡
3		Positive	32.34 ± 3.41 $^{*\#}$	38.09 ± 3.61 $^{*\#}$	17.57 ± 2.02 $^{*\#}$	0.521 ± 0.029 $^{*\#}$
4	Purple Passion Fruit Peel Extract (mg of Purple Passion Fruit Peel Extract per kg of body weight)	125	40.97 ± 4.18 $^{*\#\ddagger}$	54.07 ± 4.94 $^{*\#\ddagger}$	24.14 ± 3.24 $^{*\#\ddagger}$	0.559 ± 0.031 $^{*\#\ddagger}$
5		250	32.59 ± 3.32 $^{*\#}$	38.33 ± 3.71 $^{*\#}$	17.67 ± 2.25 $^{*\#}$	0.518 ± 0.028 $^{*\#}$
6		500	30.84 ± 3.22 $^{*\#\dagger}$	33.55 ± 3.09 $^{*\#\dagger}$	13.19 ± 1.95 $^{*\#\dagger}$	0.500 ± 0.026 $^{*\#\dagger}$
7	Red Passion Fruit Peel Extract (mg of Red Passion Fruit Peel Extract per kg of body weight)	125	41.15 ± 4.19 $^{*\#\ddagger}$	53.57 ± 4.91 $^{*\#\ddagger}$	31.99 ± 4.08 $^{*\#\ddagger}$	0.675 ± 0.042 $^{*\#\ddagger}$
8		250	32.13 ± 3.30 $^{*\#}$	38.69 ± 3.76 $^{*\#}$	24.56 ± 3.13 $^{*\#\ddagger}$	0.595 ± 0.036 $^{*\#\ddagger}$
9		500	30.34 ± 3.18 $^{*\#\dagger}$	33.99 ± 3.12 $^{*\#\dagger}$	17.69 ± 2.52 $^{*\#}$	0.534 ± 0.032 $^{*\#}$
10	Yellow Passion Fruit Peel Extract (mg of Yellow Passion Fruit Peel Extract per kg of body weight)	125	66.21 ± 6.94 $^{*\#\ddagger}$	75.04 ± 7.14 $^{*\#\ddagger}$	32.24 ± 4.10 $^{*\#\ddagger}$	0.671 ± 0.041 $^{*\#\ddagger}$
11		250	43.75 ± 4.49 $^{*\#\ddagger}$	49.74 ± 4.71 $^{*\#\ddagger}$	24.22 ± 3.07 $^{*\#\ddagger}$	0.591 ± 0.035 $^{*\#\ddagger}$
12		500	32.94 ± 3.53 $^{*\#}$	37.88 ± 3.48 $^{*\#}$	18.01 ± 2.59 $^{*\#}$	0.530 ± 0.030 $^{*\#}$

Note: value represents as mean ± standard deviation; $^{*}p < 0.05$, a significant difference compared with the normal control group (n = 10); $^{\#}p < 0.05$, a significant difference compared with the negative control group (n = 10); $^{\dagger}p < 0.05$, a significant difference (lower) compared with the positive control group (n = 10) $^{\ddagger}p < 0.05$, a significant difference (higher) compared with the positive control group (n = 10).

The normal control group that was not given a protector and was not given an inducer showed normal liver biochemical value (alanine transaminase value < 35.0 IU/L and aspartate transaminase value < 45.0 IU/L) and normal kidney biochemical value (urea value < 24.0 mg/dL and creatinine value < 1.20 mg/dL). The negative control group that was not given a protector and was given an inducer showed significantly increased in liver biochemical value (alanine transaminase value > 35.0 IU/L and aspartate transaminase value > 45.0 IU/L) and significantly increased in kidney biochemical value (urea value > 24.0 mg/dL and creatinine value > 1.20 mg/dL) compared to the normal control group. This indicates that the hepatotoxic inducer given and nephrotoxic inducer given have been able to cause hepatotoxic in the liver organ and nephrotoxic in the kidney organ.

The positive control group that was given a protector and was given an inducer showed significantly decreased in liver biochemical value (alanine transaminase value and aspartate transaminase value) and significantly decreased in kidney biochemical value (urea value and creatinine value) compared to the normal control group and the negative control group. Although the positive control group results showed significantly different from the normal control group, but the results obtained were within the normal range of the biochemical value (alanine transaminase value < 35.0 IU/L and aspartate transaminase value < 45.0 IU/L) and normal range of kidney biochemical value (urea value < 24.0 mg/dL and creatinine value < 1.20 mg/dL).

The test group that was given a passion fruit extract and was given an inducer showed significantly decreased in liver biochemical value (alanine transaminase value and aspartate transaminase value) and significantly decreased in kidney biochemical value (urea value and creatinine value) compared to the negative control group. This result means that the passion fruit peel extract has hepatoprotective activity and has nephroprotective activity. But only several treatment doses of the passion fruit peel extract were given a similar (not significantly different) to the positive control group.

The hepatoprotective activity for positive control (250 mg of curcumin per kg of body weight) was similar (not significantly different) to the 250 mg of purple passion fruit peel extract per kg of body weight, 250 mg of red passion fruit peel extract per kg of body weight, and 500 mg of yellow passion fruit peel extract per kg of body weight. The nephroprotective activity for positive control (50 mg of silymarin per kg of body weight) was similar (not significantly different) to the 250 mg of purple passion fruit peel extract per kg of body weight, 500 mg of red passion fruit peel extract per kg of body weight, and 500 mg of yellow passion fruit peel extract per kg of body weight.

Discussions

Transaminase is a type of intracellular enzyme that is involved in nutrition metabolism. Transaminase enzymes are present in the cells of several organs such as the heart, liver, kidneys and pancreas. The alanine transaminase enzyme and the aspartate transaminase enzyme are present in hepatocytes cell and are released into the bloodstream in response to hepatocyte injury or death (hepatitis). Elevation of alanine transaminase enzyme or aspartate transaminase enzyme on the blood test for liver profile indicates the abnormality in the liver

organ. The good liver function will give a low value for alanine transaminase parameters and aspartate transaminase parameters [32], [33], [34], [35].

Both urea and creatinine are metabolic waste products that are excreted by the kidneys through urine, and only a small amount is left in the blood. If there is a disruption in kidney function, then there is an increase in these two parameters. Certain medical conditions can cause an increase in these two parameters, for example, chronic uncontrolled hypertension, uncontrolled diabetes mellitus, kidney stones, kidney inflammation, kidney infection, dehydration, and others [36], [37], [38], [39].

The hepatoprotective activity and the nephroprotective activity of an extract, in general, is a dose-dependent activity [40]. Purple passion fruit peel extract has the best hepatoprotective activity and the best nephroprotective activity compared to red passion fruit peel extract and yellow passion fruit peel extract. Although the purple passion fruit has the same genus with the red passion fruit and has the same species with the yellow passion fruit, due to genetic differences (differences in species or differences in varieties) there are morphological differences (colors and sizes) and genetical differences (sequences) [41], [42]. Also, due to differences in species or differences in varieties, it can cause qualitative differences in phytochemical contents and/or quantitative differences in phytochemical contents, also pharmacological differences and toxicological differences [43], [44].

The hepatoprotective activity possessed by the passion fruit peel extract may be due to the phytochemical content in the passion fruit peel. The phytochemical content in an extract is a good prospect for the development of phytotherapy [45], [46], [47]. The greater the content of alkaloids, flavonoids, and saponins in an extract, the higher the hepatoprotective activity possessed by the extract. Alkaloids are found in abundance in almost all parts of plants and have activities in scavenging the reactive oxygen species which can damage hepatocytes and are often useful compounds in medicinal chemistry for the development of new drugs. Flavonoids are polyphenol compounds that have been proven for hepatocytes protection from free radical scavenging activity. Saponins can directly protect hepatocytes from apoptosis through a mechanism of inhibition of the production of Tumor Nuclear Factor Alpha (TNFα) [48], [49], [50].

The nephroprotective activity of the passion fruit peel extract is produced by the complex phytochemical content and varied phytochemical content contained in the passion fruit peel. An extract is thought to have nephroprotective activity through the mechanism of its antioxidant activity [51]. High flavonoid content extracts are reported to have high nephroprotective activity through an antioxidant mechanism [52]. The nephroprotective mechanism is also shown by tannins compounds and which have good antioxidant activity [53]. Antioxidant compounds can protect the kidneys from alteration of kidney proteins and prevented the medical histopathological change of kidney tissue [54].

In conclusion, the extracts were shown a dose-dependent activity in hepatoprotective activity and nephroprotective activity. Purple passion fruit peel extract and red passion fruit peel extract have better hepatoprotective activity than yellow passion fruit peel extract. Purple passion fruit peel extract has better nephroprotective activity than red passion fruit peel extract and yellow passion fruit peel extract. The best hepatoprotective activity and nephroprotective activity showed by purple passion fruit peel extract compared to red passion fruit peel extract and yellow passion fruit peel extract.

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