CHAPTER I
INTRODUCTION

1.1 Research Background

The kidney is an essential organ for maintaining the stability of the body's environment. It selectively reabsorbs water, electrolytes, and non-electrolytes through blood filtration and excretes the excess in urine to regulate the body's fluid, electrolyte, and acid-base balance. The kidneys are susceptible to the toxic effects of drugs and chemicals as they receive 25% of cardiac output.[1] In Indonesia, the prevalence of chronic kidney failure based on a doctor's diagnosis in the population aged ≥15 years reached 713,783 people in 2018.[2] Meanwhile, according to the report from the Ministry of Health of the Republic of Indonesia (Kemenkes RI), there were 269 cases of atypical progressive acute kidney injury (AKI) in 2022.[3]

Oxidative stress is one of the causes of damage the glomerular or tubular epithelium, causing loss of nephron and kidney function.[4] One of the oxidation processes in the body is due to frequent consumption of drugs. Drugs are one of the indirect triggers for the formation of Reactive Oxygen Species (ROS), which in turn causes mitochondrial dysfunction, such as in people who consume toxic doses of paracetamol.[5] The American Association of Poison Control Centers' national poisoning data system reported 67,187 cases of toxicity due to a single paracetamol

[1] Sasikala M. Chinnappan, Annie George, Praveen Thaggikuppe, YogendraKumar Choudhary, Vandana K. Choudhary, Yesha Ramani & Rashmi Dewangan, 'Nephroprotective Effect of Herbal Extract Eurycoma longifolia on Paracetamol-Induced Nephrotoxicity in Rats', in Yuri Clement (ed.), *Evidence-Based Complementary and Alternative Medicine*, vol. 2019, Hindawi, 2019, pp. 1–6.

[2] Riskesdas, *Laporan Nasional Riskesdas 2018*, Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan (LPB), Jakarta, 2018.

[3] Kemenkes RI, *Profil Kesehatan Indonesia Tahun 2021*, Kemenkes RI, Jakarta, 2022.

[4] Ni Putu Eka Frastika Sari & I Wayan Cahya Mahastya, *Terapi Antioksidan Sebagai Nefroprotektor*, *Essence of Scientific Medical Journal*, vol. 20, ojs.unud.ac.id, no. 2, 2022, pp. 81–86.

[5] Ita Dwi Rafita, Tiwi Kusmiawati, & Nur'ain, 'Kayu Manis (Korteks Sinamum) Terhadap Gambaran Histopatologi Ginjal Tikus (Rattus Norwegittus) Yang Diinduksi Parasetamol', *Jurnal Sain dan Teknologi*, vol. 13, no. 2, 2015.

ingestion.[6] Paracetamol's well-tolerated pharmacological profile, minimal side effects, and over-the-counter availability make it a consumer-preferred antipyretic. This has led to paracetamol being one of the most frequent drugs causing deaths due to self-poisoning.[7] The mechanism of paracetamol toxicity occurs due to the conversion of the drug into a reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), by cytochrome P450 enzymes. Elevated levels of NAPQI cause the substance to be carried by the bloodstream towards the kidneys. NAPQI, therefore, causes tubular damage that can eventually lead to kidney failure, apart from causing intracellular damage followed by necrosis (cell death) of the liver.[8]

Compounds that protect the kidneys from the toxic effects of paracetamol are needed. These beneficial phytochemical compounds can be derived from various herbal plants, such as watermelon rind, which is rarely considered for efficacy. As Allah SWT says in Surah 'Abasa verses 24-32, which reads:

فَلْيَنْظُرِ الْاِنْسَانُ اِلٰى طَعَامِهٖٓ ۙ اَنَّا صَبَبْنَا الْمَاۤءَ صَبًّا ۙ ثُمَّ شَقَقْنَا الْاَرْضَ شَقًّا ۙ فَاَنْۢبَتْنَا فِيْهَا حَبًّا ۙ

وَّعِنَبًا وَّقَضْبًا ۙ وَّزَيْتُوْنًا وَّنَخْلًا ۙ وَّحَدَآئِقَ غُلْبًا وَّفَاكِهَةً وَّاَبًّا مَّتَاعًا لَّكُمْ وَلِاَنْعَامِكُمْ ؕ

Meaning: "*So, let man take care of his food (24). Indeed, we have abundant poured-out water (from the sky). (25) Then, We divided the earth as best We could (26) Then, We planted in it grains, (27) grapes, vegetables, (28) olives, date palms, (29) shady gardens, (30) fruits, and grasses (31) (All that is provided) for your enjoyment and that of your livestock (32"* (Q.S. 'Abasa 24-32)

[6] Mowry, JB, Spyker, DA, Brooks, DE, McMillan, N, & Schauben, JL, *Annual Report of The American Association of Poison Control Centers' National Poison Data System (NPDS)*, Annual Report, 32nd, 2014.

[7] Chinnappan et al., 'Nephroprotective Effect of Herbal Extract Eurycoma longifolia on Paracetamol-Induced Nephrotoxicity in Rats'.

[8] Harisyah Rezanty, 'Efektivitas Hibiscus Sabdariffa Terhadap Ginjal Tikus Yang Terinduksi Paracetamol : Ditinjau Dari Kadar Il-10, Kadar Kreatinin, Dan Gambaran Histopatologi Ginjal', Skripsi, Universitas Hasanuddin, Makassar, 2020.

The above Qur'anic verse explains Allah's gift of food and natural resources for humans. Interpretation of scholars, such as Sayyid Qutb in *Fi Zilal al-Qur'an*[9], , emphasize the importance of being grateful and using Allah's gifts wisely. Although watermelon is not specifically stated in this context, watermelon rind, know the health benefits such as antioxidant effects and kidney protection, can be considered part of Allah's blessings mentioned in the verse. The use of watermelon rind for health is a form of gratitude and good use of Allah's bounty following the guidance of this verse.[10] The watermelon is used only for its flesh, while its rind is discarded as waste. Each person generates about 0.68 kg of waste each day. On a national scale, 67.8 million tons of waste are generated annually, and organic waste is the most significant component.[11]

Watermelon rind has several pharmacological activities, such as antibacterial, antimicrobial, antioxidant, anti-inflammatory, gastroprotective, analgesic, laxative, anti-diarrheal, and hepatoprotective.[12] Among other parts, watermelon rind has the highest antioxidant and antimicrobial activities. This is evidenced by the low Inhibition Concentration 50% (IC50) value of 14.729 mg/ml, which indicates that watermelon rind is classified as a very potent natural antioxidant.[13] Antioxidant compounds are known to improve kidney function damaged by acetaminophen. These antioxidant compounds can reduce free radical compounds generated by the metabolic process of acetaminophen and prevent kidney damage. These various properties cannot be separated from watermelon rinds' content of secondary metabolites, such as alkaloids, flavonoids, phenols,

[9] Sayyid Qutb, *Fi Zilal al-Qur'an (In the Shade of the Qur'an)*, Dar al-Shorouk, Cairo, 2000.

[10] Mahmud Rifaanudin, 'Manfaat Tumbuhan Dalam Al Qur'An Bagi Kesehatan (Pendekatan Tafsir 'Ilmi)', *Al Muhafidz: Jurnal Ilmu Al-Qur'an dan Tafsir*, vol. 2, no. 1, 2022, pp. 87–100.

[11] KLHK RI, *Status Lingkungan Hidup Indonesia 2020*, Kementerian Lingkungan Hidup dan Kehutanan, Republik Indonesia, Jakarta, 2020.

[12] A. Deshmukh & S. Dongre, *Natural yellow colour from corolla of Nyctanthes arbor-tristis Linn. for dyeing and painting on cotton and silk for value addition*, *Biolife*, 2015.

[13] D. J. Hikmat, F. Filmaharani, Yaya, Nur Hatidjah Awaliyah Halid & Jastria Pusmarani, 'Formulasi Gel Hand Sanitizer Dari Ekstrak Metanol Kulit Semangka (Citrullus lanatus)', *Jurnal Mandala Pharmacon Indonesia*, vol. 8, jurnal-pharmaconmw.com, no. 1, 2022, pp. 11–24.

saponins, and tannins.[14] In addition, watermelon rind also contains citrulline, which is indirectly responsible for maintaining stability of kidney through the urea cycle.[15]

Kidney problems will cause many losses. Therefore, new alternatives are needed to prevent or help patients overcome kidney disease. One of the things that can be used as an alternative material is natural phytochemical metabolites from plants. Based on explanation above, this study was designed to determine the effect of watermelon rind extract (*Citrullus lanatus*) on the histopathologic picture of the kidneys of male white rats (*Rattus norvegicus*) induced by paracetamol.

1.2 Research Problem

The problem of this research is:

1. Does the content of watermelon rind affect the histopathology of male white rat kidneys induced by paracetamol?
2. What concentration of watermelon rind extract has the optimal effect on the histopathology of paracetamol-induced white rat kidneys?

1.3 Research Objectives

The objectives of this study are:

1. Knowing the substances in watermelon rind extract that affect the kidneys of male white rats induced by paracetamol.
2. Knowing the concentration of watermelon rind extract with the most optimal effect.

1.4 Research Benefits

1. Theoretical Benefits

The results of this study can be used as reference material for further research on kidney physiology, especially the effect of watermelon extract on kidney damage.

[14] Edi Kurniadi, Diah Wulandari Rousdy & Ari Hepi Yanti, 'Aktivitas Nefroprotektif Ekstrak Metanol Buah Lakum (Cayratia trifolia (L.) Domin) terhadap Induksi Parasetamol', *Jurnal Labora Medika*, vol. 2, no. 1, 2018, pp. 14–21.

[15] Mardiana Mardiana, Nur Khofifah & Yanesti Lestari, 'Branched Chain Amino Acid (BCAA), Sitrulin, Bromelain Dan Muscle Injury', *Bookchapter Kesehatan Masyarakat Universitas Negeri Semarang*, 2022, pp. 128–160.

2. Practical Benefits

The results of this study are expected to add to the repertoire of science and provide insight to readers, especially herbal medicine users, about the effects of watermelon extract on kidney damage.

1.5 Authenticity Research

Research on the effect of an extract on rat kidneys has been carried out by several researchers, as shown in Table 1 below.

Table 1. Authenticity Research

Title of Research	Research Methods	Variable	Result	Research Differences
Histopathology of Kidney of white rats given anthill extract induced by a toxic dose of paracetamol [16]	Experimental	**Dependent:** Histopathologic features **Independent:** Anthill extract and paracetamol	Peroral administration of toxic doses of paracetamol can cause changes in the histopathological picture of white rat kidneys. Administration of anthill extract at a dose of 250mg/kg BW can improve the toxic effects of toxic doses of paracetamol.	**Dependent:** Kidney damage score **Independent:** Watermelon rind extract and paracetamol
Gastroprotective activity of watermelon methanol extract in aspirin-induced rats[17]	Experimental	**Dependent:** Gastric lesion score **Independent:** Aspirin and watermelon rind methanol extract	Watermelon rind extract was given a test dose treatment given watermelon rind extract 200 mg/kibbe;	**Dependent:** Kidney damage score **Independent:** Watermelon rind extract

[16] I Wayan Sudira, I Made Merdana, Ida Bagus Oka Winaya & I Kadek Parnayasa, *Perubahan Histopatologi Ginjal Tikus Putih Diberikan Ekstrak Sarang Semut Diinduksi Parasetamol Dosis Toksik*, *Buletin Veteriner Udayana*, vol. 11, download.garuda.kemdikbud.go.id, no. 2, 2019, pp. 136–142.

[17] La Ode Hasiadin Alwi, Jastria Pusmarani, & Risky Juliansyah Putri, 'Aktivitas Gastroprotektif Ekstrak Metanol Kulit Semangka (Citrullus lanatus L.) Pada Tikus (Rattus norvegicus) Yang Diinduksi Aspirin', *Jurnal Pharmacia Mandala Waluya*, vol. 1, garuda.kemdikbud.go.id, no. 1, 2021, pp. 21–36.

		400 mg/kgBB; 800 mg/kgBB. Watermelon rind extract (Citrullus lanatatus L.) provides optimal gastroprotective effects at doses of As seen from the lesion score, 400 mg/kgBB and 800 mg/kgBB, with a significant value of p = 0.037 <0.001. significant p = 0.037 <0.05 against the induction control.	was given a 200 mg/200gBB test dose treatment. 200 mg/200gBB; 400 mg / kgBB; 600 mg / kgB given for 8 days