

1  
2 **Toxicity of Local Natural Ingredients from East 3**  
**Java, Indonesia Yam Bean (*Pachyrhizus 4 erosus*)**  
**and Avocado (*Persea americana Mill*) 5 on the Liver**  
**and Kidney Structure of *Sprague***  
6 ***Dawley Rats***

Commented [U1]: Here and next sites it should be in full Botanical name like <https://wfo.plantlist.org/taxon/wfo-0000183119-2024-06?page=1>

20  
21 **ABSTRACT**  
22

**Aims:** The aim of the research was to test the toxicity of jicama (*Pachyrhizus erosus*) and avocado (*Persea americana Mill*) on the structure of liver and kidney tissue in Sprague Dawley rats.

**Study Design:** Female Sprague Dawley rats aged 5 months, 24 animals. Treatment of synthetic and natural ingredients. 6 treatment groups were given daidzein (P1), 6 treatment groups were given niacin (P2), 6 treatment groups were given jicama (*Pachyrhizus erosus*) (P3) and 6 treatment groups were given avocado (*Persea americana Mill*) (P4). Each treatment was carried out for 28 days. On the 29th day, surgery was performed and the liver and kidneys were removed, followed by HE staining.

**Result:** The results showed that the structure of liver and kidney tissue given daidzein and niacin experienced necrosis, increased vascularization, hemorrhage and fatty degeneration.

**Conclusion:** The use of natural ingredients does not produce toxic (harmful) effects in the body compared to synthetic substances. The percentage of kidney necrosis with daidzein administration is 24%, and with niacin administration, it is 29%. The percentage of liver necrosis with daidzein administration is 20%, and with niacin administration, it is 24%.

Formatted: Highlight

23  
24 *Keywords:* toxicity, natural ingredients, liver, kidney  
25

26  
27 **1. INTRODUCTION**  
28  
29

30 Biodiversity is a wealth of Indonesia's natural resources and contributes to various aspects of  
31 life. Various plant species in each region originate from different countries or are native to  
32 Indonesia, thriving well in this tropical country. One aspect of biodiversity is medicinal plants.  
33 To date, medicinal plants have not been cultivated or utilized optimally. The utilization of  
34 medicinal plants as a potential local wisdom is declining due to the dominance of  
35 pharmaceutical developments in the health sector. Synthetic substances have dominated the  
36 pharmaceutical industry, leading to the extinction of local plants with medicinal potential due  
37 to underutilization.

38 Modern society views treatment with medicinal plants as unscientific and unreliable in terms  
39 of safety. People prefer treatment with synthetic substances over natural ingredients. The  
40 pharmaceutical field has significantly advanced with the production of synthetic compounds  
41 considered more effective and efficient for treatment. Modern society prefers treatment using  
42 synthetic compound formulations over medicinal plants.

43 Medicinal plants have very complex chemical compounds that interact with each other [1], [2],  
44 [3]. The use of medicinal plants as natural ingredients with multi-component compounds differs  
45 from the use of synthetic substances [2], [4]. This is because synthetic substances are single  
46 compounds with one activity and one target [5], [6]. Natural ingredients as medicines usually  
47 consist of one or more mixtures processed together, making the compounds more complex  
48 [7], [8]. Additionally, their pharmacokinetics and pharmacodynamics become more complex  
49 due to interactions between multi-component compounds within the biological system of the  
50 body [9], [10].

51 There is a growing trend of lifestyle changes towards 'back to nature,' utilizing natural  
52 ingredients as therapy for various diseases. *Pachyrhizus erosus* (yam bean) is one local plant  
53 that grows very well in tropical climates like Indonesia. In Indonesia, yam bean is usually  
54 consumed fresh in salads, fruit salads, and juices. Its development has reached the cosmetic  
55 industry. However, its utilization in the health sector in Indonesia has not yet been realized.  
56 Research findings indicate that yam bean tubers contain phytoestrogen compounds, such as  
57 daidzein and genistein, which are isoflavone compounds with a chemical structure similar to  
58 estrogen hormone [11], [12], [13]. These compounds can be used for estrogen replacement  
59 therapy [14], [15], [16].

60 *Persea americana* Mill (avocado) is another local plant that thrives in tropical climates. In  
61 Indonesia, avocados are usually consumed fresh in desserts and as a bread topping. The  
62 development of avocados in the cosmetic industry includes hand lotions, moisturizers, and  
63 face masks. Research findings indicate that avocados contain complex compounds beneficial  
64 for lowering cholesterol levels [17], [18]. Avocados contain several active ingredients  
65 suspected to lower cholesterol levels, including pantethine, niacin (vitamin B3), beta-sitosterol,  
66 vitamin C, vitamin E, vitamin A (beta carotene), pantothenic acid, oleic acid, folic acid,  
67 selenium, amino acids, and fiber [18], [19].

68 Medicinal plants have complex compounds that can interact within the body's system [1], [20].  
69 The interaction of complex compounds in medicinal plants can provide physiological potential  
70 within the body's system. Long-term use of medicinal plants does not pose adverse effects on  
71 the body [21], [22], [23]. Medicinal plants contain various bioactive compounds that enhance  
72 physiological activity within the body, providing better effects [24], [25], [26].

73 The metabolism of plant compounds occurs in the kidneys and liver. One of the kidney's  
 74 functions is to cleanse the body of waste products from digestion or metabolism [27], [28]. The  
 75 liver also functions as a detoxification organ [29], [30]. Therefore, the effectiveness and safety  
 76 of medicinal plants for health applications require toxicity testing. Toxicity tests are conducted  
 77 to analyze the safety of treatments concerning liver and kidney necrosis. The purpose of this  
 78 study is to examine the preclinical effects of yam bean and avocado consumption on test  
 79 animals by observing changes in the histological structure of the kidneys and liver.

80

## 81 2. MATERIAL AND METHODS

### 82 Materials

83 Yam bean tubers were obtained from the plantations on the slopes of Mount Wilis in Madiun  
 84 Regency, East Java, Indonesia. Avocado fruits were obtained from plantations in Dolopo,  
 85 Madiun Regency, East Java, Indonesia. The yam bean tubers and avocado fruits were  
 86 harvested when ripe. Male Sprague Dawley rats, 5 months old, 24 in total, were used. Rat  
 87 feed included pellet milk A, 10% formalin, liquid paraffin, xylene, xylol, Hematoxylin-Eosin  
 88 (HE), 70% alcohol, 80% alcohol, 96% alcohol, paraffin, physiological NaCl 0.9%, 50% alcohol,  
 89 70% alcohol, absolute alcohol, xylol, a mixture of xylol-alcohol with xylol ratios of 1:3, 2:2, and  
 90 3:1, Li<sub>2</sub>CO<sub>3</sub> solution, 1% HCl, PBS, eosin, 3% formalin and haupt, 25 mg/kg daidzein, 10  
 91 mg/kg niacin, 1.5 ml yam bean tuber juice, and 1.5 ml avocado juice.

### 92 Method

#### 93 Maintenance and Treatment of Test Animals

94 Male Sprague Dawley rats, 5 months old, were obtained from LPPT Gadjah Mada University.  
 95 A total of 24 rats, weighing 250-350 grams, were kept in group cages and acclimatized for 7  
 96 days. The rats were divided into 6 treatment groups: daidzein administration (P1), niacin  
 97 administration (P2), yam bean tuber juice administration (Pachyrhizus erosus) (P3), and  
 98 avocado juice administration (Persea americana Mill) (P4). The treatment lasted for 28 days,  
 99 and on the 29th day, surgery and organ (liver and kidney) removal were performed, followed  
 100 by HE staining.

#### 101 Data Analysis

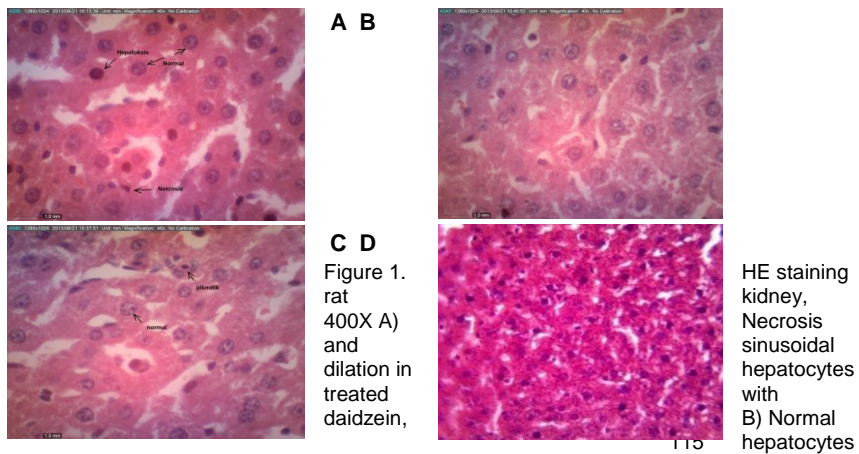
102 Descriptive data analysis was conducted using an Optilab microscope to observe changes in  
 103 the structure of hepatocyte and glomerular cells. The percentage of necrotic cells in the  
 104 hepatocytes and glomeruli was calculated.

## 105 3. RESULTS AND DISCUSSION

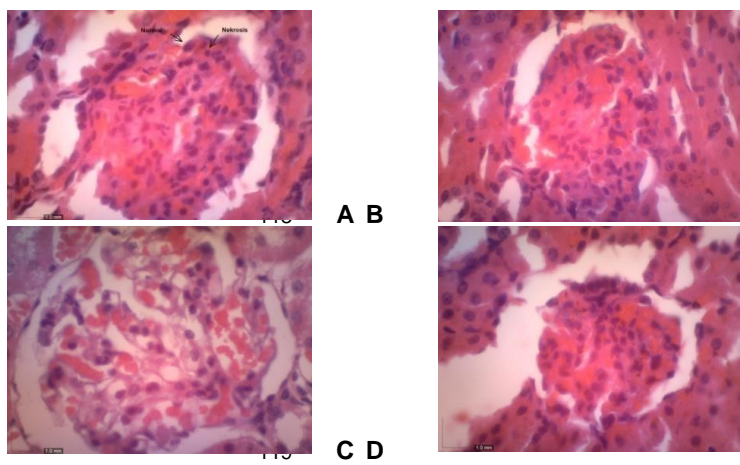
**Commented [U2]:** In the ABSTRACT you told us about female rats. Here- about male rats. What sex of rats you used? According the rules, it should be mix

**Formatted:** Highlight

**Commented [U3]:** You divided into 6 groups, but wrote about only 4. Where did news about P5 and P6? What you treated? You just added in food of health animals some things? You divided into 6 groups, but wrote about only 4. What did news about P5 and P6? What did you treated in rats? You just added in food of health animals some things?



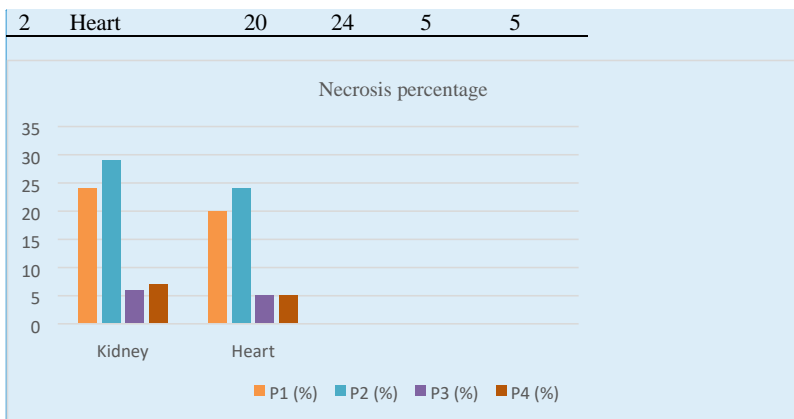
116 in yam bean tuber treatment, C) Necrosis and sinusoidal dilation, pyknosis of nuclei in  
 117 hepatocytes treated with niacin, D) Normal hepatocytes in avocado treatment.



120 Figure 2. HE staining rat glomerulus, 400X A) Necrosis and vascularization in treatment with  
 121 daidzein; B) normal glomerulus in yam bean tuber treatment; C) Necrosis, fatty degeneration  
 122 and vascularization in treatment with niacin; D) normal glomerulus in avocado treatment

123 Table 1. Percentage kidney and glomerulus necrosis in rats

No	Organ terdeteksi	Sel nekrosis (%)			
		P1	P2	P3	P4
124	Kidney	24	29	6	7



125  
126

Figure 3. Necrosis Percentage

127 The liver is an important organ in the body that functions to detoxify various substances  
 128 ingested by the digestive tract. The functional unit of the liver is the liver lobule, which is  
 129 cylindrical in shape, surrounding the central vein that flows into the hepatic vein, and then into  
 130 the vena cava [31], [32]. The liver is crucial in metabolism, detoxification, storage, and  
 131 excretion of xenobiotics and their metabolites, and is particularly susceptible to damage [33].  
 132 Accumulation of toxic substances in the liver parenchyma can cause hepatocyte cell damage  
 133 due to exposure. Histological changes vary depending on the dose, type, effects of the  
 134 substance, or other diseases, and susceptibility [34]. Liver damage from toxic substances is  
 135 influenced by several factors, such as the type of chemical involved, the dose given, and the  
 136 duration of exposure [35], [36].

137 The basic functional unit of the kidney is the nephron, which regulates water and solutes,  
 138 especially electrolytes in the body, by filtering the blood [37], [38]. It then reabsorbs fluids and  
 139 molecules through the capillaries that are still needed by the body [39], [40]. Chemicals  
 140 entering the body through various administration routes generally undergo absorption,  
 141 distribution, metabolism, and excretion [41], [42]. The metabolism of medicinal plant  
 142 compounds occurs in the kidneys [43], [44]. The kidney is highly susceptible to the toxic effects  
 143 of drugs and chemicals. Examination of glomerular and tubular necrosis is one way to  
 144 demonstrate kidney cell damage [45].

145 Various phytochemicals in yam bean tubers and avocado fruits can work complexly within the  
 146 body. Natural chemical compounds are complex and non-toxic compared to synthetic or  
 147 isolated single compounds [46], [47]. Daidzein in yam bean tubers, a compound similar to  
 148 17 $\beta$ estradiol, has enantiomeric structures, including *cis*-tetrahydrodaidzein and *trans*-  
 149 tetrahydrodaidzein, which have chiral structures [48]. This increases the number of  
 150 daidzeinlike compounds that can actively enter the bloodstream. Daidzein is followed into the  
 151 bloodstream by genistein and quercetin, phytoestrogen compounds from yam bean tubers  
 152 [49], [50]. Avocado fruits contain potassium, phosphorus, calcium, magnesium, niacin,  
 153 pyridoxine, riboflavin, thiamine, and biotin [51]. Niacin is a chemical compound that can lower  
 154 cholesterol [52], [53].

**Commented [U4]:** I see investigation about heart cells. It must be news about liver cells.

155 Consuming natural ingredients has better effects on the body than consuming isolated  
156 synthetic substances [54]. This is because natural ingredients have complex chemical

147 compounds that interact with each other, creating beneficial physiological effects [55], [56]. All 148 medicinal plants contain mixtures of active compounds with pharmacological activities [56].

149 Consuming fresh natural ingredients, without processing, shows beneficial effects on the body. 150 This is because the compounds in plants have not been damaged during processing. Non151 processed food is considered to have a better chemical composition compared to ultra152 processed food, making the consumption of non-processed food in large quantities and over 153 a long period safe and non-toxic. The complexity of natural compounds allows them to work 154 in the body with the principle of balance metabolism, as some compounds enhance and others 155 reduce effects, making complex compounds non-toxic. Based on this analysis, natural 156 ingredients are more moderate compared to synthetic or isolated substances.

157

#### 158 4. CONCLUSION

159

160 The use of natural ingredients does not produce toxic (harmful) effects in the body compared 161 to synthetic substances. The percentage of kidney necrosis with daidzein administration is 162 24%, and with niacin administration, it is 29%. The percentage of liver necrosis with 163 daidzein administration is 20%, and with niacin administration, it is 24%.

164

165

166

#### 177 REFERENCES

178

179 [1] C. G. Awuchi, "Medicinal plants: the medical, food, and nutritional biochemistry and 180 uses," *Int. J. Adv. Acad. Res.*, vol. 5, no. 11, pp. 220–241, 2019.

181 [2] N. Vaou *et al.*, "Interactions between medical plant-derived bioactive compounds: 182 focus on antimicrobial combination effects," *Antibiotics*, vol. 11, no. 8, p. 1014, 2022.

183 [3] F. Noor, M. T. ul Qamar, U. A. Ashfaq, A. Albutti, A. S. Alwashmi, and M. A. Aljasir, 184 "Network pharmacology approach for medicinal plants: review and assessment," 185 *Pharmaceuticals*, vol. 15, no. 5, p. 572, 2022.

186 [4] M. Bunse *et al.*, "Essential oils as multicomponent mixtures and their potential for 187 human health and well-being," *Front. Pharmacol.*, vol. 13, p. 956541, 2022.

188 [5] C. J. Gerry *et al.*, "Real-time biological annotation of synthetic compounds," *ournal Am.* 189 *Chem. Soc.*, pp. 8920–8927, 2016.

190 [6] G. Martelli and D. Giacomini, "Antibacterial and antioxidant activities for natural and 191 synthetic dual-active compounds," *Eur. J. Med. Chem.*, vol. 158, pp. 91–105, 2018.

192 [7] G. Joana Gil-Chávez *et al.*, "Technologies for extraction and production of bioactive 193 compounds to be used as nutraceuticals and food ingredients: An overview," *Compr. 194 Rev. food Sci. food Saf.*, vol. 12, no. 1, pp. 5–23, 2013.

195 [8] F. F. Y. Stéphane, Bankeu Kezetes Jean Jules, G. E. Batiha, Iftikhar Ali, and 196 Lenta

Ndjakou Bruno, "Extraction of bioactive compounds from medicinal plants and herbs,"

- 197 *Nat Med Plants*, 2021.
- 198 [9] A. Kumar, A. Adlakaha, and K. Mukherjee, "The effect of perceived security and  
199 grievance redressal on continuance intention to use M-wallets in a developing country,"  
200 *Int. J. Bank Mark.*, vol. 36, no. 7, pp. 1170–1189, 2018, doi: 10.1108/IJBM-04-  
201 20170077.
- 202 [10] G. M. Husain, M. A. Khan, M. Urooj, and M. H. Kazmi, "Pharmacodynamic Evaluation:  
203 Herbal Medicine," *Drug Discov. Eval. Methods Clin. Pharmacol.*, pp. 483–497, 2020.
- 204 [11] C. N. Primiani, "The phytoestrogenic potential of yam bean (*Pachyrhizus erosus*) on  
205 ovarian and uterine tissue structure of premenopausal mice," *Biol. Med. Nat. Prod.*  
206 *Chem.*, vol. 4, no. 1, pp. 5–9, 2015.
- 207 [12] P. Trisunuwati, "Efficacy of Water Clover Extract (*Marsilea crenata*) Against Blood  
208 Estrogen Progesteron Balance, Blood Calcium Levels and Impact on Dense of Bone  
209 Tissue of Rat (*Rattus norvegicus*)," *Res. J. Life Sci.*, vol. 4, no. 1, pp. 50–55, 2017.
- 210 [13] E. F. Hadiningsih *et al.*, "The effect of bengkuang (*Pachyrhizus erosus*) ethanol extract  
211 on the number of ovarian follicles, amount of epithelium and endometrium stroma cells  
212 in DMPA-treated *Rattus norvegicus*," in *AIP Conference Proceedings*, 2020.
- 213 [14] D. M. Țiț, A. Pallag, C. Iovan, G. Furău, C. Furău, and S. Bungău, "Somatic-vegetative  
214 symptoms evolution in postmenopausal women treated with phytoestrogens and  
215 hormone replacement therapy," *Iran. J. Public Health*, vol. 46, no. 11, p. 1528, 2017.
- 216 [15] D. M. Tit *et al.*, "Effects of the hormone replacement therapy and of soy isoflavones on  
217 bone resorption in postmenopause," *J. Clin. Med.*, vol. 7, no. 10, p. 297, 2018.
- 218 [16] J. Li *et al.*, "Efficacy and safety of phytoestrogens in the treatment of perimenopausal  
219 and postmenopausal depressive disorders: A systematic review and meta-analysis,"  
220 *Int. J. Clin. Pract.*, vol. 75, no. 10, 2021.
- 221 [17] A. L. Ramos-Aguilar *et al.*, "The importance of the bioactive compounds of avocado  
222 fruit (*Persea americana* Mill) on human health," *Biotechnia*, vol. 21, no. 3, pp. 154–162,  
223 2019.
- 224 [18] P. Harnis, Y. A. Sari, and M. A. Rahman, "Segmentasi Citra Kue Tradisional  
225 menggunakan Otsu Thresholding pada Ruang Warna CIE LAB," *Pengemb. Teknol.*  
226 *Inf. Dan Ilmu Komput*, p. 2548, 2019.
- 227 [19] G. James-Martin, P. Brooker, G. Hendrie, and W. Stonehouse, "A Review of the  
228 Health Effects of Avocados," 2022.
- 229 [20] A. Gurib-Fakim, "Medicinal plants: traditions of yesterday and drugs of tomorrow," *Mol.*  
230 *Aspects Med.*, vol. 27, no. 1, pp. 1–93, 2006.
- 231 [21] S. Kumar, G. J. Dobos, and T. Rampp, "The significance of ayurvedic medicinal plants,"  
232 *J. Evid. Based. Complementary Altern. Med.*, vol. 22, no. 1, pp. 494–501, 2017.
- 233 [22] Ćwieląg-Drabek *et al.*, "Health risks from consumption of medicinal plant dietary  
234 supplements," *Food Sci. Nutr.*, vol. 8, no. 7, pp. 3535–3544, 2020.
- 235 [23] C. Meng *et al.*, "Ecological and health risk assessment of heavy metals in soil and  
236 Chinese herbal medicines," *Environ. Geochem. Health*, pp. 1–12, 2022.
- 237 [24] G. Mustafa, R. Arif, A. Atta, S. Sharif, and A. Jamil, "Bioactive compounds from  
238 medicinal plants and their importance in drug discovery in Pakistan," *Matrix Sci.*  
239 *Pharma*, vol. 1, no. 1, pp. 17–26, 2017.
- 240 [25] S. Mickymaray, "Efficacy and mechanism of traditional medicinal plants and bioactive  
241 compounds against clinically important pathogens," *Antibiotics*, vol. 8, no. 4, p. 257,  
242 2019.
- 243 [26] L. Rathor, "Medicinal plants: A rich source of bioactive molecules used in drug  
244 development." Evidence Based Validation of Traditional Medicines: A comprehensive  
245 Approach," pp. 195–209, 2021.

- 246 [27] B. Meijers, R. Farré, S. Dejongh, M. Vicario, and P. Evenepoel, "Intestinal barrier  
247 function in chronic kidney disease," *Evenepoel*, vol. 10, no. 7, p. 298, 2018.
- 248 [28] J. E. Hall and Michael E. Hall, *Guyton and Hall Textbook of Medical Physiology*. 2020.
- 249 [29] J. C. Ozougwu, "Physiology of the liver," *Int. J. Res. Pharm. Biosci.*, vol. 4, no. 8,  
250 pp. 13–24, 2017.
- 251 [30] M. Hassani, "Liver Structure, Function and its Interrelationships with Other Organs," *Int*  
252 *J Dent Med Sci Res*, vol. 4, no. 1, pp. 88–92, 2022.
- 253 [31] J. Bruslé and G. G. i Anadon, "The structure and function of fish liver," *Fish Morphol.*,  
254 pp. 77–93, 2017.
- 255 [32] S. S. Usanov, "Anatomical and Histological Parameters of the Liver of White Nonbored  
256 Rats in Normal," *BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY*  
257 *JURNALI*, vol. 2, no. 1, pp. 123–128, 2022.
- 258 [33] M. . Brzoska, J. Moniuszko-Jakoniuk, B. ilat-Marcinkiewicz, and B. Sawicki, "Liver and  
259 kidney function and hystology in rats exposed to cadmium and ethanol," *Alcohol*  
260 *Alcohol.*, vol. 38, no. 1, pp. 2–10, 2003.
- 261 [34] Cramer K, T. Charrois, and S. Vohra, "Valerian practical management of adverse  
262 effects and drug interactions," *Can. Pharm. J.*, vol. 139, no. 3, pp. 39–41, 2006.
- 263 [35] D. E. Hinton, H. Segner, and T. Braunbeck, "Toxic responses of the liver," *Target organ*  
264 *Toxic. Mar. Freshw. teleosts*, pp. 224–268, 2017.
- 265 [36] "The liver as a target organ for toxicity," *Timbrell, John A.* , pp. 145–173, 2020.
- 266 [37] D. . Eaton and J. . Pooler, "Vander's renal physiology. Mc Graw Hil Medicall.," 2009.
- 267 [38] M. Nair, "The renal system," *Fundam. Anat. Physiol. Nurs. Healthc. Students.*, 2016.
- 268 [39] O. Nakonechna, S. Stetsenko, and A. Bondareva, *Water-salt and mineral metabolism.*  
269 *Urinary function of kidney*. 2020.
- 270 [40] Л. М. Ростока, А. Д. Сіткап, and Я. Ю. Бурмістрова, "Functional biochemistry of  
271 blood, liver and kidneys.," 2021.
- 272 [41] T. A. Mace *et al.*, "Bioactive compounds or metabolites from black raspberries  
273 modulate T lymphocyte proliferation, myeloid cell differentiation and Jak/STAT  
274 signaling," *Cancer Immunol Immunother.*, vol. 63, no. 9, pp. 889–900, 2014, doi:  
275 10.1007/s00262-014-1564-5.Bioactive.
- 276 [42] J. W. Osborn, R. Tyshynsky, and L. Vulchanova, "). Function of renal nerves in kidney  
277 physiology and pathophysiology," *Annu. Rev. Physiol.*, vol. 83, pp. 429–450, 2021.
- 278 [43] R. . Yudhani, R. . Pesik, S. Azzahro, A. . Anisa, and R. Hendriyani, "Renal function  
279 parameter on acute toxicity test of kapulaga (Amomum cardamom) seed extract in  
280 rat.," *IOP Conf. Ser. Mater. Sci. Eng.*, vol. 578, 2019.
- 281 [44] A. Salazar-Gómez, J. C. Ontiveros-Rodríguez, S. S. Pablo-Pérez, E. Vargas-Díaz, and  
282 L. Garduño-Siciliano, "The potential role of sesquiterpene lactones isolated from  
283 medicinal plants in the treatment of the metabolic syndrome–A review," *South African*  
284 *J. Bot.*, vol. 135, pp. 240–251, 2020.
- 285 [45] Sancho-Martinez, Sandra M, J. M. Lopez-Novoa, and Lopez-Hernandez,  
286 "Pathophysiological role of different tubular epithelial cell death modes in acute kidney  
287 injury," *Clin. Kidney J.*, vol. 8, no. 5, pp. 548–559, 2015.
- 288 [46] Melfi Francesco *et al.*, "Natural products as a source of new anticancer chemotypes,"  
289 *Expert Opin. Ther. Pat.*, vol. 33, no. 11, pp. 721–744, 2023.
- 290 [47] jemilat A. ibrahim, O. H. Egharevba, and K. S. Gamaniel, "Chemical and biological  
291 screening approaches to phytopharmaceuticals," *J. Int. Sci.*, vol. 6, no. 10, pp. 22–31,  
292 2017.
- 293 [48] U. Mariko, "Isoflavone metabolism and bone-sparing effects of daidzein-metabolites,"  
294 *J. Clin. Biochem. Nutr.*, vol. 52, no. 3, pp. 193–201, 2013.

- 295 [49] S. Lecomte, F. Demay, F. Ferriere, and Pakdel Farzad, "Phytochemicals targeting  
296 estrogen receptors: beneficial rather than adverse effects?," *Int. J. Mol. Sci.*, vol. 18,  
297 no. 7, p. 1381, 2017.
- 298 [50] Q. Wang, B. Spenkelink, R. Boonpawa, and I. M. Rietjens, "Use of physiologically  
299 based pharmacokinetic modeling to predict human gut microbial conversion of  
300 daidzein to S-Equol.," *J. Agric. Food Chem.*, vol. 70, no. 1, pp. 343–352, 2021.
- 301 [51] J. Ebbage, "Avocado Nutrition Desktop Research and Best Minds Panel," *Hortic.  
302 Innov.*  
303 *Aust. Sydney.*, 2015.

303 [52] P. Mani and A. Rohatgi, "Niacin therapy, HDL cholesterol, and cardiovascular disease: 304 is the HDL hypothesis defunct?," *Curr. Atheroscler. Rep.*, vol. 17, pp. 1–9, 2015. 305 [53] S. Rahman, "Effect of Avocades to LDL Cholesterol as a preventive risk of 306 atherosclerosis," *Atherosclerosis*, vol. 4, p. 6, 2019.

307 [54] B. Olas, J. Bialecki, K. Urbanska, and M. Brys, "The effects of natural and synthetic 308 blue dyes on human health: A review of current knowledge and therapeutic 309 perspectives," *Adv. Nutr.*, vol. 12, no. 6, pp. 2301–2311, 2021.

310 [55] S. A. Hussain, N. R. Panjagari, and G. R. Patil, "Potential herbs and herbal 311 nutraceuticals: food applications and their interactions with food components," *Crit. 312 Rev. Food Sci. Nutr.*, vol. 55, no. 1, pp. 94–112, 2015.

313 [56] J. Qishu, R. Wang, Y. Jiang, and B. Liu, "Study on the interaction between active 314 components from traditional Chinese medicine and plasma proteins," *Chem. Cent. J.*, 315 vol. 12, pp. 1–20, 2018.

316