



## Review Article: Study of The Toxicity of Herbal Plants on Vital Organs of Experimental Animals

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### Abstract

**Background:** Indonesia is a tropical country with many natural resources, including flora and fauna. Herbs are natural plants with therapeutic qualities but can also be harmful. Therefore, numerous studies assess the toxicity of herbal plants and conduct clinical trials to ensure the safety of the necessary herbal medicines for treatment purposes. This article aims to learn more about the harmful effects of compounds not found in acute and subchronic toxicity tests.

**Methods:** A review study conducted through searches of articles in Google Scholar, Science Direct, Research Gate, Garuda, and Pubmed. Several Indonesian-accredited scientific papers, including Sinta 4 and Sinta 5, were accepted. Fifteen articles were found to be relevant to the topic.

**Results:** The classification of herbs includes non-toxic, slightly toxic, and highly hazardous categories. Other factors that can affect the results of the toxicity test are the selection of the species of test animal, age, animal weight, sex of the animal, how to administer the test preparation, how to choose the test dose, side effects on the test preparation, testing techniques, and mechanisms, including how to handle animals during the experiment.

**Conclusion:** Herbal plants are relatively safe to use, but long-term usage may need more critical consideration.

**Keywords:** *Herbal plants, Toxicity of vital organs, Toxicity test.*

### Introduction

Indonesia is a tropical country with a lot of flora and animals. Indonesia, a country with abundant natural resources, provide herbal plants to strengthen the body's defenses against disease<sup>1</sup>. Herbal plants are plants that grow naturally and offer therapeutic qualities. Herbal plants can also increase the body's immune system. Since many studies supported herbal plants quality, it is still used by Indonesian people until today<sup>2</sup>.

Toxicity test comprises three main components: (a) determining if a substance has the potential to be toxic; (b) identifying the biological and environmental elements that lead to the formation of toxic consequences; and (c) characterizing the action or impact. There are two kinds of poisoning tests: specific and broad toxicity<sup>3</sup>.

Organs are groups of distinct tissues, each of which has a distinct function inside the body. The body's organs are arranged in the organ system based on their respective roles. Between them are vital organs, which are necessary for an organism to survive. The vital organs are the heart, lungs, liver, kidneys, and stomach. If one of these organs has necrosis, this could be lethal. Then, it's critical to

comprehend the potential consequences of using a medication that has negative side effects on the body's vital organs.

Given the above context, we were motivated to conduct a review to determine result of toxicity tests on various herbal plants in vital organs of animals regarding their harmful effects. The range of dosage percentages that potentially have a damaging impact can be determined by testing the level of dose variance. The purpose of this review article is to find out what herbal plants have toxic effects on the organs of experimental animals.

### Methods

The review involves searching the literature of research journals using databases such as Google Scholar, Science Direct, Research Gate, Garuda, and Pubmed. Several Indonesian-accredited journals, including Sinta 2, 3, 4, and 5, from 2007-2023, were found in several scientific articles using the keyword "Testing of Herbal Plants Toxicity Against Animal Vital Organs Trials". Based on the search results, 100 articles were found, and a screening was carried out. 75 articles were obtained and used as a reference for this review article library.

## Result

**Table 1.** Toxicity Test of Herbaceous Plants on Organ Histopathology of Experimental Animals

No.	Types of Toxicity	Plant	Result
<b>Toxicity Study on Heart Organ Parameters</b>			
1	Acute Toxicity <sup>5</sup>	Male papaya calina leaf ( <i>Carica papaya</i> L.)	The preparation is non-toxic.
2	Toxicity Subchronic <sup>6</sup>	Katuk leaf ( <i>Sauropus androgynus</i> (L.) Merr.)	Non-toxic to heart organ weight and left vertical heart wall thickness, subchronically toxic to heart muscle cells.
3	Toxicity Subchronic <sup>7</sup>	Orange skin ( <i>Citrus nobilis</i> Lour.)	Affects the level of damage to heart muscle cells.
4	Acute Toxicity <sup>8</sup>	Sirih leaf ( <i>Piper betle</i> L.) and gambir ( <i>Uncaria gambir</i> R.)	Does not indicate the presence of toxicity in the heart organ.
5	Acute Toxicity <sup>9</sup>	Kirinyuh/jack in the bush leaf ( <i>Chromolaena odorata</i> (L.) R.M King & H. Rob)	Does not show any toxic effects
6	Acute Toxicity <sup>10</sup>	Wualae ( <i>Etlingera elatior</i> (Jack) R. M.Smith)	The heart organ shows symptoms of necrosis.
7	Toxicity Subchronic <sup>11</sup>	Pinang.yaki ( <i>Areca vestiaria</i> )	Does not have any effects that can damage the heart.
8	Toxicity Subchronic <sup>12</sup>	Rambai skin ( <i>Baccaurea motleyana</i> )	It does not affect the relative weight of the heart organ.
9	Acute Toxicity <sup>13</sup>	Dayak shallot ( <i>Eleutherine americana</i> Merr.) and pinang yaki ( <i>Areca vestiaria</i> Giseke)	It does not affect the macroscopic picture of the heart organ.
10	Acute Toxicity <sup>14</sup>	Klausena leaf ( <i>Clausena anisata</i> Hook.f.)	It does not have a spectrum of significant toxic effects.
11	Toxicity Subchronic <sup>15</sup>	Celebes pepper leaf ( <i>Piper crocatum</i> Ruiz & Pav)	No toxic spectrum was found.
12	Acute Toxicity <sup>16</sup>	Ruku-Ruku ( <i>Ocimum sanctum</i> L.)	Has no adverse effects.
13	Acute Toxicity <sup>17</sup>	Tempuyung leaf ( <i>Sonchus arvensis</i> L.)	The presence of symptoms of toxicity
14	Acute Toxicity <sup>18</sup>	Bajakah tampala stem ( <i>Spatholobus littoralis</i> Hassk.) and yellow bajakah stem ( <i>Arcangelisia flava</i> (L.) Merr.)	Practically non-toxic.
15	Acute Toxicity <sup>19</sup>	Herba meniran ( <i>Phyllanthus niruri</i> auct. Non L.), tempuyung ( <i>Sonchus arvensis</i> L.) and black jinten ( <i>Nigella sativa</i> L.)	Almost non-toxic.

**Toxicity Study on Lung Organ Parameters**

1	Acute Toxicity <sup>20</sup>	Male papaya calina ( <i>Carica papaya</i> L.)	Showned lethal dose 50 (LD50) pseudo-above the dose of 15 g/kg that the preparation was non-toxic. In high doses, it can potentially be toxic to the lungs.
2	Acute Toxicity <sup>21</sup>	Pecut kuda/blue snake weed ( <i>Stachytarpheta</i> (L.) <i>jamaicensis</i> VAHL)	
3	Acute Toxicity <sup>18</sup>	Bajakah tampala ( <i>Spatholobus littoralis</i> Hassk.) and yellow bajakah ( <i>Arcangelisia flava</i> (L.) Merr.)	It does not cause 50% of the deaths of test animals, so it is included in the "practically non-toxic" criterion.
4	Acute Toxicity <sup>22</sup>	Dayak shallot ( <i>Eleutherine americana</i> Merr.) and pinang yaki ( <i>Areca vestiaria</i> Giseke)	Did not exert a damaging effect based on macroscopic images on the lung organs of male white rats of the wistar strain ( <i>Rattus norvegicus</i> ).
5	Acute Toxicity <sup>23</sup>	Kayu Jawa/Indian ash tree ( <i>Lannea coromandelica</i> (Houtt.) Merr.)	The LD50 value is more significant than 5,000 mg/kg, categorized as practically non-toxic to the lungs.
6	Acute Toxicity and Subchronic <sup>24</sup>	Katuk ( <i>Sauropus androgynus</i> (L.) Merr)	Has an LD50 value > 5,000 mg/kg is included in the practical criteria of non-toxicity and does not cause toxicity in repeated use.
7	Acute Toxicity <sup>25</sup>	Kacapiring/cape jasmine ( <i>Gardenia jasminoides</i> Ellis)	Does not significantly influence the organ index, so it is included in the category of practically non-toxic.
8	Acute Toxicity <sup>9</sup>	Kirinyuh/lack in the bush ( <i>Chromolena odorata</i> (L) R.M King & H. Rob)	Practically non-toxic because it has an LD50 >15 g/kg. Delayed toxicity can be seen from the doses of 4 g/kg, 8 g/kg, and 16 g/kg, causing toxic effects on body weight, drinking water volume, and relative weight of lung organs significantly (P<0.05).
9	Acute Toxicity <sup>26</sup>	Melinjo ( <i>Gnetum gnemon</i> L.)	Included in the practically non-toxic organ indices category, including lungs with an LD50 greater than 5,000 mg/kg, and did not cause death in test animals or affect acute toxicity parameters.
10	Subchronic Toxicity <sup>27</sup>	Simpur/elephant leaf ( <i>Dillenia indica</i> L.)	The organ index of male mice showed that the lung organs experienced significant differences in the 1,000 mg/kg dose group compared to the control group. This can happen because the upper dose contains more compounds that can cause toxicity, which is thought to affect rats' respiratory tract organs, so the lung organ index decreases significantly.
11	Subchronic Toxicity <sup>28</sup>	Secang wood/sappan wood ( <i>Caesalpinia sappan</i> L.)	Doses of 400 mg/kg and 1,000 mg/kg do not indicate toxic effects on the lungs.
12	Acute Toxicity <sup>29</sup>	Land Kangkong ( <i>Ipomoea reptans</i> , Poir)	Giving for 24 hours doses of 480mg/kg, 1200mg/kg, 3,000mg/kg, 7,500mg/kg experienced changes in microscopic conditions. One of these conditions is perivascularitis, or inflammation of the kidneys and lungs.
13	Acute Toxicity <sup>30</sup>	Senggugu ( <i>Clerodendrum serratum</i> L. Moon)	Administration of the test preparation is non-toxic/does not affect the lung organs of the test animal.
14	Subchronic Toxicity <sup>31</sup>	Valerian ( <i>Valeriana officinalis</i> )	The administration of graded doses of extracts of 9 mg/kg/day, 18 mg/kg/day, and 36 mg/kg/day affected the microscopic picture. The value of the score for changes in the histopathological structure of the lungs increased according to the dose of valerian extract given. At a specific dosage range, the concentration of the drug on the receptor not only causes therapeutic effects but can also cause toxic effects.
15	Acute Toxicity <sup>19</sup>	Herba meniran ( <i>Phyllanthus niruri</i> auct. Non L.), Tempuyung ( <i>Sonchus arvensis</i> L.) and black jinten ( <i>Nigella sativa</i> L.)	The highest dose can technically be administered orally, 8,100 mg/kg, which has not caused toxic effects on white rats of the SD strain.

Toxicity Study on Gastric Organ Parameter		
1	Subchronic Toxicity <sup>32</sup>	White teak ( <i>Gmelina arborea</i> Roxb.) The results of the study showed that there was an injury to the stomach. It was causing peptic ulcers at a dose of >1,625 g/kg.
2	Acute Toxicity <sup>33</sup>	Dewa ( <i>Gynura pseudochina</i> (Lour.) DC) The results obtained from the observation of experimental animals showed under normal conditions, indicating that administering standard control extracts, negative controls, and doses of 50, 100, 200, 400 and 800 mg/kg did not produce toxic effects on the gastric organs.
3	Subchronic Toxicity <sup>34</sup>	Pisang kayu ( <i>Musa Paradisiaca</i> L. Var. Kayu) Preparing green meniran leaf extract with a dose of > 5,000 mg/kg is practically non-toxic to gastric organs.
4	Acute Toxicity <sup>35</sup>	Meniran hijau/chamberbitte ( <i>Phyllanthus Urinaria</i> ) The LD50 value of the acute toxicity test results shows a practically non-toxic category. However, the results of histopathological examinations showed damage to the intestinal mucosa and stomach lining.
5	Acute Toxicity <sup>36</sup>	Sirih/Betel vine (Piper betle L.) and gambir ( <i>Uncaria gambir</i> R.) The administration of a single dose of oral test preparation did not cause toxic effects during the 15th day.
6	Acute toxicity <sup>37</sup>	Land kangkong ( <i>Ipomoea reptans</i> , Poir) Have a relatively secure subchronic security profile.
7	Subchronic Toxicity <sup>38</sup>	Kelor ( <i>Moringa stenopetala</i> (Baker f.) Cudof and <i>Mentha spicata</i> L.) The administration of FH at 75mg/kg for seven weeks did not cause damage/lesions of the gastric organs.
8	Subchronic Toxicity <sup>39</sup>	Gambir ( <i>Uncaria gambir</i> ) and sappan wood ( <i>Caesalpinia sappan</i> ) The results of the acute toxicity test analysis can be said to be almost non-toxic.
9	Acute Toxicity <sup>40</sup>	Herba Meniran ( <i>Phyllanthus niruri</i> auct. Non L.), tempuyung ( <i>Sonchus arvensis</i> L.) and Black jinten ( <i>Nigella sativa</i> L.) Delayed toxicity was seen at doses of 4 g/kg, 8 g/kg, and 16 g/kg, significantly causing toxic effects on body weight, drinking water volume, and relative weight of gastric organs (P<0.05).
10	Acute Toxicity <sup>9</sup>	Kirinyuh/jack in the bush ( <i>Chromolaena Odorata</i> (L) R.M. KING & H. ROB) It does not cause 50% of the deaths of test animals, so it is included in the "practically non-toxic" criterion.
11	Acute toxicity <sup>18</sup>	Bajakah tampala ( <i>Spatholobus littoralis Hassk</i> ) and yellow bajakah stem ( <i>Arcangelisia flava</i> (L.) Merr.) Administration of extracts at doses of 17.5 mg/kg, 35 mg/kg, and 70 mg/kg did not change the histopathological picture of the gastric mucosa of mice.
12	Subchronic Toxicity <sup>41</sup>	Mahkota Dewa/god's crown ( <i>Phaleria Macrocarpa</i> ) Based on the results of an acute toxicity test for 14 days of rambutan fruit peel extract administration, it was proven that it did not cause toxic effects in test animals with pseudo-LD50 up to a dose of 17,150 mg/kg.
13	Acute Toxicity <sup>42</sup>	Rambutan ( <i>Nephelium lappaceum</i> L.) In this study, chronic exposure to M. Pudica bay leaf extract at doses of 400 and 600 mg/kg did not cause damage in the form of bleeding and hyperplasia in the gastric organs of male mice.
14	Chronic Toxicity <sup>43</sup>	Putri malu/shameplant ( <i>Mimosa Pudica Leaf</i> ) The administration of ethyl acetate fraction and turmeric rhizome hexane in acute intoxication tests increased the number of parietal cells in the stomach.
15	Acute Toxicity <sup>44</sup>	Turmeri ( <i>Curcuma longa</i> Linn)

**Toxicity Study on Liver Organ Parameter**

1	Subchronic Toxicity <sup>45</sup>	Asam kandis/false xanthochymus)	mangosteen ( <i>Garcinia mangosteen</i> )	Does not cause toxicity to the liver.
2	Acute Toxicity and subchronic <sup>46</sup>	Kelor ( <i>Moringa Oleifera</i> L)		Practically non-toxic and relatively safe for the liver; it is used for a long time and requires attention.
3	Acute Toxicity <sup>47</sup>	Benalu teh ( <i>Scurrula atropurpurea</i> )		Practically non-toxic and causes abnormalities in the liver, kidneys, and spleen.
4	Acute Toxicity <sup>48</sup>	Cinnamon ( <i>Cinnamomum</i> )		Administration up to a maximum dose of 2,000 mg/kg did not cause death, so it was included in category 5, which has a low level of toxicity.
5	Acute Toxicity <sup>49</sup>	Turmeric ( <i>Curcuma longa</i> L)		In the liver and kidneys, toxic doses of turmeric result in necrosis of parenchymal cells.
6	Subchronic Toxicity <sup>50</sup>	Mahogany ( <i>Swietenia macrophylla</i> )		Does not show any influence is not toxic.
7	Acute Toxicity <sup>51</sup>	Purwoceng ( <i>Pimpinella pruatjan</i> Molk)		The study's results did not cause histopathological differences and were not toxic.
8	Subchronic Toxicity <sup>52</sup>	Putut/large-leaved orange ( <i>Bruguiera gymnorhiza</i> )		The study results found that herbal plants do not cause toxicity to the liver of mice.
9	Acute Toxicity <sup>53</sup>	Bidara/indian plum ( <i>Ziziphus mauritiana</i> L)		The results showed that 600 and 2,000 mg/kg doses had a toxic effect (sig. 0.66) with changes in the histopathological structure of male mouse liver cells ( <i>Mus musculus</i> ).
10	Subchronic Toxicity <sup>54</sup>	Pisang kayu ( <i>Musa paradisiaca</i> L.Var. Kayu)		Does not cause toxic effects in all treatment groups.
11	Acute Toxicity <sup>55</sup>	Alang-Alang/Cogon grass ( <i>Imperata cylindrica</i> )		Giving a dose of 20,000 mg/kg causes necrosis in the liver of mice, while providing a dose below 20,000 mg/kg does not cause necrosis.
12	Subchronic Toxicity <sup>39</sup>	Gambir ( <i>Uncaria gambir</i> ) and Sappan wood ( <i>Caesalpinia sappan</i> )		The results of the study did not show the presence of toxicity if the dose was appropriate.
13	Acute Toxicity and subchronic <sup>56</sup>	Turmeric with pegagan ( <i>Curcuma domestica</i> , <i>Cintella asiatica</i> )		The results of the study showed that the combination of turmeric extract and gotu gotu did not cause toxicity.
14	Acute Toxicity <sup>57</sup>	Pakis ( <i>Radix primaria</i> )		The results obtained from the study showed that it was not toxic.
15	Acute Toxicity <sup>58</sup>	Pucuk merah ( <i>Syzygium oleana</i> )		A single dose of SGOT and SGPT values in male white rats ( <i>Rattus norvegicus</i> ) of the Sprague-Dawley strain in the dose group of 2,000 mg/kg and 5,000 mg/kg. Doses less than 2,000 mg/kg do not cause toxicity.

**Toxicity Study on Kidney Organ Parameters**

1	Subchronic Toxicity <sup>59</sup>	Bidara ( <i>Ziziphus mauritiana</i> L.)	Ethanol extract of bidara leaves ( <i>Ziziphus mauritiana</i> L.) causes toxic symptoms to the ratio of the weight of kidney organs and macroscopic kidney organs.
2	Subchronic Toxicity <sup>60</sup>	Yacón ( <i>Smallanthus sonchifolius</i> )	The administration of yacon tuber syrup can have a toxic effect on the histopathological picture of the kidneys of male rats.
3	Subchronic Toxicity <sup>2</sup>	Kelor ( <i>Moringa oleifera</i> )	The administration of moringa leaf extract does not cause toxicity to the kidney organs.
4	Acute Toxicity <sup>61</sup>	Miana/coleus ( <i>Culleus scutellarioides</i> )	Administration of miana leaf extract causes low-category toxicity to the kidneys.
5	Subchronic Toxicity <sup>62</sup>	Pegagan ( <i>Centella asiatica</i> )	The administration of gotu gotu extract did not cause toxicity in the kidneys of white rats.
6	Subchronic Toxicity <sup>63</sup>	Benalu the/tea mistletoe ( <i>Scurrula atropurpurea</i> (Bl.) Dans) and benalu mangga/malayan mistletoe ( <i>Dendrophthoe pentandra</i> )	Does not cause toxicity to the kidneys of female wistar rats.
7	Subchronic Toxicity <sup>64</sup>	Tali putri/love vine ( <i>Cassytha filiformis</i> L.)	Administration of love vine ethanol extract causes toxicity with increased kidney organ weight.
8	Subchronic Toxicity <sup>45</sup>	Asam kandis/cowa mangosteen ( <i>Garcinia cowa</i> Roxb.)	Does not cause toxicity to the weight of the kidney organs.
9	Subchronic Toxicity <sup>65</sup>	Pucuk Merah ( <i>Syzygium Myrtifolium</i> Walp.)	Does not have a toxic effect on the kidneys.
10	Subchronic Toxicity <sup>66</sup>	Sungkai/grey poplar ( <i>P. Canescens</i> )	Does not cause toxic effects on the kidney organs.
11	Subchronic Toxicity <sup>32</sup>	Jati putih/White teak ( <i>Gmelina arborea</i> Roxb.)	Does not cause toxic effects on the kidneys.
12	Subchronic Toxicity <sup>67</sup>	Pisang kayu ( <i>Musa paradisiaca</i> L.Var. Kayu)	It showed no changes in organ morphology in all groups and did not cause toxic effects at doses of 50, 100, 200, 400, and 800 mg/kg.
13	Subacute Toxicity <sup>68</sup>	Afrika/Bitter leard ( <i>Vernonia amygdalina</i> Del.)	Does not cause toxicity to mouse kidneys.
14	Acute Toxicity <sup>69</sup>	Cinnamon ( <i>Cinnamomum burmanni</i> )	Does not cause toxic effects on the kidneys.
15	Acute Toxicity <sup>70</sup>	Tea mistletoe ( <i>Scurrula</i> sp.)	Does not have a toxic effect on the kidney organs.

## Discussion

The test used to determine the harmful effects of a substance on biological systems is known as a toxicity test. Test animals are commonly used in toxicity testing to determine whether test preparations do not cause biochemical, physiological, or pathological effects in humans. The in vivo acute test is one of the toxicity tests used to establish the safety limit, which can cause the test animal to die 50% of the time (LD50 / fatal dose 50%). Six categories include toxicity classifications based on LD50 values: practically non-toxic (LD50 5–15 g), mildly toxic (LD50 500–5,000 mg), moderately toxic (50–500 mg LD50), toxic (1–50 mg LD50) and highly toxic ( $550 < 1 \text{ mg/kg LD50}$ ). Relatively harmless (LD50 > 15 g) is the first category. The choice of the species of the test animal, the species and number of animals, the age and weight of the animal, the sex of the animal, the method of administration of the test preparation, the process of selecting the test dose, the side effects on the experimental test supply, the test technique and mechanism including the care of the animals during the experiment, are some of the factors that can affect the results of the in vivo toxicity test<sup>4</sup>.

Plants that are toxic to the heart are citrus nobilis (1,000 mg/kg), wualae (500–1,500 mg/kg), and tempuyung leaves (>2,000 mg/Kg). Male papaya calina leaves dose of 10-15g/kg, a mixture of betel leaves and dry extract from gambir, a dose of kirinyuh leaves from 4-16g/km, a dose of pisang kayu from 400-1,200 mg/kg, rambai skin, a mixture of dayak shallot and pisang kayu, a dose of katuk leaves >1,500g/kgs, a dose of betel leaves, celebes pepper leaf, a mixture of bajakah tampala steam and yellow bajakah stems, and a mixture of black jinten seeds at a dose of 8,100 mg/kg do not cause toxic effects.

The cause of toxicity in herbs to the heart organ is the content of chemical compounds in plants, such as glycosides, which can interfere with the rhythm and contraction power of the heart, alkaloids, which can interfere with nerve impulses and cause cardiac arrhythmias, and saponins, which may damage heart cells and damage heart function, can be the cause of toxicity of herbal plants in the heart organs of animals. The dosage element comes next because the risk of toxicity increases with the number of herbs administered.

Plants that cause toxicity to the lungs are blue snake weed at a dose of 2,000 mg/kg, bajakah tampala and yellow bajakah stem 4–16 g/kg, elephant leaf dose 1,000 mg/kg, land kangkong at a dose of 480–7,500 mg/cm, *Valeriana officinalis* at a dose of 9–36

mg/mm, and a mixture of herba meniran and tempuyung leaves at a dose of 8100 mg/mg are among the plants that are toxic to the lung organs. On the other hand, some plants do not produce harmful effects, such as papaya calina leaves, katuk, melinjo leaves at a dose of >5,000 mg/mg; secang wood dosage 400-1,000 mg/mcg; senggugu dose 10-15g/mcg, tempala sticks and yellow piraka, dayak shallot, and pinang yaki >5,000 mg/ml; kacapiring dosage 200 mg/mg.

The cause of toxicity is the content of chemical compounds found in this herbal plant, such as alkaloids (damaging alveoli/tiny air sacs in the lungs and interfere with gas exchange), and phenolic compounds (causing oxidative stress and inflammation in the lungs, which may damage lung tissue). The dosage may increase the risk of toxicity with the number of herbs administered.

Plants harmful to gastric organs included white teak ethanol extract at a concentration of 10 mg/g and dewa administered to Wistar rats at a rate of more than 1,625 g/kg. After that, use a dose of 4 g/Kg, 8 g/Kg, and 16 g/kg from jack in the bush extract. The combination of ethanol leaf extract and gambir extract has been proven to have an LD50 value of 13.99 g/km. The toxicity effect on organ index was observed at doses of 5.4 g/kg, 10.8 g/kg, 21.6 g/kg, and 43.2 g/kg. In addition, plant extracts from yellow bajakah stem at concentrations of 5,000 mg/KG, 1,250 mg/KG, 2,500 mg/kg, and 625 mg/kg were used. Extraction of 480 mg/kg, 1,200 mg/kg, and 3,000 mg/kg terrestrial cutter extracts, up to a maximum dose of 7,500 mg/kg. Leaf extracts from chamberbitte 2,000 and 5,000 mg/kg fixed doses. Furthermore, there were *Spirulina platensis* plants in group III dose (10.4 mg *Spirulina*/20 g scatch), group II dose (5.2 mg *Spirulina*/20g scatch), and dose I (2.6 mg *spirulina*/20 g scatch).

There are several reasons why herbal plants can be toxic to the stomach organs of animals, including the presence of chemical compounds called alkaloids (including solanine and aconitine, which can irritate the stomach and cause vomiting, diarrhea, and nausea). Furthermore, cyanide glycoside poisoning manifests itself as nausea, vomiting, bitterness, weakness, and, in severe cases, death.

Plants that cause toxicity to the liver include turmeric rhizomes with a dose above 150 mg/kg, bidara leaves at 600-2,000 mg/kg, and reed root at 2,000 mg/kg. Meanwhile, plants that do not cause toxic effects include the skin of the kandis acid fruit <150 mg/k, *Moringa* leaves <150 mg/kg, benalu >150 mg/kg, cinnamon leaf dosage 200 mg/kg, Mahogany Seeds <150 mg/kg, Purwoceng root dosage 25

mg/300gram, Bruguiera fruit dosage 5,000 mg/kg, Leaf Peanut Fence Dosage 100 mg/kg, Uncaria Gambir and *Caesalipinia sappan* with dosage of 75 mg/kg, turmeric rhizomes and gotu gotu plants 100mg/kg, ofpakis dosage tanker 75 mg/kg, Red Shoot Leaves 200 mg/kg.

The cause of toxicity of herbal plants to the liver organs of experimental animals can be caused by several factors, including the content of chemical compounds contained in the plant, such as alkaloids that have the potential to cause liver damage, tannins that can interfere with the absorption of essential nutrients and cause liver damage, saponins that can interfere with cell membranes and cause liver toxicity. Then the next factor is the dosage factor. The higher the dose of herbal plants given, the greater the risk of toxicity.

Plants that cause toxicity to the kidneys include bidara leaves at a dose of 200-800 mg/kg, yacon at a dose of 3-4 mL/250g, miyana leaves at a dose of 4,000-10,000 mg/kg, and love vine at a dose of 1.25-5mg/kg. Meanwhile, plants that do not cause toxic effects include moringa leaves at a dose of 5.56mL-8.18mL/195g /day, gotu-gotu leaves at a dose of 200-400mg/kg, a combination of tea mistletoe and malayan mistletoe at a dose of 250-1,000mg/kg, Asam kandis at a dose of 500-1,000mg/kg, pucuk merah leaves at a dose of 300mg/kg, sungkai at a dose of 100-800mg/kg, jati putih at a dose of 10mg/kg, gambir and sappan wood at a dose of 75-300mg/kg, bitter liead at a dose of 10%-30%b/v, cinnamon leaf at a dose of 200-5,400mg/kg, benalu at a dose of 1-20g/kg.

The cause of toxicity of herbal plants to the kidney organs of experimental animals can be caused by several factors, including the content of chemical compounds contained in the plant, such as flavonoids, phenolics, and steroids whose levels have exceeded the dosage so that they cause damage to the glomerulus. The dose can cause toxic effects if given excessively, so the cells in the kidneys will experience nephrotoxication because the compound is carried along with the bloodstream to the kidneys.

It is possible to conclude that a herbal plant does not induce toxicity in the vital organs of experimental animals due to the fact that the dose is still classified as low, specifically at a level of less than 500 mg/kg. It can also be caused by the maintenance factors of the experimental animals, such as the provision of comfortable experimental animal bedding, adequate food and water, adequate air circulation, and the optimization of the experimental animals' condition to prevent them from being in a state of discomfort. The study's limitations include

the following: the inability to identify journals that address the same type of toxicity; its exclusive focus on a single organ; the outdated reference year; and the new research only focuses on the liver and kidney organs.

## Conclusions

Based on the results of reviewing the data of acute and sub-chronic toxicity tests, it can be concluded that there are several plants that are practically toxic, almost toxic and non-toxic. Other factors that can affect the results of the toxicity test are seen from the selection of the species of test animal, age, animal weight, sex of the animal, how to administer the test preparation, how to choose the test dose, side effects on the test preparation, testing techniques, and mechanisms, including how to handle animals during the experiment. Herbal plants are relatively safe to use, but if used long-term, they need to be considered again.

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## Author Contribution

Study design	: AWN
Data acquisition	: LSS, HMN, KA, ADS, YKIR,
Data analysis	: LSS, HMN, KA, ADS, YKIR,
Manuscript writing	: AG, AO, BFA

## Competing Interests

There is no conflict of interest between authors or outside parties in preparing this review article.

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