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Thevetia peruviana (Pers.) K. Schum.: Poisonous and its potential

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Abstract

Thevetia peruviana is a poisonous plant but also has potential as a medicine. This study aims to explain the botany, toxicity and bioactivity of *T. peruviana*. The research method is through a literature study on articles, books published online, especially on Google Scholar, using the keywords *T. peruviana*, *T. peruviana* toxicity and *T. peruviana* bioactivity. In Indonesia, *T. peruviana* is easy to find in the surrounding environment such as yards, yards, and roadsides, which are used as ornamental plants because they have beautiful flower colors and structures. All parts of *T. peruviana* are toxic because they contain various cardiac glycosides including neriifolin, thevetin A, thevetin B, and oleandrin, so consuming any of these parts can result in death in both animals and humans. Clinical-pathological features of *T. peruviana* poisoning include vomiting, diarrhea, drowsiness and dilated pupils, rapid, weak and irregular pulse. Although *T. peruviana* is a poisonous plant, several studies have reported the bioactivity of *T. peruviana* as anti-cancer, fertility, abortion and antimicrobial, but the processing and use need strict control so that its toxicity is minimized.

Keywords: *Thevetia peruviana*; Thevetin; Poisonous plant; Medicine

1. Introduction

Plants have many benefits such as food, medicine, and construction, but on the other hand there are plants that are poisonous. Some poisonous plants that are toxic that can cause human death such as *Nerium oleander* and *Thevetia peruviana* [1,2]. *Thevetia peruviana* or known by local Indonesians as *daun mentega* is easy to find in various fields such as yards, yards, and roadsides and is often used as an ornamental plant because it has beautiful flowers. The beautiful color and structure of the flower is the reason this plant is cultivated to beautify the scenery in the tropics and subtemperate regions [2].

All parts of *T. peruviana* are toxic due to various cardiac glycosides including neriifolin, thevetin A, thevetin B, and oleandrin [1]. *Thevetia peruviana* causes poisoning in children, especially in India and Sri Lanka [1,2]. Ingestion of any part of *T. peruviana* causes nausea, vomiting, abdominal pain, diarrhea, dysrhythmias, and hyperkalemia [1] (which can lead to death. The main symptoms of *T. peruviana* poisoning are bradycardia, rapid and irregular pulse, dilated pupils [3] whereas Gastrointestinal effects include nausea, vomiting, diarrhea and abdominal pain [4].Post mortem analysis of poisoning showed renal tubular necrosis, obliteration of the hepatic lumen, local necrosis around the central vein, uneven bleeding and dilation of the central vein [3].

Although *T. peruviana* is toxic, the various secondary metabolites it produces have the potential to be used as medicinal ingredients, but caution must be exercised in their use as medicinal ingredients. The cardiac glycoside is an indicator of *T. peruviana* toxicity [5]. *Thevetia peruviana* contains its cardiac glycosides, which are traditionally used as antipyretic,

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emetic, diuretic and tonic [6], cardiotonic and treating edema [7]. The extract of *T. peruviana* inhibits spermatogenesis in mice so that it has the potential to be developed as a male contraceptive herb or as an anti-fertility agent [9].

The bioactivity of *T. peruviana* is thought to be related to the content of its secondary metabolite compounds. The *T. peruviana* is a rich source of alkaloids, flavonoids, saponins, cardiac glycosides, anthraquinone glycosides, coumarins, phenols, tannins, steroids, oils and fats [6]. The latex of *T. peruviana* is rich in metabolites as a source for fighting cancer and pathogenic microorganisms [9]. Tian et al [10] reported that cardiac glycoside *T. peruviana* inhibits lung cancer cells, gastric cancer cells and human pancreatic cancer cells via apoptotic mechanism.

Poisoning in children is usually due to eating the fruit or out of curiosity [2]. The use of medicinal plants, especially those that are toxic, requires special knowledge to avoid their fatalities. This study will discuss the botany, bioactivity and toxicity of *T. peruviana* so that its fatality can be reduced and its potential utilization can be increased.

2. Methods

The method used in this study is a literature review obtained online, especially from Google Scholar. Some of the keywords used in document search are *T. peruviana*, uses *T. peruviana* and bioactivity *T. peruviana*. The information obtained was synthesized so as to explain the botany, toxicity and bioactivity of *T. peruviana*. To complete the botanical information, an exploration was carried out in the surrounding environment to obtain photographs including habitus, leaves, flowers and fruit.

3. Results and discussion

3.1. Botany of *T. peruviana* (Pers.) K. Schum.

Thevetia peruviana is a type of poisonous plant from the Apocynaceae. The *Thevetia* is adaptation of the name of Andre Thevt a member of the French missionary who collected this plant from South America. This plant is native in the Mexico, South and Central America but is now often grown throughout the tropics and subtropics of the world as an ornamental.

Figure 1 *Thevetia peruviana*. A. Habitus. B. Flowers; C. The young fruit

3.1.1. Description

Thevetia peruviana is a tree or shrub growing to about 10-15 feet (Figure 1A). The roots and bark have numerous lenticels, scales, cracks and fissures on the outer surface; rough lines and wrinkles and inner surface tissue and granular

fractures (Datta and Datta 1977). The stems are green and turn silver/grey with age. Bard stems, milk sap. The leaves are spirally arranged, linear and about 13-15 cm long, lanceolate and green. The leaves are alternate, spirally arranged, simple and branched (Fig. 1A). Inflorescence is terminal or supra-axillary, scorpioid cymes, slightly flowering; bracts subulate, deciduous. The flowers are ebracteolate, pedicellate, bisexual, actinomorphic and pentamerous (Fig. 1B). The fruit is drupe, ovoid, fleshy epicarp, black when ripe; four seeds in one fruit and seeds are endospermic (Figure 1C). The leaf surface is covered with a wax coating to reduce water loss. The flowers are Yellow, like trumpet flowers and the fruit is dark red/black in color enveloping the large seeds [7].

3.2. Toxicity

Thevetia peruviana has been long known as a plant, especially in its home countries such as Peru, India and Sri Lanka. Various compounds produced by *T. peruviana* have lethal effects, so they are classified as poisonous plants. In South Asian countries such as India and Sri Lanka, *T. peruviana* is often used as an ingredient for suicide [1] by ingesting its seeds or leaves [2,5]. Poisoning in children is usually due to eating the fruit or out of curiosity [2]. Ingestion of *T. peruviana* seeds is becoming a popular method of suicide in Northern Sri Lanka [11]. Mortality due to *T. peruviana* poisoning varies between 3-10% depending on the resources available for treatment. The main symptom of *T. peruviana* poisoning is bradycardia, irregular pulse. Gastrointestinal effects include mainly nausea, vomiting, diarrhea and abdominal pain [4].

The seeds of *T. peruviana* contain cardiac glycosides [10], which cause poisoning, so they are important indicators for forensic and pharmacological surveys [5]. Thevetin is a glycoside group that has cardiotoxic and gastrointestinal effects [4]. Thevetin B is the most toxic group of cardenolides compounds and is the most common compound in *T. peruviana* whose structure is similar to digoxin cardenolide [4]. The toxic glycoside *T. peruviana* is highly concentrated in roots and seeds which produces digoxin-like effects and inhibits the enzyme Na+-K+ ATPase in the cardiovascular system [2].

Most patients with acute *T. peruviana* poisoning have symptoms of conduction effects affecting the sinus node, atrioventricular node, or both [11]. In experimental rats treated with *T. peruviana* extract, poisoning symptoms were indicated by pilomotor and tail erection, ataxia, limb paralysis, and paroxysmal tachycardia, diarrhea and diuresis in *T. peruviana* poisoned rats [12]. Along with the number of deaths caused by *T. peruviana*, the search for an antidote continues. Mandal [4] reported that digoxin antibody when available is the primary choice for cardiotoxicity reversal. Administration of activated charcoal and digoxin-specific Fab Fragments was reported to reduce the impact of *T. peruviana* poisoning [1].

Studies of the toxic effects of *T. peruviana* have been tested in mice as reported [13]. The effects of *T. peruviana* toxins vary depending on the dose, ingredients used and processing methods. The lowest lethal dose of *T. peruviana* was (507 mg/kg) with concentrated aqueous kernel extract, and the highest (5700 mg/kg) with feed formulated using 40% seed flour [13]. Mice that consumed bait (fresh or aged raw water extract) of *T. peruviana* kernel showed symptoms of poisoning within 30 minutes and then died between 2 to 30 hours after administration [12].

Rats given crude aqueous extract from the bark, leaves and seeds of *T. peruviana* by intraperitoneal injection showed poisoning with symptoms indicating serious cardiac, neuromotor and mental damage, and manifested as tachycardia, arrhythmia, paralysis, ataxia, and disorientation. Mice given aqueous *T. peruviana* kernel extract injection died more quickly within 10 hours, compared to mice given aqueous leaf extract or bark extract that died after 260 hours [13]. Extracts of leaves, stems and roots of *T. peruviana* tested against mature *Callosobruchus maculatus* (a type of beetle) resulted in their toxicity death according to the order of solvent: petroleum spirit > ethyl acetate > acetone > methanol. The root extract was the most toxic to *C. maculatus* and females were more tolerant than males [14].

The rabbits fed *T. peruviana* raw ground seed cake resulted in a 100% reduction in body weight and mortality at the inclusion rate at 14 days (group C/10%) and between 21 and 28 days (group B/5%). No deaths were recorded in rabbits from groups D and E (treated with 5% and 10% oven-dried *T. peruviana* seeds) and did not experience significant weight gain. Reduced feed intake, diarrhea, roughness, dry coat, mydriasis and hyper aesthesia were shown by most of the victims; while muscle spasms, ataxia, hind limb paralysis and severe convulsions preceded death. Anemia and polycythemia were more severe in rabbit groups D and E. The seed cake of *T. peruviana* even with soybean meal replacement as low as 5% of the diet, was highly toxic and lethal to rabbits. Fat-removal and autoclaving treatment appears to remove some toxic and anti-nutritive factors, but still does not support productive growth [15].

Poisoning caused by *T. peruviana* is thought to be related to the content of its bioactive compounds. *T. peruviana* seeds contain cardiac glycosides which cause vomiting, dizziness, and cardiac dysrhythmias such as conduction block affecting the sinuses and atrioventrikular node [11]. The bark *T. peruviana* contains peruvianursenyl acetate A, peruvianursenyl

acetate B, isolupenyl acetate, peruvianursenyl acetate C, lupedienyl acetate and peruvianursenyl tri glucoside, amirin acetate and lupeol acetate [15]. The seeds contain Thevetin A, thevetin C and acetylthevetin C, thevetin B and acetylthevetin B [5]. TV leaves contain flavonol glycosides, kaempferol 3-glucosyl (1 → 4) [6‴-sinapoylglucosyl] (1 → 2) galactoside and 3-[2‴″-sinapoylglucosyl] (1 → 4) [6‴-sinapoylglucosyl] (1 → 2) galactoside and kaempferol and quercetin 3-[6‴-sinapoylglucosyl] (1 → 2) galactoside, kaempferol and quercetin 3-glucosyl (1 → 2) galactoside [17].

3.3. Bioactivity and Potential Utilization

Although *T. peruviana* is known as a poisonous plant, various researchers have reported its use as medicine. Bioactivity of *T. peruviana* has antimicrobial [18], anti-abortion, anti-fertility and anti-cancer and will be explained further.

3.3.1. Anti-Microbial

When explored further, the bioactivity of *T. peruviana* as an antimicrobial is more prominent than the others. The development of drug resistance in human pathogens has implications for the re-excavation of traditional medicines as a source of anti-bacterial including the leaves and skins of *T. peruviana* fruit [19]. Compounds that inhibit the growth of bacteria are called anti-bacterial. The bioactivity of *T. peruviana* as an antimicrobial can be applied in industry. Oil from *T. peruviana* seeds thus has potential value for the manufacture of bactericidal soap [20]. The kernel oil of *T. peruviana* in India is used to treat skin diseases due to its anti-bacterial activity. The bioactivity of *T. peruviana* as an antimicrobial has been reported by Saxena et al [20], Alhashimi et al [21], and Rahman et al [19]. *T. peruviana* seed oil is used to make wood surface coatings with antifungal activity and antibacterial properties [22].

Thevietia peruviana has antimicrobial activity against *Bacillus cereus* [19, 21], *Staphylococcus aureus* [21-23], *Pseudomonas aeruginosa* [21], *Escherichia coli*, *B. subtilis* [19, 22], X*anthomonas* sp [19], *Candida albicans* [22], *Shigella flexineri*, *Salmonella typhi*, *Klebsiella* sp, and *Shigella sonnei* [23]. The bioactivity of the *T. peruviana* extract depends on the concentration of [22], *Salmonella typhimurium*. The *S. typhimurium* was most sensitive to the petroleum ether leaf extract of *T. peruviana* [24]. The most sensitive *T. peruviana* latex growth inhibitor to latex was *B. subtilis* followed by *E. coli* [9]. The leaf methanol extract showed a narrow zone of inhibition on bacteria *S. flexineri*, *S. typhi*, *Klebsiella* sp, *S. aureus* and *S. sonnei* [23].

The bioactivity of *T. peruviana* as an antimicrobial is thought to be related to the content of its bioactive compounds. The bioactivity of *T. peruviana* leaf extract against typhimurium was related to the content of the leaf extract containing alkaloids, cardiac glycosides, flavonoids, polyphenols, saponins and tannins [23]. Transmission electron microscope examination showed ultrastructural changes in cell walls and cell membranes of *S. aureus* and *P. aeruginosa* treated with *T. peruviana* latex [9]. The seeds of *T. peruviana* contain the glucoside neriifolin, acetyl neriifolin and thevetin. Distilled *T. peruviana* seed oil has been found to contain anti-bacterial activity. *T. peruviana* seeds contain quercetin, kaempferol and quercetin-7-o-galactoside [25]. On the other hand bioactivity as an antimicrobial can be used as a fungicide. The n-hexane or dichloromethane extract of *T. peruviana* seeds inhibited the growth of the fungus *Cladosporium cucumerinum*. Pulegone, linoleic acid and palmitic acid are the main compounds of *T. peruviana*. Terpenes appear to be the main substances with antifungal photoactivity [26].

3.3.2. Anti-Fertility and Abortion

Antifertility compounds are compounds that are able to inhibit fertility so it is very potential to be developed as a contraceptive. Abortion is the practice of terminating a pregnancy by destroying the fetus in the womb. The potential of *T. peruviana* as an antifertility agent has been reported by Gufta et al [8] and Mondal et al [27]. Traditionally, the leaves of *T. peruviana* are used as an abortion drug [28]. Some cases of pregnancy require abortion due to developmental abnormalities in the fetus. *T. peruviana* has cardioactive glycosides such as thevetin A, thevetin B, neriifolin, peruvoside, thevetoxin, and ruvoside. The leaves *T. peruviana* contain quercetin and kaempferol. The methanol extract of *T. peruviana* leaves is able to induce uterine contractions, prolong the estrus cycle and is anti-implantation by lowering progesterone levels [28]. The *T. peruviana* inhibits spermatogenesis in mice, indicating the possibility of developing herbal contraceptives for herbal men [8].

The methanol extract of the bark of *T. peruviana* given orally to male rats (a dose of 100 mg/head/day) did not cause a significant reduction in body weight, but significantly reduced the weight of reproductive organs [8] which is directly or indirectly related to fertility. It was further stated that the administration of *T. peruviana* extract significantly reduced the total protein and sialic acid content of the testes, epididymis, seminal vesicles and ventral prostate, as well as testicular glycogen content. The methanol extract of the stem bark of *T. peruviana* caused a decrease in spermatogenic elements, namely preleptogenic and pachytene spermatocytes, secondary spermatocytes, round spermatids and mature

Leydig cells. At this dose rate the diameter of the Leydig cell nucleus, the diameter of the seminiferous tubules and the Sertoli area were significantly reduced [8].

The methanol-water extract of *T. peruviana* affects sperm motility directly and is directly proportional to its concentration [27]. Sperm viability decreased significantly at higher concentrations of *T. peruviana* extract, and all spermatozoa were found to be non-viable after 10 min when given *T. peruviana* extract (160 mg/ml). The percentage of DNA damage in spermatozoa was four times greater than in the control group. The hydro-methanolic extract of *T. peruviana* leaf has quite strong spermicide activity through an in vitro model [27]. Bioactivity as antifertility is thought to be related to the content of secondary metabolites such as -amyrin acetate, lupeol acetate, -amyrin, -amyrin, lupeol and thevetigenin [8].

3.3.3. Antioxidant and Anti-Cancer

Exploration of natural materials that have anti-cancer activity continues to be carried out because they are considered cheaper and relatively safer. Plants used as anticancer are plants that produce secondary metabolites that can inhibit cell growth. Free radicals are directly or indirectly associated with many causes of cancer, therefore anti-free radical compounds (antioxidants) are widely associated with their anti-cancer activity. Cancer is one of the main causes of human death. Cancer cells have uncontrolled division properties that interfere with metabolic processes in the body.

The bioactivity of *T. peruviana* as an anticancer has been reported by Cheng et al [29], Miyagawa et al [30], Haldar et al [31], Al-Rajhi et al [9], and El-Sawi et al [32]. *T. peruviana* seeds containing cardiac glycosides have cytotoxicity properties against cancer cell lines P15 (human lung cancer cells), MGC-803 (human gastric cancer cells), SW1990 (human pancreatic cancer cells), and normal hepatocyte cells LO2 indicates that compounds from *T. peruviana* can selectively inhibit cancer cell proliferation with IC50 from 0.05 to 0.15 M [29]. The pro-apoptotic activity revealed that the secondary metabolite *T. peruviana* induced apoptosis of MGC-803 cancer cells in a dose-dependent manner involving the intrinsic apoptotic pathway. Secondary metabolites of *T. peruviana* may exhibit anticancer activity with their ability to induce intrinsic apoptosis and cell cycle arrest in the G2/M phase [29].

It was also reported by Haldar et al [31] that *T. peruviana* fruit methanol extract (METP) showed remarkable antitumor activity in rats caused by augmentation of endogenous antioxidant mechanisms. METP significantly decreased lipid peroxidation and restored reduced glutathione, superoxide dismutase, and catalase to normal levels compared to the EAC control group [31]. The bark extract of *T. peruviana* demonstrated a reversal effect on TNF-related apoptosis-inducing ligand (TRAIL) resistance in a human gastric adenocarcinoma cell line. Ethanol extracts from *T. peruviana* flowers increased TNF-α and TRAIL-mediated cell death through activation of the caspase, poly (ADP-ribose) polymerase and cleavage of death domain agonists interacting with BH3. The ethanolic extract of *T. peruviana* flower has the potential to sensitize HeLa cell apoptosis induced by tumor necrosis factor-α (TNF-α) and inducer of TNF-associated apoptosis through intrinsic and extrinsic pathways. [33].

The *T. peruviana* latex exhibited 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, had strong antioxidant activity with an IC50 of 43.9 g/mL to scavenge DPPH. The anticancer potential of *T. peruviana* latex was recorded against PC-3 (97.11% toxicity) and MCF-7 (96.23% toxicity) at 1000 g/mL with IC50 of 48.26 g/mL and 40.31 g/mL, respectively [9]. Cytotoxic activity was increased in mice fed the *T. peruviana* emulsion fraction against MCF7 breast and liver carcinoma cell line HEPG2 [32]. The bioactivity of *T. peruviana* as an anti-cancer and antioxidant is thought to be related to its bioactive compounds. The polar fraction of *T. peruviana* contained rutin, major flavonoid (7.33 mg/g) and rosmarinic acid (13.48 mg/g) the most abundant phenolic acid [32]. Flowers of *T. peruviana* are palmitic acid, (E)-β-ionone and 1,8-cineole [34], cardiac glycoside, thevetins a and b, peruvoside, theveside, theviridoside and terpenoids [18]. The antioxidant bioactivity is related to the content of phenolic compounds and flavonoids. The main flavonoids found in *T. peruviana* latex include rutin, quercetin, naringin, and hisperdin, while the phenolics are chlorogenic, syringenic, and ferulic acid [9]. The cardenolide glycoside of *T. peruviana* inhibited the growth of human gastric adenocarcinoma cells, and thevefolin increased the mRNA expression of the cell death receptor [30].

4. Conclusion

- All parts of *T. peruviana* are toxic because they contain various cardiac glycosides including neriifolin, thevetin A, thevetin B, and oleandrin, so consuming any of these parts can result in death in both animals and humans.
- Clinical-pathological features of *T. peruviana* poisoning is vomiting, diarrhea, drowsiness and dilated pupils, rapid, weak and irregular pulse.
- The bioactivity of *T. peruviana* as anti-cancer, fertility, abortion and antimicrobial.

Compliance with ethical standards

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