

Bioactivity and uses of *Cnidoscolus aconitifolius* (Mill.) I.M. Johnst

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Abstract

Cnidoscolus aconitifolius has been long used by ethnic groups in Indonesia for vegetables and traditional medicine. This study aims to explain the benefits of *C. aconitifolius* for food and its bioactivity. The method for writing is library research on scientific articles published online at Google Scholar by using the keywords: uses of *C. aconitifolius* and bioactivity of *C. aconitifolius*. All available articles were synthesized to provide comprehensive information on *C. aconitifolius* for food and its bioactivity. *C. aconitifolius* has two to three times more nutrients than spinach, spinach, Chinese cabbage, and lettuce. *Cnidoscolus aconitifolius* bioactivity includes antimicrobial, antidiabetic, hepatoprotective, antioxidant, antihypercholesterol, analgesic, antianemia, and kidney protection. *Cnidoscolus aconitifolius* leaves contain macronutrients such as carbohydrates, proteins, fats, vitamins and minerals so that they have the potential to be developed for cheap and easily available food. On the other hand, *C. aconitifolius* also contains anti-nutrients such as phytate and oxalate but with proper processing the antinutrients will be degraded.

Keywords: *Cnidoscolus aconitifolius*; Antimicrobial; Diabetes mellitus; Bioactivity

1. Introduction

Plants are one of the alternatives used by humans for the treatment of various diseases, especially in developing countries such as Indonesia. Exploration of nutraceutical plants, which are food ingredients and gives a healthy effect, continues to be carried out. *Cnidoscolus aconitifolius* has long been used by various ethnic groups as a vegetable [1] and in traditional medicine. This plant is easy to find in the surrounding environment such as yards, roadsides, and cultivated land [2]. The beautiful leaf structure with dense branching pattern makes *C. aconitifolius* often used as decoration and living fence.

The use of plants as food ingredients is related to their nutritional content, while their use as traditional medicine is related to their secondary metabolite content [3]. *Cnidoscolus aconitifolius* has two to three times more nutrients than spinach (*Amaranthus* sp.), cabbage (*Brassica* sp), and lettuce (*Lactuca* sp) [4]. Fresh leaves contain protein (4.38%), fat (1.20%), fiber (2.39%) and carbohydrates (85.36%) [5] or nutrients (mg/100 g) namely carbohydrates (41.895), protein (7.68), and crude fat (1.145) and crude fiber (31.165) [4]. In addition, *C. aconitifolius* also contains essential amino acids, vitamins such as carotene, niacin, riboflavin, and thiamine [4]. The mineral content includes sodium, potassium, calcium, magnesium, zinc, copper and iron [4,6]. *C. aconitifolius* leaves are rich in vitamin A, vitamin B2, vitamin B1, vitamin B9, vitamin C, vitamin D, vitamin E and vitamin K [4,7], vitamin B3, vitamin B6, vitamin B12, and vitamin E [7].

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Besides being used as food, *C. aconitifolius* is also used for traditional medicine. Bautista-Robles et al [8] stated that *C. aconitifolius* is efficacious for treating skin irritation, wounds, insect bites, and snake bites. *C. aconitifolius* was reported as a potential antimicrobial agent [6], having antitumor, antidiabetic, antimicrobial and hematopoietic activity [4]. The bioactivity is related to its secondary metabolites such as terpenoids, alkaloids, coumarins, phenolics and flavonoids [9,10]. The content of secondary metabolites is influenced by the processing process. Babalola and Alabi [11] stated that the concentration of alkaloids and flavonoids in the fresh leaf extract was higher than that of the boiled leaves, but the content of phytate and tannins decreased significantly in the boiled leaves compared to the fresh leaves.

Although plants as traditional medicines are relatively safe, knowledge of processing processes and dosages needs to be increased so that side effects can be minimized. Lennox and John [5] reported that *C. aconitifolius* contains antinutrients in the form of phytic acid (60.44 mg/100g), oxalate (40.30 mg/g) but not detrimental to health. Oyeyemi and Ajani [12] stated that the use of 20 or 30% aqueous extract of *C. aconitifolius* leaves for four weeks reduced testosterone concentrations in sheep so that in the long term it could lead to decreased sexual function, decreased libido and erectile dysfunction, triggering anemia and finally infertility in male animals. However, the effective use of *C. aconitifolius* should be used with caution because of the possibility of dose- and time-dependent toxicity [13]. Therefore, it is necessary to provide comprehensive information on the bioactivity of *C. aconitifolius*. This study aims to explain the utilization and bioactivity of *C. aconitifolius*.

2. Methods

The method of writing this article is a literature study that has been published online on Google Scholar. The keywords to search for scientific articles are *C. aconitifolius*, uses of *C. aconitifolius*, and bioactivities of *C. aconitifolius*. The information was analyzed and synthesized so as to explain the benefits and bioactivity of *C. aconitifolius* comprehensively.

3. Results and discussion

3.1. Botany of *Cnidoscolus aconitifolius* (Mill.) I.M. Johnst

Euphorbiaceae is one of the large families estimated has 334 genera [14] has more than 8,000 species [15], spread mainly in the tropics in several types of vegetation and habitats. *Cnidoscolus* is a genus that is used as food and traditional medicine. On the island of Java, the genus *Cnidoscolus* Pohl. has only one species, namely *C. aconitifolius* (but has 2 subspecies, namely *C. aconitifolius* subsp. *aconitifolius* and *C. aconitifolius* subsp. *Polyanthus* [2].

C. aconitifolius is shrubby to small tree, up to 4 m high, with milky latex. Terete trunk, with large scars; bark fawn, cracked, with milky latex. Glossy green branches, white patches, with or without stinging hairs. Stipules narrow lanceolate, 2-3 × 1 mm, apex acuminate, brown, early caducous. Leaves simple, alternate with slender petioles, 5.5–28 cm long, green, glabrous; lamina 3-lobed or 5-7(-9)-partitioned, 6-23 × 7-30 cm; dark green above, yellowish green below, sub-coriaceous; Nectar glands are present at the base. flower terminal, dichasial sub-umbelliform; stalks up to 29 cm long with few short pilose hairs, green; triangular-linear bracts and bracteoles. Stamina salverform flower, congenital sepal petaloid, 5-lobed; tube 6-10 mm long, green; obovate to orbicular lobe, 3-4 × 4-5 mm, white, green below; stamens 10, 2-coiled, outer stamens 4 mm long; inner stamen length 7 mm; filiform filaments, white; anthers oblong, 1-2 × 0.5-1 mm, white, dorsibasifixation; Pistillode present, stringy, white. Pistil campanulate flowers, petaloid 5 petals, free, lobes oblong, 6-7 × 3 mm, white; 5-lobed disc, glabrous, white; ovary superior, ellipsoid, 3 mm long, trilobulate, glossy green, glabrous; very short force, ±1 mm; stigma forked, white, glabrous. Fruit capsule, unbroken, ovoid, 1, × 0.6cm (Figure 1). Seeds fail [2].

The cultivated *C. aconitifolius* variety has more branches and leaves, and the leaves are softer and have fewer trichomes than the wild variety. This difference may be reinforced by the fact that desirable traits (number of branches and leaves) were negatively correlated with undesirable traits (trichome number and toughness) [16].



Figure 1 The habitus and leaves *Cnidocolus aconitifolius*

4. Uses and Bioactivities

The empirically *C. aconitifolius* has long been used as food and traditional medicine. The genus *Cnidocolus* has analgesic, anti-inflammatory, antibiotic, diuretic, anticancer [17], anti-free radical [9] effects. *C. aconitifolius* is a potential antimicrobial agent for the treatment of infections [6] and has antitumor, antidiabetic, antimicrobial and hematopoietic activity [4]. We will discuss further about the bioactivity of *C. aconitifolius* such as anti-microbial, antidiabetic mellitus, hepatoprotective, antioxidant, anti-hypercholesterolemia, analgesic, antianemia, kidney protection.

4.1. Anti-microbial

Antimicrobial compounds are compounds that inhibit the growth of microorganisms such as bacteria and fungi. The bioactivity of *C. aconitifolius* leaves as antimicrobial has been reported by Fagbohun et al [4] and Ogbu and Igboanusi [18], Oyagbemi et al [19], Hamid et al [20], and Adeniran et al [21]. The *C. aconitifolius* extract inhibited the growth of bacteria such as *Escherichia coli* [4,5,18-21], *Psuedomonas aeruginosa*, *Staphylococcus aureus* [4,18-20], *Klebsiella*

pneumonia [4,20], *P. fluorescens* [18], *Klebsiella*, *Salmonella enterica*, *Gallinarum*, *Candida albicans* [19], *Bacillus subtilis* [21], *Salmonella typhi* and *Streptococcus pyogenes* [5]. The inhibition zone of the *C. aconitifolius* extract was influenced by the type of microbe, contact time, and concentration. Bacterial sensitivity to *C. aconitifolius* extract varied, namely *P. fluorescens* > *P. aeruginosa* > *S. aureus* > *E. coli* [18]. The inhibition zones of *C. aconitifolius* leaf methanol extract with concentrations of 125 mg/ml and 500 mg/ml were different, namely *Klebsiella pneumoniae* (1.0 mm – 4.5 mm), *Pseudomonas aeruginosa* (1.5 mm – 5.0 mm), *Escherichia coli* (1.0 mm - 3.5 mm), *Staphylococcus aureus* (1.0 mm - 6.5) [4]. The *C. aconitifolius* extract 10 g/ml resulted in a zone of inhibition in *Salmonella typhi* (20.5 mm) and *Streptococcus pyogenes* (26 mm). The zones of inhibition of standard antibiotics were gentamicin 10 g/ml against *E. coli* (19 mm), ofloxacin at 5 g/ml against *K. pneumoniae* (21mm) and methicillin at 10 g/ml against *S. pyogenes*, *K. pneumoniae* and *E. coli* (16mm) [5].

In addition to inhibiting bacterial growth, *C. aconitifolius* extract also inhibited fungal growth. The crude extract of *C. aconitifolius* leaves inhibited the growth of fungi (*Candida albicans*, *Aspergillus niger*, *Penicillium notatum* and *Rhizopus stolonifer* [20]. The inhibition zones of *C. aconitifolius* methanol extract with concentrations of 125 mg/ml and 500 mg/ml inhibited the growth of different fungal mycelium such as *Aspergillus tamari* (22% - 100%) within 24 hours [4]. The extract inhibited *A. niger* by 9% (31.25 mg/ml) and 91% (500 mg/ml) after 24 hours [4]. These differences are related to differences in cell wall composition, metabolism, properties, resistance to antibiotics or local environmental factors [18]. The bioactivity of the *C. aconitifolius* extract as an antimicrobial is related to the content of its secondary metabolites. Extracts of n-hexane, ethyl acetate and methanol from the aerial part of *C. aconitifolius* has anthraquinones, glycosides, steroids, flavonoids, tannins, saponins and terpenoids [20] while aqueous and ethanolic extracts of *C. aconitifolius* leaves did not contain flavonoids, anthraquinones, and anthraquinones [22].

4.2. Anti-diabetes Mellitus

Diabetes mellitus is a type of metabolic disorder that causes blood glucose levels to be above normal. Diabetes mellitus has been associated with several complications caused by oxidative stress [23]. One of the problems of diabetes pharmacotherapy is an effective and safer approach to the management of prediabetics and diabetes [13]. Changes in body weight, blood glucose and serum lipids were assessed as indicators of the severity of diabetes and its complications [24]. Compounds used as anti-diabetes mellitus are compounds that are able to inhibit the breakdown of carbohydrates into glucose or have hypoglycemic properties or compounds that stimulate the pancreas to produce insulin [24].

Cnidioscolus aconitifolius has hypoglycemic properties so that it can be used as a medicine for diabetes mellitus [24]. In the laboratory, Streptozotocin (STZ) is a compound used to stimulate diabetic rats. The *C. aconitifolius* leaf aqueous extract given orally every day at concentrations of 400, 600 and 800 mg/kg BW showed a decrease in blood sugar levels in STZ-induced rats [7]. The *C. aconitifolius* leaf extract with concentrations of 100, 150 and 200 mg/Kg reduced diabetic blood glucose 41.76; 71.11 and 73.46 [13]. The diabetic rats induced with STZ, then treated with *C. aconitifolius* leaf extract (100-200 mg/kg bw) increased liver enzymes in comparison with 10 mg glibenclamide (standard drug) indicating that *C. aconitifolius* has an adverse effect on the liver [25]. *C. aconitifolius* has insulinogenic properties that may stimulate inactive cells to secrete insulin. Islets of Langerhans were preserved in a group of mice treated with *C. aconitifolius* [26]. The ethyl acetate fraction of leaves *C. aconitifolius* inhibited the activity of -amylase and -glucosidase, acetylcholinesterase, butyrylcholinesterase, monoamine oxidase, tyrosinase, arginase, Ecto-5'-nucleotidase, phosphodiesterase-5, angiotensin-I-converting enzyme and increased the activity of Na⁺/K⁺-ATP ase [27].

4.3. Hepatoprotective

Hepatoprotective is a compound that has a therapeutic effect, to restore, maintain, and treat damage to liver function [28]. The *C. aconitifolius* had a protective effect of leaf extract against carbon tetrachloride (CCl₄)-induced hepatotoxicity and chemotoxicity in experimental animals [29]. The CCl₄ also caused significant increases in serum transaminases (ALT and AST) and phosphatase (ALP), resulting in significant increases in serum blood urea nitrogen (BUN) and creatinine compared to normal mice. Pre-exposure to *C. aconitifolius* leaf extract greatly reduced the effect of CCl₄ on blood parameters and ameliorated liver damage enzymes (ALT, AST and ALP) [29]. The addition of *C. aconitifolius* leaf aqueous extract to the rat diet at 100, 200, and 400 mg/kg body weight for 28 days histopathological showed that the organs of the animals studied were not damaged [30].

4.4. Antioxidants

Stress, excessive consumption of processed foods will cause oxidative stress and damage to genetic material which directly or indirectly causes various diseases of diabetes, hypertension, cancer and metabolic syndrome [31]. Antioxidants are compounds that have activity to inhibit free radicals. Aqueous and methanol extracts of *C. aconitifolius* leaves protected mice induced by oxidative stress and genotoxic damage from exposure to low-dose arsenic and

streptozotocin. The *C. aconitifolius* contains ferulic acid, protocatechuic acid, riboflavin, kaempferol and beta carotene which are thought to be associated with a protective effect against genotoxic damage [31].

The hydroalcoholic extract of *C. aconitifolius* leaves contains phenolic compounds such as gallic acid, vanillic acid, vanillin, chlorogenic acid, caffeic acid, ferulic acid, rosmarinic acid, p-coumaric acid, resveratrol, luteolin and apigenin. The *C. aconitifolius* boiled leaves have higher antioxidants than raw leaves. Boiled leaves have a higher polyphenol content so that they become a source of antioxidants [32]. The bioactivity as an antioxidant is related to the content of phenolic compounds [27,32]. The ethyl acetate fraction of *C. aconitifolius* leaves contains coumaric acid, amentoflavones, hesperidin, protocatechuic acid, kaempferol, dihydromyricetin, quercetin, and rutin. The *C. aconitifolius* leaves have extraordinary antioxidant potential [27].

Ethyl acetate and methanol extract of *C. aconitifolius* leaves showed antioxidant activity and free radical scavenging DPPH (2,2-difenil-1-pikrilhidrazil) IC 12.14 and 93.85 g/ml, respectively. Phytols were the most abundant constituents in the extracts of n-hexane, ethyl acetate and methanol with the corresponding abundance percentages of 41.07%, 35.42% and 35.07% [20]. The *C. aconitifolius* extract reduces oxidative stress by increasing the activity of several antioxidant enzymes and can prevent cell death due to lipid peroxidation [33].

4.5. Anti-hypercholesterolemia

Hypercholesterolemia is a condition characterized by high levels of cholesterol in the blood and if it accumulates and narrows the blood vessels, it directly or indirectly affects the circulatory system. The *C. aconitifolius* leaf extract has anti-hypercholesterolemic potential [34]. Rats given 200-800 mg/kg BW aqueous and ethanol extract of *C. aconitifolius* leaves showed a significant reduction in total cholesterol (TC), low density lipoprotein (LDL) and triglyceride (TG) with an increase in high density lipoprotein (HDL) which was dose dependent and therefore beneficial in the treatment of coronary heart disease [34].

4.6. Anti-anemia

Anemia is a condition when the number of red blood cells is lower than normal. Iron supplements can be used for iron and vitamin B deficiency. Onuoha et al [35] stated that anemic rats then given 5-15 ml of *C. aconitifolius* leaf raw juice showed a significant increase in hemoglobin, solid cell volume, red blood cells and white blood cells. The bioactivity is thought to be related to the mineral and vitamin content in *C. aconitifolius* leaves. The *C. aconitifolius* has vitamin B3, vitamin B6, vitamin B12 [7] and minerals Sodium, Potassium, Calcium, Magnesium, Zinc, Copper, Iron [4,6].

4.7. Lower Testosterone

Testosterone is one of the androgen hormones produced by the testes in males which is very important in reproduction. Lowering the testosterone hormone is one way to regulate birth. Lucky and Festus [36] reported that rats fed 1.5 g/kg body weight showed significantly reduced testosterone levels and significantly increased levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH). The testosterone/estrogen ratio also increased depending on the duration of treatment [36]. The bioactivity is thought to be related to the *C. aconitifolius* steroid content. The *C. aconitifolius* leaves contain tannins, saponins, cyanogenic glycosides, alkaloids, phenols, flavonoids, and steroids [30].

4.8. Overcoming Stomach Ulcers

Ulcers are wounds caused by damage to the epithelium and basement membrane. The *C. aconitifolius* in traditional medicine for the treatment of gastric ulcers. The methanol extract of *C. aconitifolius* leaves has gastro-protective activity in rats induced by diclofenac in causing gastric mucosal lesions by increasing the ulcer index inhibition against gastric mucosal damage induced by diclofenac [37].

4.9. Analgesic

Various human diseases are accompanied by pain, therefore one of the goals of drug administration is to reduce pain. Compounds used to reduce pain are called analgesics. In laboratory experiments, pain was induced by formalin, acetic acid and hot plate tests. The *C. aconitifolius* extract (100 or 200 mg/kg b.w.) inhibited rat acetic acid-induced irritation comparable to indomethacin (10 mg/kg bw). Carrageenan-induced edema was significantly inhibited by the extract (100 and 200 mg/kg bw) compared to control mice [38].

4.10. Anti-cancer

The *C. aconitifolius* in ethnomedicine is used to treat cancer. Methanol extract of leaves, stems, and bark of CA roots has the effect of treating breast cancer (MCF-7) and lung (NCI-H460). Leaf extract at a concentration of 100 g/mL showed

remarkable growth inhibition against breast cancer and lung cancer in vitro. The *C. aconitifolius* extract contains saponins, terpenes, cardiac glycosides, and phenolic compounds [39].

4.11. Protect The Kidney

Rats given *C. aconitifolius* leaf methanol extract (MECA) at doses (100 and 200 mg/kg) had a renal protective effect by attenuating the oxidative stress function caused by chronic ethanol administration. Administration of *C. aconitifolius* leaf methanol extract (MECA) in mice significantly weakened the biochemical index above close to normal. Ethanol poisoning caused a significant decrease in the levels of catalase (CAT), superoxide dismutase (SOD) and reduced glutathione (GSH) in the rat kidney. MECA attenuated ethanol-induced increases in renal serum and MDA, and also improved the antioxidant status of mice by increasing CAT, SOD and GSH levels [40].

5. Conclusion

Cnidoscopus aconitifolius bioactivity includes antimicrobial, antidiabetic, hepatoprotective, antioxidant, antihypercholesterolemia, analgesic, antianemia, and kidney protection. The *C. aconitifolius* leaves contain macronutrients such as carbohydrates, proteins, fats, vitamins and minerals so that they have the potential to be developed for cheap and easily available food. On the other hand, *C. aconitifolius* also contains anti-nutrients such as phytate and oxalate but with proper processing the antinutrients will be degraded.

Compliance with ethical standards

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