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Trichosanthes cucumerina: A perspective on various medicinal uses or activities

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Abstract

In Sri Lankan and Indian traditional systems of medicine, *Trichosanthes cucumerina* Linn. (Family: Cucurbitaceae) is one of the medicinal plants frequently utilised to create formulations to treat a range of illnesses and conditions. Along with other plant components, the aerial parts of *T. cucumerina* are used to treat indigestion, bilious fevers, boils, sores, and skin eruptions like eczema, dermatitis, psoriasis, inflammation, ulcers, and diabetes. The research on *T. cucumerina*'s pharmacology and toxicology is summarised in the current review.

Keywords: *Trichosanthes cucumerina*; Cucurbitaceae; Bio-activities; Toxicity

1. Introduction

In various areas, *Trichosanthes cucumerina* is known as snake gourd, viper gourd, snake tomato, or long tomato. It is an annual climber of the Cucurbitaceae family that is widely grown, has 24 genera and 54 species in West Africa, and 41 species in 21 genera have been identified in Nigeria. These species are either cultivated or wild, and the majority are in Asian nations such as Sri Lanka, India, Malaysia, the Peninsula, and the Philippines [1]. There are around 118-130 genera and 800-825 species native to Asia in this family [2]. Dentate hairy leaves are 10- 25 cm long and 15 cm wide. They emit a foul odour when they are injured. White, monoecious, and axillary flowers. Male flowers are produced by long racemes with peduncles up to 30 cm long. In nature, female blooms are solitary. Fruits are cylindrical with a waxy surface, slender and tapering, and measure 40 to 120 cm in length and 4 to 10 cm in diameter [3]. Because of its excellent nutritional value, fruit is commonly consumed as a vegetable. Flavonoids, carotenoids, phenolic acids, soluble and insoluble dietary fibres, and vital minerals are abundant in the plant, making it pharmacologically and therapeutically active [4]. [5]. Proteins, fats, fibre, carbs, minerals, and vitamins A and E are all abundant in the plant. Potassium (121.6 mg/100 g) and phosphorus (135 mg/100 g) are the most abundant mineral elements, with sodium, magnesium, and zinc also present at significant levels [6]. *T. cucumerina* was employed in the treatment of headaches, alopecia, fever, abdominal tumours, bilious, boils, acute colic diarrhoea, haematuria, and skin allergies in ancient medicine. It is used extensively in therapeutic systems such as Ayurveda and Siddha. Antidiabetic, antibacterial, anti-inflammatory, anthelmintic, antifebrile, gastroprotective, and antioxidant activity have been documented for the entire plant, including roots, leaves, fruits, and seeds [7].

2. Phytochemical profile

The phytoconstituents and antioxidant activity of *Trichosanthes cucumerina* L. fruit pulp have not been described in the literature, so it was investigated. The investigations used two identified morphotypes of this plant (Morphotype I [V1], which has long fruit with a deep green background and white stripes, and Morphotype II [V2], which has light green coloured long fruit). The pulp of the V1 and V2 had dry matter contents of 10.9 and 9.6 g/100 g fresh weight (FW), respectively, and ascorbic acid contents of 25.7 and 24.8 mg/100 g fresh weight (FW), and lycopene concentrations of

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18.0 and 16.1 mg/100 g FW. V2 had 46.8 per cent more total phenolics, 78.0 per cent more total flavonoids, and 26.2 per cent more total ferric reducing antioxidant power (FRAP) than V1 (P 0.05). Lutein, which has concentrations of 15.6 and 18.4 mg/100 g FW for V1 and V2, respectively, makes up the majority of the carotenoids. V1 and V2 had -carotene concentrations of 10.3 and 10.7 mg/100 g FW, respectively, whereas V1 and V2 had -carotene values of 2.4 and 2.8 mg/100g FW. The findings of this study show that the two morphotypes of *T. cucumerina* have excellent nutraceutical qualities[8].

2.1. Hepatoprotective activity

Studies were done and it was found that due to metabolic activation, the hepatotoxic drug CCl_4 causes selective toxicity in liver cells and also causes alterations in the cell membrane's functionality and morphology. Hepatic cells have larger levels of AST (Aspartate transaminase) and ALT (Alanine transaminase) in their cytoplasm. The leakage of the plasma causes a rise in hepatospecific enzymes in serum as a result of the injury to hepatic cells. Elevated serum enzyme levels, such as AST and ALT, indicate cellular leakage and the functional integrity of the liver's cell membrane. Because of the hepatotoxin's liver injury, the liver's bile excretion is impaired, resulting in elevated levels of bile in the blood. Oral administration of TCME (Methanol extract of *Trichosanthes cucumerina*) at doses of 250 and 500 mg/kg b.w. lowered serum TB levels significantly. Intoxication with CCl_4 promotes the disassociation and disruption of polyribosomes on the endoplasmic reticulum, decreasing protein production. By preserving the polyribosomes, the TCME pre-treatment effectively restored protein production. Lipid peroxidation is indicated by an increase in MDA or a decrease in GSH levels. The groups that got only the CCl_4 treatment showed considerable lipid peroxidation, whereas the groups that received the TCME pre-treatment showed significant protection. This also points to TCME's antioxidant capability and its defence mechanism against reactive oxygen species. The histopathology examinations were performed and the damage to cells around the central vein was visible in the groups that received only CCl_4. In studies involving TCME pre-treatment, however, the severity of the injury was found to be lower [9].

2.2. Cardioprotective activity

Cardiotoxic symptoms caused by doxorubicin include arrhythmias, while chronic toxicity can lead to irreparable cardiomyopathy, which affects 30–40% of patients who receive a cumulative dose of 500 mg/mm2. Enzyme activity in plasma increased as a result of DOX (Doxorubicin). They are not specific for myocardial injury, but a combination of these enzymes could be a sign of myocardial injury. The considerable increase in LDH and CK-MB produced by DOX was reduced in the TC500 and TC1000 treatment groups. Arrhythmia is another kind of doxorubicin cardiotoxicity that can develop at any time and after any dose. Only DOX-injected animals have a significant increase in ST, QT, and QRS intervals. DOX administration did not affect the ST, QT, or QRS intervals in the TC500 and TC1000 groups. Both systolic and diastolic cardiac functions are inhibited by doxorubicin. In both humans and laboratory animals, doxorubicin has been shown to reduce cardiac function. In one study, DOX caused a drop in systolic and diastolic pressure which was reversed in the TC500 and TC1000 treatment groups.

The antioxidant activity of cucurbitacin B, cucurbitacin E, carotenoids, and ascorbic acid has been documented in TC. Antioxidants decrease oxidative damage by delaying the oxidation of other molecules by inhibiting the oxidative chain reaction caused by free radicals. Cancer and cardiovascular disease may arise as a result of oxidative damage. T. curcumina (TC) has a variety of antioxidant components that defend against harmful free radicals, which are closely linked to reduced health [10].

2.3. Gastroprotective activity

Ethanol is an ulcerogenic substance that causes severe damage to the stomach mucosa by encouraging mucosal microcirculation abnormalities, ischemia and the appearance of free radicals, endothelin release, mast cell degranulation, prostaglandin inhibition, and a decrease in gastric mucus production. Indomethacin is a nonsteroidal anti-inflammatory medicine (NSAID) that blocks prostaglandin production, resulting in increased acid production and decreased cytoprotective mucus formation, which can cause gastrointestinal ulcers. *Trichosanthes cucumerina* has potent gastroprotective qualities, such as its ability to significantly reduce the length and quantity of gastric lesions caused by 100% ethanol and indomethacin. The gastroprotective activity of a 750 mg/kg dose of hot water extract (HWE) was comparable to that of cimetidine and sucralfate.

In rats, HWE (hot water extract) can considerably increase gastric mucus secretion while lowering stomach acidity. The amount or thickness of the layer covering the mucosal surface determines the mucus barrier's protective characteristics. HWE administration significantly enhanced the amount of mucus generated by the rat gastro mucosa. As a result, increased mucus secretion following HWE administration may aid to protect against absolute ethanol and indomethacin-induced damage by preventing acid and pepsin from attacking the stomach mucous epithelium. It's also

widely known that significant amounts of prostaglandins produced by the gastrointestinal mucosa can prevent ulcers caused by ulcerogenic in the lab. When ulcer lesions are generated by 100% ethanol or indomethacin, the antiulcer agent's cytoprotective effect is mediated via endogenous prostaglandins. As a result, it's possible that HWE stimulates prostaglandin secretion or contains prostaglandin-like compounds.

Inhibition of acid secretion is another key protective factor because when acid levels surpass mucosal defence mechanisms, ulcers occur. With an increase in stomach pH, HWE induced a considerable suppression of acidity. HWE's antihistamine action could be related to its reduction of gastric juice acidity, as it is well known that antihistamine medicines like cimetidine, which block H2 receptors in the stomach, lower gastric juice acidity. Although H2 receptor blockers are expected to diminish gastric juice output, no such impact was seen. As a result, HWE's antihistamine action may play a role in its ability to protect against indomethacin-induced stomach lesions [11].

2.4. Antidiabetic activity

An aqueous extract of *Trichosanthes cucumerina* significantly ($P < 0.01$) attenuated the rise in blood glucose levels in NIDDM-induced rats. Blood glucose levels in diabetic animals peaked after 45 minutes and remained elevated after 2 hours. In the theTrichosanthes, cucumerina treated group, blood glucose levels peaked after 30 minutes and then declined for up to 2 hours. The drug significantly ($P<0.01$) lowered postprandial blood glucose levels in diabetic animals. We found that glycogen content in insulin-dependent tissues such as liver and skeletal muscle was improved by 62% and 58.8%, respectively, in *Trichosanthes cucumerina* compared to NIDDM controls. Therefore, *Trichosanthes cucumerina* has antidiabetic activity. The drug improved oral glucose tolerance in NIDDM subjects. Increased tissue glycogen content indicates the drug's effect on glucose uptake by peripheral tissues and reduces insulin resistance in NIDDM [12]. A study of the AET (aqueous extract from *Trichosanthes cucumerina*) treatment group in contrast to the significantly higher but consistently decreasing BGL further establishes the hypoglycemic or hypoglycaemic effect of AET. This suggests that AET may have the ability to enhance pancreatic islet B-cell function and improve glucose uptake by body tissues [13]. HWE of *T. cucumerina* aerial parts can significantly lower blood glucose levels and improve glucose tolerance in normoglycemic and STZ-induced diabetic rats. *T. cucumerina* exerts its hypoglycemic action through a mechanism similar to that of sulfonylureas. Thus, *T. cucumerina* did not affect intestinal glucose absorption, but significantly increased hepatic glycogen and adipose tissue triglyceride accumulation. On the other hand, insulin inhibits glycogenolysis, and insulin deficiency results in increased glycogenolysis and decreased hepatic glycogen content. Subchronic oral administration of *T. cucumerina* HWE significantly increased hepatic glycogen levels in normoglycemic and STZ-induced diabetic rats. In diabetes with insulin deficiency, serum triglyceride concentrations increase as a result of efflux of free fatty acids from fat deposits and decreased activity of lipoprotein lipase. Subchronic administration of *T. cucumerina* HWE increased adipose tissue triglyceride levels in both normoglycemic and STZ-induced diabetic rats. Low doses of STZ (50 mg/kg) incompletely destroy pancreatic B cells, but permanently diabetic rats. Administration of *T. cucumerina* extract reduced elevated serum glucose levels in STZ-induced diabetic rats. This ability to lower blood glucose levels in STZ-induced diabetic rats also suggests that HWE may act as an insulin secretagogue and sensitize insulin receptors [14].

2.5. Antifertility activity

Specific components of folliculogenesis are regulated by pituitary hormones, as well as growth factors and steroids generated from the gonads. Follicular secretion of ovarian androgens and inhibins may play a role in the regulation of FSH secretion and follicular dynamics. The hypothalamopituitary unit plays a critical role in ovarian function regulation. These glycoprotein hormones, in turn, play an important role in folliculogenesis regulation. Treatment of intact rats with ethanol extract of *Trichosanthes cucumerina* L. at a high dose resulted in a considerable reduction in ovarian weight, which could be linked to inhibition of tropic pituitary gonadotropin release due to the drug`s estrogenic negative feedback mechanism. When circulating pituitary gonadotropins like Folical Stimulating Hormone (FSH) and Leutinizing hormone (LH) are assessed in both treatment groups compared to control rats, this effect is further reflected. The difference in oestrous cycle duration between the control and treatment groups is related to vaginal cornification, which is influenced by the extract's estrogenic nature, which produces more oestrogen. This could be due to a decrease in pituitary gonadotropin support, as FSH is a key regulator of follicle growth and development. The suppression of pituitary FSH secretion in extract-treated rats may have resulted in a protein deficiency. Reduced ovarian glycogen concentration in rats treated with ethanol extract of *Trichosanthes cucumerina* L. The drop in ovarian function is mirrored by the decrease in pituitary gonadotropins FSH and LH after therapy. Steroidogenesis requires FSH and LH, with cholesterol serving as the ovary's primary starting molecule for steroid hormone production. At all doses, cholesterol levels considerably rose in the ovaries treated with ethanol extract of *Trichosanthes cucumerina* L. indicating that gonadotropins play a role in cholesterol consumption for steroid hormone production in the ovary.

After treatment with a high dose of ethanol extract *Trichosanthes cucumerina* L. When compared to the control group, findings imply that ethanol extract therapy impairs ovarian steroidogenic activity and reduces pituitary gonadotropin secretion. These plant extracts inhibited the release of LH and FSH. The plant extract's blockade of ovulation and the oestrous cycle could be explained by a significant drop in LH and FSH [15].

2.6. Anti-cancer

Only MDA-MB-231 and MCF7:5C cells were radio sensitized by cucurbitacin B, and SKBR-3 cells were not. Flow cytometric analysis of DNA content showed that cucurbitacin B caused G2/M arrest in her MDA-MB-231 and MCF7:5C, but not in SKBR-3 cells. Furthermore, real-time PCR and western blot analysis revealed that p21 expression was upregulated before irradiation. This is thought to be the cause of cell cycle arrest. Therefore, the combination of cucurbitacin B and radiotherapy may be suitable for the experimental treatment of breast cancer [16].

Cucurbitacin B may inhibit the proliferation of human breast cancer cells through disruption of the microtubule network and down-regulation of c-Myc and nucleophosmin/B23 as well as the perturbation in nucleophosmin/B23 trafficking from the nucleolus to the nucleoplasm, resulting in G2/M arrest [17].

Decreased expression of cyclin D1, c-Myc and b-catenin was observed, increased PARP cleavage, decreased Wnt-related signalling molecules b-catenin, galectin-3, cyclin D1 and c-Myc, and phosphorylated GSK. Treatment with cucurbitacin B inhibited nuclear translocation of β-catenin and galectin-3. T-cell factor (TCF)/lymphoid enhancer factor (LEF)-dependent transcriptional activity was disrupted in cucurbitacin B treated cells, as tested by the TCF reporter assay. Treatment of cells with the cucurbitacin B compound for 24 hours decreased relative luciferase activity. Therefore, cucurbitacin B can induce apoptosis and exert growth inhibitory effects. Cucurbitacin B from *T. cucumerina* Lynn. It has cytotoxic effects against breast cancer cell lines SKBR-3 and MCF-7 with IC50s of 4.60 and 88.75 mg/ml, respectively [18].

wild-type (wt) BRCA1, mutant BRCA1, BRCA1 knockdown and BRCA1 overexpressing breast cancer cells were treated with cucurbitacin B to examine the inhibitory effects on cell proliferation, migration and invasion independent of anchorage. Loss of BRCA1 expression results in increased survivin expression and reduced sensitivity to paclitaxel. Cucurbitacin B inhibited knockdown and mutant BRCA1 breast cancer cells more than wild-type BRCA1 breast cancer cells in terms of cell proliferation, migration, in vasion and anchorage-independent growth. Cells forced to overexpress wild-type BRCA1 reduce the effectiveness of cucurbitacin B to inhibit the proliferation of endogenous mutant BRCA1 cells. Stimulation of p21/Waf1 and p27Kip1 expression and suppression of survivin expression was observed by cucurbitacin B. Survivin may be an important target of cucurbitacin B in BRCA1-deficient breast cancer cells [19].

2.7. Anti-bacterial activity

T. cucumerina has antibacterial components that are effective against wound pathogens such as S. aureus, S. pyogenes, E. coli, and P. aeroginosa. Furthermore, the CEE (Cold ethanolic extract) can regularly outperform the HWE (Hot water extract) in terms of antibacterial activity. The polarity of antibacterial chemicals contained in *T. cucumerina* may explain the differential in the activity of the HWE and CEE. Strong antibacterial action is indicated by a 9-15 mm zone of inhibition. At a very low concentration (12.5 g/disc) of both extracts, E. coli and P. aeroginosa were shown to be the most susceptible to *T. cucumerina*, with an inhibition zone greater than 9 mm. Secondary metabolites of plants such as tannins, saponins, flavonoids, alkaloids, and various other aromatic chemicals serve as defensive mechanisms against predation by a variety of microbes, insects, and other herbivores.

T. cucumerina extracts also contain tannins, saponins, flavonoids, and alkaloids as important chemical ingredients, according to phytochemical studies. As a result, these phytochemicals may have a role in their antibacterial properties. E. coli and P. aeroginosa were shown to be more vulnerable to the action of *T. cucumerina* extracts.

Finally, *T. cucumerina* extracts displayed antibacterial action against both grammes (+) ve and gramme (-) ve bacterial strains such as S. aureus and S. pyogenes, indicating the existence of a broad spectrum of antibacterial chemicals in the plant [20].

2.8. Anti-oxidant activity

2.8.1. DPPH (2, 2-diphenyl-l-picryl hydrazyl) radical scavenging assay.

The results of the free radical scavenging ability of a methanolic extract of the plant material and callus at different concentrations are expressed as the percentage of inhibition of free radicals by antioxidants present in the extract. The

results on DPPH scavenging activity suggested that there is an increase in the percentage of radical scavenging activity with an increase in the concentration of the extract. Among the extracts, the highest scavenging activity at 500 mg/ml extract concentration was recorded (91.85 %) for an in vivo plant sample extract. For the callus extract, the maximum scavenging activity recorded was 63.48% [21].

2.8.2. Ferric reducing antioxidant power (FRAP) assay

In the FRAP assay, a linear increase in reducing power was observed over the concentration range of 100–500 mg/ml. Extracts from naturally grown *T. cucumerina* indicated ferric reducing power either greater than or at comparable levels with the standard ascorbic acid. The reducing capacity of callus was lesser than the wild plant when compared. In conclusion, the executed study demonstrated that extracts from tissues of both in vitro (callus) and in vivo (wild plant) samples of Trichosanthes possess strong antioxidant activity.

Antioxidant activity was observed by comparing ethanolic extract of *Trichosanthes cucumerina* with ascorbic acid as standard the maximum percentage inhibition was 86.2% was shown at a concentration of 150 ug mL whereas, at 50 ug mL it showed percentage inhibition of 62.9 and at 100 ug mL it showed percentage inhibition 79.9 [22].

2.9. Anti-inflammatory activity of areal parts

In a carrageenan-induced paw oedema model, *Trichosanthes cucumerina* suppressed oedema in both the early phase mediated by (histamine and serotonin release) and late phases (mediated by neutrophil infiltration, eicosanoid release, production of free radicals, and release of other neutrophil-derived mediators), of acute inflammation. Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) expressions are known to be highest in the early and late stages of carrageenan-induced paw oedema, respectively. This suggests that *Trichosanthes cucumerina* may have inhibitory effects on both COX-1 and COX-2. *Trichosanthes cucumerina*'s significant gastroprotective action against ethanol or indomethacin-induced gastric ulcers implies that the COX-2 inhibitory activity of *Trichosanthes cucumerina* is greater than the COX-1 inhibitory impact.

The HWE protects the rat red blood cell (RBC) membrane from lysis caused by heat at concentrations of 50–300 g/mL. Because the RBC membrane system and the lysosomal membrane system are so similar, protection against hypotonicity or heat-induced lysis of RBC is frequently extrapolated to lysosomal membrane stability and utilised as a biochemical measure of anti-inflammatory action.

Plants with membrane stabilising qualities interfere with the early phase of inflammatory mediator release, specifically by modulating the release of phospholipase A2, which stimulates the formation of inflammatory mediators. As a result, the membrane stabilising effect of HWE may contribute to the prevention of paw oedema in the early stages of carrageenan-induced paw oedema.

In the carrageenan model, histamine is a potent mediator of the early stages of inflammation. Mast cell histamine has been shown to activate endothelial cells, increasing vascular permeability. Hot water extract of *Trichosanthes cucumerina* aerial parts has antihistamine action. As a result, the HWE's antihistamine action may contribute to the impairment of carrageenan-induced paw oedema's early stages.

The HWE has a substantial inhibitory effect on rat peritoneal cell NO generation. In the carrageenan-induced paw oedema model, NO diffuses into vascular smooth muscle and activates single guanylate cyclase, which dilates blood vessels, increases the volume of exudates, and therefore increases oedema formation. It is possible to conclude that *Trichosanthes cucumerina* is therapeutically effective for the treatment of inflammatory illnesses [23].

2.10. Toxicity

The public and some health care practitioners believe herbal treatments are gentle and safe, although there is no scientific basis for this belief. Plant extracts contain compounds that are similar to those found in pure pharmaceuticals and have the same potential for major side effects. Any drug's utility is determined not only by its therapeutic efficacy but also by its lack of toxicity or negative side effects. It's crucial to look into the acute and chronic side effects of *T. cucumerina* aerial parts.

Using mice as the experimental model, it was recently proven that extracts (HWE or CEE) of *T. cucumerina* aerial parts had no major toxic effects or cause mortality at levels up to 30 g/kg. Oral administration of HWE or CEE (cold ethanolic extract) for 14 or 42 days did not result in any overt signs of toxicity (salivation, diarrhoea, lacrimation, tremors, ataxia, yellowing of hair, hair loss, postural abnormalities, or behavioural changes), stress (fur erection or exophthalmia),

aversive behaviours (biting paw and penis, intense grooming behaviour, scratching behaviour, licking at tail Food and drink intake were normal in HWE and CEE treated mice. The HWE and CEE-treated mice had identical facial consistency and urine colour to their respective control groups. The extracts also showed no symptoms of hepatotoxicity or renotoxicity, nor did they have any negative impact on male or female fertility (as evident from the effects of the HWE and CEE on early abortifacient activity and implantation in female rats and spermicidal activity in vitro) [24].

3. Conclusion

The leakage of the plasma causes a rise in hepato specific enzymes in serum as a result of the injury to hepatic cells. Because of the hepatotoxin's liver injury, the liver's bile excretion is impaired, resulting in elevated levels of bile in the blood. The considerable increase in LDH and CK-MB produced by DOX was reduced in the TC500 and TC1000 treatment groups. The gastroprotective activity of a 750mg/kg dose of hot water extract was comparable to that of cimetidine and sucralfate. Follicular secretion of ovarian androgens and inhibins may play a role in the regulation of FSH secretion and follicular dynamics. As a result, these phytochemicals may have a role in their antibacterial properties. E.coli and *P. aeroginosa* were shown to be more vulnerable to the action of T.cucumerina extracts.

Compliance with ethical standards

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Disclosure of conflict of interest

The Authors do not have any personal financial interests related to the subject matters discussed in this manuscript.

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