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THE MEDICAL USES OF *COCCINIA GRANDIS* L. VOIGT: A REVIEW

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ABSTRACT: *Coccinia grandis* Linn. Voigt, also known as *Coccinia indica* belongs to the family Cucurbitaceae. It is extensively used in traditional medicine for the treatment of leprosy, jaundice, asthma, bronchitis, skin eruptions, burns, tongue sores, earache, indigestion, eye infections, nausea, insect bites, and fever. Phytochemical studies reveal the presence of phenols, tannins, saponins, terpenoids, flavonoids, arabinose, xylose, mannose, galactose, glucose and rhamnose. Studies on the plant extract particularly the leaf extract shows that it possesses antihyperglycemic, xanthine oxidase inhibitory, analgesic, anti-inflammatory, and antipyretic, antioxidant, antihyperlipidemic, antimicrobial, anti-hepatotoxic and anti-insecticidal activities. Among these, the plant's activity against diabetes has been extensively investigated. Current studies on its antioxidant activity reveal its potential in cancer therapy. The plant leaf extract also shows significant activity chemoprotective effect against cyclophosphamide, commonly used in the treatment of cancer and autoimmune diseases. A review of the various studies on the plant is provided to understand its medicinal properties.

INTRODUCTION: Alternatives to allopathic treatments are being investigated given the side effects and complications resulting from synthetic drugs and surgery. Hence, the medicinal properties of various plants are being studied for their effect on several diseases and disorders. One of the plants on which comprehensive studies have been made is *Coccinia grandis*. *Coccinia grandis* Linn. Voigt, commonly called the ivy gourd, is a perennial herb or a vine found extensively from Africa to Asia. It is also known as *Coccinia indica*. The plant belongs to the family Cucurbitaceae. The fruits, roots, the stem of this plant were used traditionally to treat diseases like leprosy, jaundice, asthma, bronchitis, skin eruptions, burns, tongue sores, earache, indigestion, eye infections, nausea, insect bites, and fever.

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The tender green fruits were cooked and eaten, sometimes also raw. The leaves of this plant were used to treat diabetes [1, 2]. The fruits of the plant were used in the treatment of diabetes [3]. The studies showed that the leaves of the plant possess antioxidant properties [4, 5], and produce an analgesic, antipyretic and anti-inflammatory effect in rats [6]. Several biochemical studies have been performed to reveal the medicinal uses of the plant parts.

Phytochemical Analysis: Phytochemical analysis of hydroethanolic extract of leaves of *Coccinia grandis* indicated the presence of phenols, tannins, saponins, terpenoids, and flavonoids. The presence of saponins, flavonoids, and polyphenols may contribute to the antioxidant and anti-inflammatory activity of the leaves [7].

Elemental analysis of the ash of the plant parts revealed the presence of copper (Cu), manganese (Mn) and zinc (Zn) at 0.030 mg/100 mg of ash, 0.213 mg/100 mg of ash and 0.108 mg/100 mg of ash respectively [8].

Fruits and leaves of the plant were found to be made of arabinose, xylose, mannose, galactose, and glucose. Studies revealed that leaves also contain rhamnose [9].

Antioxidant Activity: Antioxidants are substances which are capable of scavenging free radicals which damage biomolecules such as proteins, lipids, carbohydrates and DNA [10].

The effect of the leaf extract on streptozotocin-induced diabetic rats was studied. The study revealed that the administration of 200 mg/kg body weight extract for 45 days resulted in a decrease in thiobarbituric acid reactive substances and hydroperoxides and an increase of reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase, and glutathione-S-transferase in liver and kidney [4]. In plasma, the extract exhibited a decrease in thiobarbituric acid reactive substances, hydroperoxides, vitamin E and ceruloplasmin and increase in plasma vitamin C and reduced glutathione [5]. The antioxidant activity of *Coccinia grandis* was studied using a hydroethanolic extract of the dried powdered leaves. The hydroethanolic extract was then re-extracted with petroleum ether, chloroform, and ethyl acetate leaving behind the residue [7].

The fractions obtained were checked for the free radical scavenging activity by 1, 1-diphenyl-2-picrylhydrazyl (DPPH) assay [11]. The IC_{50} values were compared with the standard, ascorbic acid. All the fractions showed hydrogen donor activity. The chloroform fraction (IC_{50} 0.145 mg/ml) showed the highest activity followed by ethyl acetate (IC_{50} 0.164 mg/ml), petroleum-ether (IC_{50} 0.29 mg/ml) and residual fractions (IC_{50} 0.6 mg/ml) [7].

The reducing power of the fractions was studied by Fe^{3+}- Fe^{2+} transformation [12] and the resulting Perl's Prussian blue formation [13]. In this case, the residual fractions showed the highest reducing power. The other fractions (petroleum-ether, chloroform, and ethyl acetate extracts) also displayed significant reducing activity [7]. Hydroxyl scavenging activity was evaluated by the measure of the inhibitory activity of the fractions towards the degradation of deoxyribose by the hydroxyl radicals produced as a result of Fenton reaction [14, 15]. The test suggested that all the fractions showed scavenging activity. Petroleum-ether showed the highest activity with IC_{50} value of 0.141 mg/ml [7].

The hydrogen peroxide scavenging assay [16] suggested that all the fractions exhibit H_2O_2 scavenging activity. Petroleum-ether fraction showed the maximum activity of with IC_{50} 0.092. IC_{50} values of residue, chloroform and ethyl acetate fractions are 0.125, 0.186 and 0.232 mg/ml [7].

Nitric acid scavenging activity was also examined [17] which reported the highest scavenging activity for the chloroform fraction (IC_{50} 0.183 mg/ml). The other fractions also exhibited good activity. IC_{50} for residue, petroleum-ether and ethyl acetate were observed as 0.37, 0.384 and 0.553 mg/ml respectively [7].

In the peroxyl radical scavenging activity which was investigated by thiocyanate method [18,] petroleum-ether (IC_{50} 0.278 mg/ml) and chloroform fractions (IC_{50} 0.271 mg/ml) exhibited similar antioxidant activity. At high concentrations ethyl acetate (IC_{50} 0.405 mg/ml) and residual (IC_{50} 0.46 mg/ml) fractions show good antioxidant activity. Further testing by phosphomolybdate method [19] revealed that chloroform fraction had the maximum antioxidant capacity [7].

All the fractions of the leaves showed ferrous ion chelating action with chloroform fraction (IC_{50} 0.276 mg/ml) possessing maximum activity. Petroleum-ether (IC_{50} 0.393 mg/ml), ethyl acetate (IC_{50} 0.433mg/ml) and residual (IC_{50} 0.405 mg/ml) fractions possess similar chelating activity [7.]

The β carotene bleaching assay [19] of the fractions revealed that the fractions have good inhibitory activity on β carotene bleaching with IC_{50} values of 0.068, 0.099, 0.117 and 0.145 for petroleum-ether, ethyl acetate, chloroform, and residual fractions respectively [7]. The fractions were for tested for pro-oxidant activities by bleomycin dependent DNA damage [20]. The test revealed that fractions do not possess pro-oxidant activity [7]. Among the hydroethanolic extracts obtained petroleum-ether is reported to contain the highest phenolic and flavonoid content. The high phenolic and flavonoid content of the fractions contribute to their antioxidant activity [21, 7].

In - vivo studies are yet to be performed to test the antioxidant activity of *Coccinia grandis.*

Xanthine Oxidase Inhibitory Activity: Xanthine oxidase is an enzyme involved in purine metabolism. It is responsible for converting hypoxanthine to xanthine and then xanthine to uric acid. Increased activity of this enzyme causes hyperuricemia resulting in the deposition of urate monohydrate crystals in joints and kidneys. The kidney stone was found to be associated with a condition known as Gout [22].

The methanoic, aqueous and hydroethanolic extracts of the leaves of *Coccinia grandis* showed inhibitory activity towards Xanthine oxidase in both *in-vitro* and *in-vivo* studies [23].

In-vitro studies of extract of leaves revealed inhibition of xanthine oxidase activity at 25, 50 and 100 µg/ml. It showed more than 50% inhibition at 50 and 100 µg/ml of all the three extracts. The IC_{50} values for the aqueous, hydromechanics and methanolic extracts were 32.5, 21.25 and 29.75 µg/ml respectively. The standard drug used for inhibitory activity showed 93.21% inhibition (IC_{50} 6.75 µg/ml) [23]. *In-vivo* studies were carried out in Swiss albino mice. Five animals were given a single oral dose of 2000 mg/kg of body weight for testing the toxicity of the extract. LD_{50} did not reveal any acute toxicity at this level. For the hyperuricaemic study, the mice were orally given 200 mg/kg body weight, and hyperuricaemia was induced. Methanoic extract of *Coccina grandis* lowered the serum urate level from 11.42 ± 0.14 mg/dl to 3.90 ± 0.07 mg/dl which was comparable with the activity of the standard drug allopurinol treated group (3.89 ± 0.07 mg/dl) [23].

Antihyperlipidemic Activity: Hyperlipidemia refers to a group of disorders characterized by the high levels of lipid in the blood plasma. *In-vivo* studies were carried out in hamsters to study the antihyperlipidemic effect of *Coccinia grandis*. C_{60} polyprenol 1 was isolated from the ethanolic extract of the leaves of *Coccinia grandis*. Golden Syrian hamsters were fed with a high fat diet (HFD) which resulted in levels of glucose and lipids. The hamsters were administered with polyprenol about 50 mg/kg of body weight, crude ethanolic extract about 500 mg/kg of body weight and fractions about 250 mg/kg of body weight. Blood was collected from the animals, and the levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C) and glucose (Gly) were determined. The ethanolic extract decreased the levels of TG, TL, and Gly. Chloroform fraction reduced lipid levels. *n*-butanol and water-soluble fractions reduced TG and TC. The compound polyprenol showed the maximum lipid lowing activity. It reduced TG levels by 42%, TC levels by 25%, Gly levels by 12% and increased HDL-C/TC ratio by 26% [24].

HPLC fingerprinting of the chloroform fraction containing polyprenol showed that polyprenol constitutes about 0.008% w/w of the total plant [24].

Administration of 200 mg/kg of an ethanolic extract of the leaves of the plant for 45 days in streptozotocin-induced diabetic rats resulted in reduction in blood glucose, lipids and palmitic, stearic, and oleic acid level and increased in linolenic and arachidonic acid and plasma insulin levels [25].

Anti-inflammatory, Analgesic and Antipyretic Activity: Anti-inflammatory, analgesic and anti-pyretic activity of the aqueous leaf extract was studied *in-viv*o using Wistar rats and Swiss mice. In the anti-inflammatory study, the aqueous extracts were administered at various doses pre and post the inducement of paw edema on the right hind paw using carrageenan. The anti-inflammatory activity was determined from the inhibition of the edema.

The study revealed that when the rats were pretreated with the extract, it blocked the increase in the volume of the edema at all doses with maximum anti-inflammatory activity at 50 mg/kg. Post-treatment of the extract resulted in a decrease in the volume of edema at all doses except 25 mg/kg. The 50 mg/kg dose produced the same effect as the standard. It has been postulated that the anti-inflammatory activity may be due to the release of histamines after administration with extract [6]. For the analgesic activity study, Tail flick model was used in mice, and the mice were administered with different doses of the extract. The study revealed that the extract showed significant analgesic activity at higher doses although not equivalent to morphine [6].

For the antipyretic study, 10 ml/kg of Brewer's yeast (20%) was administered followed by starvation to induce hyperpyrexia. The rats were then treated with the extract at various doses and the temperatures pre and post the administration of the extract were recorded. The results reveal the extract produced anti-pyretic activity at all doses but 200 and 300 mg/kg [6].

Antimicrobial Activity: Anti-microbial peptides are molecules which are capable of forming pores by attaching and inserting into the microbial cells. These molecules are produced by plants and animals [26]. Anti-microbial activity of a protease inhibitor (PI) obtained from *Coccinia grandis* was studied. The PI obtained had a specific activity of 377.9 U/mg and a protein content of 1.4 mg. The antimicrobial activity of the PI was studied with bacterial and fungal species - *Staphylococcus aureus, Bacillus subtilus, Klebsiella pneumonia, Escherichia coli, Proteus vulgaris, Cryptococcus neoformans, Aspergillus flavus, Candida albicans, Penicillium notatum,* and *Mucor indicus.*

The study revealed that *Klebsiella Pneumoniae* (MIC 0.01 mg/ml and MBC/MFC 0.5 mg/ml) and *Aspergillus flavus* (MIC 0.08 mg/ml and MBC/MFC 0.5mg/ml) were most sensitive and *Staphylococcus aureus* (MIC 1 mg/ml and MBC/MFC 1.2 mg/ml), *Bacillus subtilus* (MIC 1 mg/ml and MBC/MFC 1.25 mg/ml), *Candida albicans* (MIC 0.63 mg/ml and MBC/MFC 0.7 mg/ml) and *Cryptococcus neoformans* (MIC 0.63 mg/ml and MBC/MFC 1 mg/ml) were most resistant to the PI. An MIT assay of the PI on HeLa cells and their proliferation revealed that it was toxic to them with IC_{50} of 25μM. Cytotoxicity study with mammalian cells showed no hemolytic activity. But it was found that PI inhibits both trypsin and chymotrypsin. PI had a stoichiometry of 1:2 with trypsin. Testing with dithiothreitol (DTT) showed that purified PI showed strong antifungal activity and reduced PI lacked antifungal activity indicating that the disulfide bonds present in PI were responsible for the antifungal activity [27].

Antidiabetic Activity: Diabetes mellitus is a metabolic disease which affects 347 million worldwide according to the World Health Organisation (WHO). WHO predicts the disease o the 7th leading cause of death by the year 2013. This chronic disorder occurs due to the decreased production of insulin by the beta cells of the islets of Langerhans in the pancreas or inability of the body to utilize the insulin produced. Low levels of insulin stimulate gluconeogenesis and as a result hepatic glucose concentrations increase. Hence, body fat is used as a source of glucose, and this can result in hypertriglyceridemia and hyper-cholesterolemia [28]. Abnormal storage of triglycerides and lipolysis in the liver can result in insulin resistance which can manifest as type 2 diabetes [29].

In-vivo studies on female albino rats of Winstar strain were made to determine the effect of *Coccinia grandis* on the liver marker enzymes such as alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) in streptozotocin-induced diabetic rats. The levels of these enzymes were found to be the indicators of tissue damages in the liver. Diabetes was induced by nicotinamide (110 mg/kg body weight) and streptozotocin (65 mg/kg body weight). The diabetic-induced rats showed increased levels of the marker enzymes in the liver and serum.

Treatment of methanolic extract of leaves of *Coccinia grandis* revealed that the marker enzymes were restored to near normal levels [30]. ALT and AST are markers of hepatocyte injuries. Their levels indicate the amount of leakage of intracellular hepatic enzymes into the blood. ALP is a marker of biliary function and cholestasis [31]. It has been identified that the flavonoids present in the extracts of the plant were responsible for the restoration of the marker enzymes to the normal levels [30]. It has been suggested that extract contains a component which acts like insulin and helps in rectifying the elevated levels of the enzymes glucose-6 phosphatase and lactate dehydrogenase in glycolytic pathway and thereby restoring the lipoprotein lipase activity in the lipolytic pathway. This, in turn, was found to control the hyperglycemia of type 2 diabetes [32].

In-vivo studies were also made on female albino rats of Winstar strain to determine the effect of the leaf extract of *Coccinia grandis* on the lipid profile of streptozotocin-induced diabetic rats. Diabetes was induced by nicotinamide (110 mg/kg of body

weight) and streptozotocin (65 mg/kg of body weight). The lipid profiles of the diabetic rats showed increased levels of total cholesterol, triglycerides, phospholipids and free fatty acids in both serum and liver. Treatment with the methanolic extract of the plant restored their levels to near normal values [30].

Anti-hyperglycemic and anti-ureogenic effects of the leaf extracts of the plant were studied in streptozotocin-induced diabetic rats. An aqueous suspension of the residue was extracted with 60% ethanol and administered to the diabetic rats after 18hrs of fasting. Blood glucose level, free fatty acids level, and hepatic arginase activity were determined. Arginase in the liver is an important enzyme in the urea cycle. Administration of the extract lowered the blood glucose level in both normal and diabetic rats by 23% and 28% respectively. Blood-free fatty acid level was also lowered in both normal and diabetic rats by 15% and 25% respectively. The activity of hepatic arginase was also significantly lowered by 14% and 22% in the normal and diabetic animals respectively revealing the anti-ureogenic activity of the extract [33].

The mechanism by which the anti hypoglycemic effect of *C. grandis* occurs was studied by an *in - vivo* study on male albino rats. A 60% ethanolic extract of the leaves of this plant was fed to the control and streptozotocin (95 mg) induced diabetic rats after 18 h of fasting. The blood glucose level had decreased in both the control and diabetic enzyme after the administration of the extracts. Assays were performed for the liver enzymes glucose 6 phosphatases [24], fructose 1, 6 bisphosphatases [35] and glucose 6 phosphate dehydrogenase [36]. The leaf extract decreased the activities of both glucose 6 phosphatase and fructose 1, 6 bisphosphatase enzymes in both normal and diabetic rats. Also, the activity of glucose 6 phosphatase enzyme was increased in both the liver and red cells. Hence, it was concluded that the extract controls hyperglycemia by suppressing gluconeogenesis by the suppression of the enzymes glucose 6 phosphatase and fructose 1, 6 bisphosphatases and by accelerating glucose metabolism *via* pentose phosphate pathway by increasing the activity of glucose 6 phosphate dehydrogenase enzymes [37].

An *in-vivo* study of the ethanolic extract of leaves of *Coccinia grandis* on normal-fed and 48hr starved rats revealed that the extract depressed the blood glucose level by 21% in normal-fed and 24% in 48 h starved rats. It was also found that in the 48hr starved rats the activity of a glucose-6-phosphatase enzyme which had increased by 3 fold was lowered by 19% after administration of the extract. Also, the activity of hepatic arginase was reduced in 48hr starved and normal-fed animals. However, the extract did not affect the increased levels of enzymes such as alanine aminotransferase and aspartate aminotransferase in starved rats. The study concluded that the blood glucose lowering activity of the extract was due to its effect on glucose-6-phosphatase activity [38].

In -vivo study was done to determine the effect of the combined extracts of *Coccinia grandis* and *Abroma agusta* on fasting blood sugar level, glucose tolerance and lipid profile in streptozotocin-induced diabetic Wistar albino rats. The rats were treated with the aqueous extract of *Abroma agusta* roots and *Coccinia grandis* leaves.

Blood glucose serum cholesterol, HDL and LDL-cholesterol, triglycerol, Glycosylated hemoglobin, total proteins, albumin and creatinine in serum and lipid peroxidation products levels were determined. The combined aqueous extracts restored the fasting blood glucose level from 166.9 ± 25.4 mg/dl to 85.4 ± 2.3 mg/dl. The combined extract also lowered the 2 h glucose level from 269 ± 92.2 mg/dl to 75.2 ± 1.0 mg/dl. 8 weeks administration of the combined extract lowered the fasting blood glucose level from 160.5 ± 32.1 mg/dl to 81.0 ± 3.5 mg/dl. The individual extracts also reduced the blood glucose levels but not as much as the combined extract. The lipid profile of the diabetic rats showed elevated levels of total cholesterol (TC), LDL cholesterol (LDL-C) and triglycerides (TG). The combined aqueous extract lowered the TC, LDL-C and LDL-C/HDL-C levels to near normal levels. A reduction in TG levels was also observed. The diabetic animals also showed tropic ulcer on the tail, slight edema in the paws of the legs and appeared lethargic and sick.

The administration of the combined aqueous extract for 8 weeks cleared these symptoms and rats appeared normal. The glycosylated hemoglobin

levels were also restored to normal levels after the 8 week treatment. Total proteins, albumin and creatinine in serum levels, total body weight and kidney weight, were increased in diabetic animals. The treatment with the combined extract restored these parameters except the total protein to normal levels. Hemoglobin levels were also improved. The study concluded that the combined extract rectified the complications of diabetes [39].

An *in-vivo* study on streptozotocin-induced diabetic Wistar male albino rats were performed to determine the antihyperglycaemic effect of the aqueous methanoic extract of *Coccinia grandis* plant leaves, and combined aqueous methanolic extract of *Coccinia grandis* leaves and *Musa Paradisiaca* roots. The diabetic rats were administered with an 80 mg / 100 g body weight of the rats. The activities of enzymes glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, hexokinase in liver glycogen content in liver and skeletal muscle were estimated.

The combined extract of the two plants restored the body weight, water and food intake of diabetic animals which were lowered after streptozotocin administration. However, the individual extract of *Coccinia grandis* leaves only partially restored the above parameters. Streptozotocin administration significantly increased fasting blood glucose level which was completely restored to normal levels by the composite extract but only partially by the individual extract. Streptozotocin decreased the glycogen content in liver and muscle which was restored by the composite extract. The diabetic rats showed increased levels of glucose-6-phosphatase and reduced levels of glucose-6-phosphate dehydrogenase which were completely restored to normal levels by the composite extract but only partially by the individual extract. Serum insulin level which was lowered in diabetic rats was restored to normal levels by the composite extract. Streptozotocin administration also significantly increased glutamate oxalate transaminase and glutamate pyruvate transaminase levels in liver and kidney which were completely restored to normal levels by the composite extract but only partially by the individual extract [40].

The effect of the leaf extract on aortic collagen in streptozotocin (45 mg/kg body weight) induced diabetic rats. The rats were then treated with 200 mg/kg of the leaf extract for 45 days. The diabetic rats showed an increase in collagen content and degree of cross-linking as a result of an increase in shrinkage temperature and a decrease in pepsin solubility. Also, the administration of the streptozotocin increased the alpha/beta ratio of type I collagen and the type I/type III collagen ratio of pepsin-soluble collagen was significantly decreased in STZ diabetic rats. The treatment of extract resulted in a decrease in collagen content and the degree of cross-linking [41].

Administration of pectins extracted from the fruits of the plant in diabetic rats at 200 mg / 100 g concentration resulted in a reduction in blood glucose level and elevation of liver glycogen content. Treatment of pectins also increased the activity of hepatic glycogen synthase [3].

One of the secondary complications of diabetes is renal neuropathy. Male Wistar rats were administered with fruits and leaves of the plant individually. The increased blood glucose level in streptozotocin-induced diabetic animals was lowered by 34% and 22% after treatment with fruits and leaves respectively. In starch fed animals, the level of reduced sugars in urine was higher compared to those fed with fruits and leaves of the plant. Glomerular filtration, kidney index rate and albumin excretion were higher in starch fed animals compared to those fed with fruits and leaves of the plant. In diabetic animals, glycoconjugates, laminin and fibronectin contents in ECM were elevated. Administration of fruits and leaves of the plant prevented the elevation of ECM contents [2].

A clinical trial conducted in the general hospital and a private hospital in Matara showed that *Coccinia grandis* possess significant blood sugar lowering activity. The trial was performed with 122 healthy volunteers. Test meal consisted of 20 g of leaves of *Coccinia grandis* with 75 g of glucose in 100 ml of water. Increase in blood glucose level was lowered in experimental group postprandially 1 h and 2 h of glucose uptake [42].

A review of the traditional medical practice in the Marakh sect of the Garo community in Bangladesh showed *Coccinia grandis* is one of the plants used

in the treatment of diabetes. Only the root and leaves plant parts were used in the treatment. The juice of the crushed leaves and roots were taken daily [43].

Chemoprotective Effect Against Cyclo-phosphamide: Cyclophosphamide is an alkylating agent which is used in the treatment of cancer and some autoimmune diseases like lupus nephritis, rheumatoid arthritis, immune-mediated neuropathies and multiple sclerosis [44]. But the metabolites of this drug are toxic to normal cells. Swiss albino male rats and Wistar rats were used for the study of chemoprotective effect of hydroethanolic extract *Coccinia grandis* leaves. The animals were treated with leaf extracts of the plant (200, 400, and 600 mg/kg) along with cyclophosphamide (50 mg/kg). Acute oral toxicity studies were carried out on the animals [45].

Oxidative stress parameters such as lipid peroxidation, catalase, and glutathione content were determined from the mice brain. Cyclophosphamide elevated malondialdehyde level which measured lipid peroxidation and lowered catalase and glutathione levels when compared to control group. Pretreatment with *Coccinia indica* extract of concentration 400 and 600 mg/kg lowered malondialdehyde level and increased catalase and glutathione levels. However, when the extract was used alone and at a concentration of 200mg/kg, it failed to produce the above effects [45].

Serum levels of alkaline phosphatase (ALP), alkaline aminotransferase (ALT), and aspartate aminotransferase (AST) were determined from the rats. Cyclophosphamide administration increased ALP, ALT, and AST levels as compared to control group. Pretreatment with *Coccinia indica* extract of concentration 400 and 600 mg/kg lowered the levels the enzymes ALP, ALT and AST thus protecting the animals against liver damage. However, when the extract was used alone and at a concentration of 200 mg/kg, it failed to produce the above effects [45]. A mouse bone marrow micronucleus test was carried out, and PCEs to NCEs ratio and total 200 cells per animal were estimated. Cyclophosphamide administration resulted in micronuclei formation. Pretreatment with *Coccinia indica* extract at various doses lowered CP-induced micronuclei formation and 600 mg/kg body weight dose elevated P/N ratio, however, when the extract was used alone it failed to produce the above effects [45]. The chromosomal aberration assay was done to determine the chromosomal aberrations caused by cyclo-phosphamide. Cyclophosphamide administration significantly increased incidence chromosomal aberrations as compared to the control group. Pretreatment with *Coccinia indica* extract at all three concentration decreased the incidence of chromosomal aberrations [45].

The study concluded that since the leaf extract of this plant reduced oxidative stress and genotoxicity in the bone marrow caused by cyclophosphamide, the plant extract could be used along with the drug to mitigate its toxicity [45].

Anti-hepatotoxic Activity: *In-vivo* study on the leaf extracts on the albino rats was performed to test the anti-hepatotoxic activity of the plant. The leaves were extracted using water, light petroleum, chloroform, alcohol, benzene, and acetone. The rats were administered with 25% carbon tetrachloride to induce liver damage and treated with the extracts to study the anti-hepatotoxic activity of each extract. serum glutamic pyruvate transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), serum alkaline phosphatase (SALP) and serum bilirubin levels of the rats were determined. The carbon-tetrachloride treated rats exhibited elevated liver weight, SGOT, SGPT, SALP and serum bilirubin levels. The elevated liver weight was attributed to the accumulation of fat in the liver. The elevated transaminase enzyme levels indicated hepatocellular liver damage.

The studies revealed that the alcoholic extract was most effective in its anti-hepatotoxic effect and lowered the SGPT level from 210.0 ± 16.080 to 136.2 ± 10.458 KU, SGOT level from 210.0 ± 9.719 to 158.3 ± 10.035 KV, SALP level from 212.6 to 149.2 ± 8.471 KA and serum bilirubin level to 3.4 ± 0.031 mg %. The alcoholic extract also lowered the liver weight and pentobarbitone sleep time which were elevated after carbon tetrachloride treatment. The light petroleum extract showed a small anti-hepatotoxic effect while the other extracts failed to produce any significant effect [46].

Insecticidal Activity: The larvicidal activity of the extracts of the leaves of the plant on mosquitos has been extensively studied.

The effect of crude hexane, ethyl acetate, petroleum ether, acetone, and methanol extracts of the leaf on the early fourth instar larvae of *Aedes aegypti*, the vector for dengue virus and *Culex quinquefasciatus*, the vector for lymphatic filariasis was studied. The study revealed that the methanol extract showed the highest larval mortality against *Aedes aegypti* and *Culex quinquefasciatus* with LC_{50} = 309.46 ppm and LC_{50} = 377.69 ppm respectively. The other extracts also revealed larvicidal activities [47].

The effect of the essential oil extracted from the leaves of the plant on the egg hatching inhibition activity of mosquitoe vector *Anopheles stephensi* larvae at 1st, 2nd, 3rd and 4th instars was studied. The study was performed at 10, 20, 40, and 60 mg/l. The LC_{50}- LC_{90} values of the oil were determined after 24hrs of treatment. The IC_{50}- LC_{90} values reported were 54.3-140.3, 65.5-155.6, 86.8-180.7 and 95.3-192.6 for the first four larval instars respectively. The IC_{50} value for the egg hatching inhibition was determined as 16.5 mg/l [48].

The ovicidal activity of the leaf extract was studied against *Culex quinquefasciatus, Aedes aegypti* and *Anopheles stephensi.* The mosquitoes were treated with varying concentrations from 50-300 ppm. The methanol extract showed 100% mortality at 150 ppm for *Culex quinquefasciatus* and 200 ppm for *Aedes aegypti* and *Anopheles stephensi* after 48 h of treatment. The repellent efficacy of the extract was also studied at 1.0, 2.5 and 5.0 mg/cm^2. 100% mortality was achieved at 5 mg/cm^2 for 270 min against *Culex quinquefasciatus* and 210 min against *Aedes aegypti* and *Anopheles stephensi* [49]. These studies indicate that the leaf extract could be used for the control of mosquito vectors early in their life cycle.

CONCLUSION: The review overviews the major biochemical and medicinal applications studied on the plant. The studies have revealed that the leaf of the plant has exceptional medicinal properties compared to any other parts. The mechanism by which the plant exhibits these properties has not been widely investigated and has left with an opportunity to carry out advanced studies on the plant.

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