

Lantana camara (Verbenaceae)

English: Lantana, shrub verbena, verbena, wild sage, red sage, Spanish flag

French: Verbene, lantanier, thé de Gambie

Spanish: Cinco negritos **German:** Wandelröschen

African vernacular names:

Shona: Chiponiwe, sumba **Swahili:** Mutululu **Zulu:** Umphema, ubukhwezane

The plant

Lantana camara is a rugged evergreen shrub growing to 1.8 m high. Stems are square in profile, with small prickles. The leaves are arranged in opposite pairs. They are broadly oval, rough with short hairs, with finely toothed edges. When crushed they have a strong smell. Flowers are a mixture of cream, pink or orange numerous small rounded heads, often in two colours, yellow and red. Fruits are fleshy berries in clusters, green ripening to black. Lantana species are widely spread weeds in warm climates. Lantana camara is poisonous to stocks and humans. In Australia it is a weed of national significance and must continuously be suppressed and destroyed. Other Lantana species and hybrids are cultivated as ornamentals under hundred of cultivar names. Butterflies are said to love lantana flowers and the shrubs always attract hordes of them when in bloom.

Plant parts used

The whole plant, the leaves, the roots, the root bark

Constituents

Belonging to the plant family Verbenaceae *L. camara* bears various groups of chemical components, but all probes show a great variation in their contents according to their origin.

Mono- and sesquiterpenes

An early work on *L. camara* deals with the essential oils and their contents in the **leaves** (0.2 %) and in the **flowers** (0.6 %). Oil from Brazilian trees contains mainly bisabolene derivatives (65 %). The sesquiterpenes are curcumenes (ca.25 %) and safrole (1.8 %). The oil has a leathery and sweaty odour and is available commercially. Noticeable differences in composition were observed in essential oils from different locations. By subcritical extraction with CO₂ the yields increase up to 1.8 % (52).

Triterpenes

In a detailed study with structural elucidation lantadenes A and B were recognised as toxic substances of *L. camara* up to a content of 2.2 % of the dry weight in **leaves** and **stems**. Further related compounds were lantadene C, reduced lantadene A, lantadene D, lantanolic and lantic acid. In *Lantana camara* var. *aculeata* amounts of single lantadenes in **young** and **mature leaves** are (mg/100dry weight, measured by HPLC):

Lantadene A: 491.5 and 805.9, lantadene B: 347.0 and 522.3, lantadene C: 191.3 and 424.8, lantadene D: 49.7 and 177.4 (40).

In the **roots** of toxic and nontoxic *Lantana* species 2 % of (non-toxic) oleanolic acid was found (32).

The **methanolic extract** of *L. camara* presented a suite of five euphane triterpene lactones in trace quantities (0.00002-0.0002 %). They all are potent inhibitors of human thrombin. The activity is comparable to that of hirudine (IC₅₀ 12 nM), a dried and refined extract of leeches (*Hirudo medicinalis*) (40).

Iridoid glycosides

The white, pink or red flowering taxa produce significant quantities of theveside, present as sodium salt (40,44). The **stems** contained 4.3 - 5.8 %, the **leaves** 1.3 – 3.6 % in spring and summer, declining significantly to 0.6 % for both **stems** and **leaves** in autumn.

Also from the **roots** geniposide, the biosynthetic precursor of theveside has been isolated together with 8-epiloganin, lamiridoside and shanzide methylester (32,33).

Flavonoids

The acetone wash of the **leaves** from *L. camara* afforded multiple methoxylated derivatives of quercetin (3-methoxy-, 3,7-dimethoxy-, 3,7,4'-trimethoxy-) and camaroside. Hispudoline was isolated from the **stems** (52). From a methanol extract of **dried leaves** verbascoside, an inhibitor of protein kinase C was isolated. In Rwanda the methanol extract of **dried leaves** produced a polymethoxylated flavone, named umuhengerin according the indigenous name. It was antimicrobially active (13,21).

Essential oil

The **leaves** contain an oil rich of sesquiterpenes (28).

Using GC technique the foliar emission of volatile organic compounds was measured. From *L. camara* the emission values were 0.1 - 87 µg per dry leaf and per 1 hour with a marked diurnal and seasonal variation (31). **Aerial parts** from *L. camara* collected at the Calicut University Campus brought a yield of 0.23 % of the shade-dried material. Main constituents measured by GC were β-caryophyllene 34.79 %, geranyl acetate 22.12 %, terpinyl acetate 5.84 %, bornylacetate 4.13 %, and D-limonene 2.27 %. The **oil** showed antibacterial and antifungal activity (14).

Miscellaneous compounds

From the stems of *L. camera* the common plant steroids β-sitosterol, campesterol, stigmasterol, β-sitosterolglucoside have been isolated (20). Five oligosaccharides (ajugose, stachyose, verbascose, verbascotetraose, lantanose) could be found and from the **roots** verbascoside, isoverbascoside, martynoside, D-rhamnosylverbascoside and some other phenylethanoids. The hexane extract from the **roots** of Shri Lanka *L. camara* produced the quinone diodantunezone (52).

Traditional uses

In many parts of the world the plant has been used to treat a wide variety of disorders, in the folk medicine especially for tumours and cancer. A tea prepared from the leaves and flowers is taken against fever, influenza and stomach ache. With other preparations of the plant fever, cold, rheumatism, asthma and high blood pressure are treated. In Central and South America the leaves were made into a poultice to treat sores, chicken pox and measles. In Ghana infusions of the whole plant are used against bronchitis. The powdered root in milk was given to children for stomach ache.

In Asian countries leaves are used for cuts, rheumatism, ulcers, and as a vermifuge. Decoctions are applied externally against leprosy and scabies (52).

In India the leaves of the plant are boiled for tea and the decoction is a remedy against cough. The decoction of the whole plant is given as treatment against tetanus,

rheumatism, malaria and ataxia of abdominal viscera. It is used as a lotion for wounds, too. Pounded leaves are applied to cuts, ulcers and swellings (47).

Results of experimental studies

Inhibition of human thrombin

Methanolic extracts from the leaves of *L. camara* inhibited human thrombin. An assay, in which thrombin activity is measured as a function of clot formation from fibrinogen was used to guide the fractionation and purification of active components. Five active substances were found, all being euphane triterpenes with a structure of 5.5-transfused cyclic lactones. The inhibitors bind tightly at the active site of alpha thrombin and alpha chymotrypsin. It seems covalently attached, suggesting an acyl-enzyme formation by reaction of the active site Ser 195 with the translactone carbonyl. The inhibitory carbonyl occupies the oxyanion hole. The observed lack of turnover is due to exclusion of water for deacylation (30,49).

Antibacterial, antifungal and antiviral activity

In Calcutta, India the root bark extracts of *L. camara* were tested by the agar well diffusion method. The water extract brought a negative result, the chloroform and methanol extracts were positive towards Gram positive bacteria and the Gram negative *Pseudomonas aeruginosa* (11).

The essential oil containing β -caryophyllene, geranyl acetate, terpinyl acetate, bornyl acetate and limonene remarkably inhibited the growth of many tested bacteria and fungi. *P.aeruginosa*, *A.niger*, *F.solani*, *C.albicans* appeared as the most sensitive ones (14). Umuhengerin, the polymethoxylated flavone, isolated from the methanol extract of dried leaves exhibited the following antibacterial and antifungal properties in vitro (MIC $\mu\text{g/ml}$): *S.aureus* 20, *S.typhimurium* 5, *Candida tropicalis* 20, *A.niger* 200, *A.fumigatus* 200, *Trichophyton mentagrophytes* 50, *Microsporum canis* 50. In all other test organisms the values were higher than 200. There was an antiviral activity, too (13).

In a village near Puebla, Mexico hexane, chloroform and methanol extracts were tested against 14 bacterial strains causing the most common gastrointestinal diseases in Mexican population. All hexane extracts showed antibacterial activity against Gram positive and Gram negative bacteria. There is a correlation suggested between the antibacterial activity and the plants used in the folk medicine (22).

In Tanzania the rootbark extract of *L. camara* showed an IC₅₀ among 5 – 10 $\mu\text{g/ml}$ measured in an in vitro antimalaria test with *Plasmodium falciparum* (48).

Different lantadenes show potent inhibitory effects on Epstein-Barr virus in Raji cells. There are differences in activity depending from the molecular structures, like methyl- or dihydro groups (23).

Toxicity

Activity in mice

In the mice intestine the *L. camara* methanolic extract shows an antimotility effect. Intestinal motility was measured by charcoal meal test. The gastrointestinal transit rate was expressed as the percentage of the distance traversed by the charcoal divided by the total length of the small intestine. The intestinal transit with methanolic extract of *L. camara* at a dose of 500 mg/kg was 26.46 %. The higher dose of 1 g/kg completely inhibited the transit of charcoal in normal mice. Plant extracts of 125 and 250 mg/kg administered intraperitoneally reduced significantly the faecal output compared with castor oil treated mice. At higher doses of 500 and 1000 mg/kg the output was stopped totally. The authors conclude a possible utility in secretory and functional diarrhoea (39).

Activity in rats

Dried alcoholic extract of fresh *L. camara* leaves, orally administered to **albino rats** of both sexes, induced photo dermatitis during exposure to clear sunlight for 1 h. Its severity was related to the dose of the extract and was maximal in rats exposed to sunlight from 4 to 14 hr after feeding and gradually declined over 40 h. Only light of wave lengths about 540 to 570 m μ was effective. The extract did not raise serum bilirubin, SGOT, SGPT or caused liver injury, as assessed by light microscopy. In a control study, the alcoholic extract of edible spinach leaves was only 1/3 in activity, and its effect lasted for less than 20 h. Alcoholic and chloroform extracts impaired the excretion of BSP by liver, proportional to the doses and also maximal at 5.5 h declining thereafter over 40 h (3). In rats the once daily administration *L. camara* leave juice at different doses (60, 300, 600, 1500 mg/kg/day) altered various haematological and biochemical parameters. All four doses increased the relative weights of adrenals significantly and the blood urea nitrogen was raised at the doses of 600 and 1500 mg/kg. With doses of 60, 600 and 1500 mg/kg total proteins, globulins, absolute lymphocyte counts and the percent lymphocyte count decreased significantly. A significant hypoglycaemic effect was observed with 1500 mg/kg only. Rats treated with 1500 mg/kg dose did not exhibit any increase in alanine or aspartate transferase, nor altered the relative kidney or liver weights. In another set of experiments with rats once daily oral administration of 1500 mg/kg for 14 days significantly inhibited the granulomatous tissue formation. This effect was comparable to that of cyclophosphamide (10 mg/kg/day) (19).

In rats the hydroalcoholic extract interfered with daily sperm production and sperm morphology in a dose-dependent manner, but did not influence the overall weight, or the weights of other internal organs (15).

Activity in guinea pigs

Lantana intoxication in guinea pigs causes a lot of effects, like decreases in liver dry weight, protein and DNA content, increases of liver lipids, biochemical changes in liver mitochondria, lysosomes, microsomes and plasma membranes. There were significant alterations in blood constituents, like increased bilirubin and haemoglobin content, urea, erythrocyte and leukocyte numbers. Alterations in blood plasma enzyme activities were accompanied by hepatic injury and cholestasis (42).

A toxin fraction from the red variety of *L. camara* orally administered to male and female guinea pigs caused icterus and photosensitising within 48 hours. All the affected animals had hepatomegaly and increases in bilirubin. The animals of both sexes had marked increases in acid phosphatase activity (42).

Activity in sheep and goats

The species *L. camara* is toxic to grazing animals, which after ingestion of leaves develop photo sensibility, hepatotoxicity and haematological changes.

In New Zealand there is a first report about a field case of *L. camara* poisoning. Two sheep were given dried leaf powder 6 and 12 mg/kg body weight. From this treatment marked cholestatic hepatopathy and renal tubular disease resulted (6).

In sheep ingestion of leaves raised the coagulation and the prothrombin time and lowered the blood sedimentation rates, the total plasma protein and fibrinogen values, furthermore. These toxic effects were attributed to the pentacyclic triterpenes, especially to the lantadenes. The symptoms could be reproduced by administering of purified lantadene A (30).

The toxic lantana substances are absorbed by all parts of the intestine, but the absorption from the small intestine was the most important. Bile was not essential for the absorption. Experiments indicated that the Lantana toxins are transported to the liver, mainly in the portal blood (35). Sheep injected intravenously the triterpene acid lantadene A in a single dose of 1-3 mg/kg showed mild hepatocellular injury characterised by transient rises in

serum enzymes, with or without hyperbilirubinaemia. Higher doses resulted in hepatic necrosis. Lower doses given repeatedly over several days caused a choleostatic syndrome. This disease model provides evidence that lantadene A is toxic itself and does not require an active metabolism in the alimentary tract of the animal (36).

Five sheep intoxicated with powdered *L. camara* leaves at the rate of 200 mg/kg daily for 110 days indicated significant reduction of both cellular and humoral immunity (18).

A Boer goat kid being part of a flock of goats was introduced from the Kalahari Thornveld, where the plant does not occur, to an area where the plant grows abundantly. At the necropsy the animal was severely icteric, dehydrated and constipated, with hepatitis, distension of the gall bladder and nephrosis, but without skin lesions. Histopathological findings of the liver confirmed moderate hepatitis with a single cell necrosis and a bile stasis (24).

Activity in cattle

From South Africa a short report was given of an acute *Lantana camara* poisoning in cattle, in which 10 of 91 animals died. The affected animals became icteric and voided soft, black faeces. The macro- and microscopical tests showed changes in livers and kidneys, comparable with those of *L. camara* poisoning. These changes were similar in two steers that developed typical signs after being dosed with fresh *L. camara* collected in the toxic camp. The pathological changes were elevated serum urea and creatinine concentrations (17).

Activity in kangaroos

Three red kangaroos (*Megaleira rufus*), an adult male, an adult female, and a yearling were fed coastal Bermuda hay that contained the toxic plant *L. camara*. The adult female died. The adult male exhibited signs of anorexia, lethargy and jaundice. That and the yearling developed exudative dermatitis of the ear margins, eyelids, muzzle and scrotum and the opacity of the corneas. The adult male had a leucocytosis, anemia, bilirubinemia, bilirubinuria, hyperproteinemia, and elevated alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, and elevated bile acid serum levels. The post-mortem examination of the adult male revealed jaundice and a swollen liver, mottled, and pale yellow to reddish yellow. The gall bladder was markedly distended. The yearling survived and was treated with fluids and antibiotics. All these findings supported the diagnosis of secondary photosensitizing and hepatotoxicity (25).

Activity in insects and worms

In a phytochemical screening different extracts of *L. camara* leaves were tested against termite workers (*Microcerotermes besoni*). Methanol and chloroform extracts were the most active ones showing the highest mortality of termites. On the basis of the LD 50 the effect of 5 % chloroform extract was the most interesting in comparison with 0.5 % chlorpyrifos solution. The results may provide a support to the use of the plant in the termite control (47).

The larvicidal effect of *L. camara* ssp. *flava* leaves and flowers, cultivated in Egypt, was tested against the maturation of *Musca domestica* larvae in the laboratory at different concentrations (0.0125 %, 0.025 %, 0.05 %, 0.1 %, and 0.2 %). The mortality rate ranged up to 80-100 %. The fecundity of emerged larvae was given at a concentration of 0.0125 %. The authors recommend these essential oils in the controlling of the *Musca domestica* larvae (1).

In Cameroon essential oil extracts from *L. camara* leaves were tested for the efficacy in the mortality of the maize grain weevil *Sitophilus zeamais* (Coleoptera, Curculionidae). Significant insect mortality was obtained with an LD 50 of essential oil on maize grains. Authors recommend these oils for insect control in stored products (12).

In Lucknow, India the rodent model with *Mastomys coucha* was used to test the antifilarial activity of *L. camara* stem extracts. The crude extract of 1 g/kg given orally

for 5 days, killed 43.05 % of the adult *Brugia malayi* parasites, and sterilized 76 % of surviving female worms.

A 34 % adulticidal activity along with sterilization of 66 % of the female worms could be demonstrated with the chloroform fraction. Furthermore the extract was effective against the subcutaneous rodent filariid *Acanthocheilonema vitae*, maintained in *Mastomys coucha*. The extract exerted strong microfilaricidal (95.04 %) and sterilization (66.6 %) efficacy with mild macrofilaricidal action (29).

Four constituents of *L. camara*, lantanoside, lantanone, linaroside, camaric acid were tested against the root knot nematode *Meloidogyne incognita*. There was a high mortality effect up to 100 % at

1 % concentration. The results were comparable with the conventional nematocide furadan (8).

Lantana flower extract in coconut oil provided protection against the bites of *Aedes* mosquitoes. The mean protection time was 1.9 h, up to 4 h with 50 % protection. No adverse effects in the human volunteers were observed till up to 3 months after the application (16).

In Africa Tsetse flies, being implicated in sleeping sickness epidemics have taken cover in plantations under the invasive bushes of *L. camara* that has invaded large areas of the Tsetse fly belt of Africa. In a wind tunnel experiment both leaves and extracts of volatile substances from the leaves of *L. camara* attracted three tsetse subspecies (*Glossina fuscipes fuscipes* (riverine), *G. brevipalpis* (sylvatica), *G. pallidipes* (savannah). In GC analysis 1-octen-3-ol and β -caryophyllene were the major attractant substances (46).

Activity in plants

Extracts of *L. camara* exhibit a phytotoxic potential against other plants, especially against the germination of spores of the liverwort *Asterella angusta*. The leaf extract brought the highest effect of inhibition (26).

In China the extract of Lantana leaves suppressed the emergence of the leaf buds of water hyacinth (*Eichhornia crassipes*) and caused the decay of the leaves by foliar spraying. In the tissue the level of H_2O_2 was overproduced. This could kill the leaf cells due to oxidative stress, because catalase of the leaves is inhibited by the lantana extract (51).

Results of clinical studies

There is only a short older information about an intoxication of **children** who ate fruits of *L. camara*. After an acute syndrome they must be treated by a physician and they recovered (50).

Therapeutic results

For cattle and sheep

Activated charcoal should be given orally to sheep for protection from toxic *L. camara*.

If 500 g charcoal administered to sheep in 4 L of electrolyte solution, given orally 6 days after the onset of lantana poisoning and then 4 L of electrolyte solution given the next day revealed recovery. The mortality was significantly higher in intoxicated sheep given only the electrolyte solution comparable in untreated sheep.

Six cows with naturally occurring Lantana poisoning were treated with 2 - 2.5 kg of charcoal in 20-30 L of electrolyte solution given by a stomach tube. All the animals recovered. These treatments of intoxicated sheep and cattle are recommended, therefore (34,35).

As a cheaper alternative, therapy against poisoning in cattle bentonite (5g/kg) is recommended, too (27).

A further way for preventing Lantana poisoning is vaccination. The toxic lantadenes A and B, isolated from *L. camara* were conjugated to bovine serum albumen or haemocyanin. The conjugates were emulsified with complete Freund's adjuvant and injected in sheep and cattle. The vaccinated animals produced antibodies against the toxic compounds. Cholestasis was less severe in vaccinated than in non-vaccinated sheep, challenged with a toxic dose of lantana. These results indicate a mild protective effect of vaccination against the hepatotoxicity of Lantana toxins (45).

Lantana camara ointment

In the Republic of Benin an ointment prepared with an ethanolic extract of *L. camara* leaves was used as a topical treatment for chronic crusty or acute lesions of dermatophilosis. The ointment induced healing of the disease in nine infected animals without recurrence. The ointment, when applied once a day for 8 - 15 days, provoked the falling of the crusts after 3 - 4 days of treatment. Hair grows on the treated areas. The wounds heal without scarring within 3 - 4 weeks after the procedure. The healed animals became free of dermatophilosis without recurrence for more than 3 years and stayed in a good health. This is opposed to the use of oxytetracycline, long acting terramycine or procaine-penicillin, antibiotics commonly used parenterally for the treatment of dermatophilosis, which could not prevent the recurrence of the disease (4).

Evaluation

Lantadene A, lantadene B and lantadene C, -comparable to reduced lantadene A-, and existing in two forms I and II, are very toxic substances. People speak about the typical lantadene toxicity, therefore. This takes a heavy toll of livestock year after year. There is no good antidote available besides of charcoal or bentonite tested for cattle.

There are many references about poisoning in guinea pigs, rats, sheep, cattle, buffalos and of a child.

The toxicity is manifested in three phases:

- Release and absorption of the toxins in the gastrointestinal tract with an accompanying photodermatitis
- hepatic phase with cholestasis and altered biochemical parameters and
- the tissue phase with cell injury, the accumulation of bilirubin and a final hepatotoxicity.

Therapeutic measures must try to arrest one or more of these phases (41).

The other compounds of the plant like iridoid glycosides and flavonoids cannot heal the damage caused by the lantadenes. On the contrary flavonoids can raise the permeability of cell walls and the toxic substances can enter better. Oleanolic acid, which could be helpful in cells, is found only in roots not in the aerial parts of the plant.

The only good report about *L. camara* is the topical treatment of the skin disease for cattle by an ointment made with alcoholic extract of the aerial parts of *L. camara*. But the observation of the treated animals was only for 3 years. No necroscopy was done, finally. Late effects of the toxic plant cannot be excluded.

There is a report of repellent activity by a flower extract in coconut oil for *Aedes* flies. This application can only be recommended for short times, because extracts of the plant are effective in the skin of animals. The suggestion to use extracts or essential oils for insect control in stored products cannot be agreed, because the grains could absorb the compounds of the plant and these could be brought into human bodies and cause damages there.

Because of its high toxicity all internal uses of *Lantana camara* for men must be excluded!

Lantana camara

Application for men internally	---
Short time application for the skin of men	---
Application for skin lesions in cattle	**
Insect control	**

References Lantana

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