

Terminalia chebula (Combretaceae)

English: Almond tree, Tropical almond **French:** Badanier
Portuguese (Brazil): Castanhola **German:** Seemandelbaum
Indian (Rangoon): Ba-dan **Chinese:** He zi

Names of the fruit:

English: Myrobalan, black myrobalan, black chebulic, chebulic myrobalan, medicinal Terminalia fruit **French:** Myrobalan indien

Chin.: Hezi **Tibet:** Harra, harro

Hindi: Har **Tamil:** Kadah kai **German:** Myrobalane

African vernacular names of the fruit:

Fulde: Wake **Hausa:** Banshe

Pharm. definition: Fructus Chebulae (Chin P IX)

The plant

The plants are trees, very large, up to 30 m high, rarely shrubs; the branches often in tiers. They grow in sunny forests and thickets, and often they are also cultivated on village commons.

Leaves are alternate or subopposite, the leaf blades are elliptic, 7 - 18 x 4.4 - 10 cm. Both surfaces are glabrous or adpressed villous, at least when young. The base is obtuse-rounded or cuneate, the apex mucronate, the lateral veins appear in 6 - 12 pairs. The inflorescences stand axillary or terminal with numerous flowers. The flowers smell slightly fragrant; the calyx tube is distally cupular, 2.5 - 3.5 mm long with five lobes, mucronate to aristate.

The fruits seem ovoid or ellipsoid, five ridged, becoming deeply wrinkled when dry, blackish-brown when ripe, 2 - 4.5 x 1.2 x 2.5 mm tall. The flowers appear May-June, the fruits July-December.

Plant parts used

The fruits, the bark, the leaves

Traditional uses

In India the fruits are available in markets. They are used as a mild laxative and as an astringent against wounds and abscesses. In the dental care dried powder is applied against stomatitis and against ulcers of the gum. The plant is used as an antidote against bites of snakes, finally.

In India and Southeast Asia the fruit is used as a popular folk medicine for antitussive, diuretic, homeostatic, laxative and cardiogenic treatments.

In China the drug is a remedy against a sore throat and cough, against long during diarrhoea connected with a prolapsed rectum.

In Tibet the dried fruit is used against ulcers and dysentery.

Constituents

In the **fruits**, in the **bark**, and in the **leaves** the characteristic compounds are tannins, triterpenes, saponines and mucous substances.

The tannins are esters of different phenol-carbonic acids. Chebulinic acid is a dimer, tergallic acid a trimere, and terchebulinic acid a tetramere of the gallic acid being connected with glucose. After hydrolysis the free monomers can be analysed. The total phenolic contents of *T. arjuna*, *T. bellerica*, *T. chebula* and *T. muelleri* leaves, bark and fruits are 72.0 - 167.2 mg/g (5).

In the **leaves** caffeic acid, ferulic acid and sinapic acid are absent.

In the **heartwood and in the bark** polyhydroxylated triterpenic acids can be found. (48).

In the **fruits** of *T. chebula* three hydrolyzable tannins chebulinic acid, chebulagic acid and 1, 3, 6-tri-O-galloyl- β -D-glucose could be determined by RP-HPLC. The contents of the first two substances were interrelated with the varieties. They seem to be suitable for evaluation for the quality assessment of the drug and for the differentiation of the varieties (8,17).

Further hydrolysable tannins were castalagin, ellagic acid, flavogallonic acid, punilagin, terchebulin (38).

In the **fruits** of *T. chebula* fourteen tannins could be separated by HPLC, combined with Capillary Electrophoresis (18).

The **kernels** of the fruits contain 49 % fatty oil. Its fatty acid composition is quite similar to that of conventional oils. Palmitic acid, linolic acid and oleic acid are the main constituents. Their yield can be raised with supercritical CO₂ extraction (46).

In Brazil the fruits of *T. catappa*, named castanhola, are included in the national biodiesel program (9). In New Delhi, India the fruits of *T. chebula* are used for the production of tannase (35).

Results of experimental studies

Antibacterial activity

The ethanolic extracts of *T. chebula* and *T. bellerica* fruits were tested for its activity against methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* strains from clinical isolates.

Both extracts showed a broad spectrum of antibacterial activity with an inhibition zone size of 11 to 27 mm, against all the test bacteria. There was a synergistic interaction of the crude extracts with tetracycline, too. TLC analysis indicated phenols and flavonoids as major active compounds (4). In a similar investigation gallic acid and its ethyl ester could be verified on the basis of spectroscopic evidence (33).

Ether, alcohol and water extracts of *T. chebula* were tested against *Helicobacter pylori* in an agar diffusion test. The water extract had a MIC value of 125 mg/L and a MBC of 150 mg/L. Plant powder, incorporated in agar gave higher MIC and MBC values (150 and 175 mg/l).

The water extract at a concentration of 1 -2.5 mg/L inhibited the activity of urease (25).

The aqueous extract of *T. chebula* strongly inhibited the growth, the sucrose induced adherence and the glucan-induced aggregation of *Streptococcus mutans*.

Mouth rinsing with a 10 % solution of the extract significantly reduced the total bacterial counts and the total streptococcal counts in the saliva samples. It successfully inhibited glycolysis of salivary bacteria for up to 90 min after rinsing (16).

Antiviral activity

Hot water extracts of *T. chebula* were examined for anticytomegalovirus activity in vitro and in vivo. In vitro they inhibited the replication of human cytomegalovirus.

In vivo they were tested in an infection model on immune suppressed mice. The herbal extract was orally administered to the mice treated with 50 mg/kg cyclosporine for one day before the intraperitoneal infection. The efficacy was evaluated by the reduction of the virus yield in the lung. The *T. chebula* extract significantly suppressed the virus yields in the lungs of the treated mice compared with the water treated animals. The authors believe that the water extracts can be beneficial for the prophylaxis from cytomegalovirus in immunocompromised patients (45).

The extract of *T. chebula* showed a strong anti-HSV-1 activity in combination with acyclovir. With doses, corresponding to the human use it limited the development of skin lesions and prolonged the mean survival times of infected mice compared with both acyclovir and with the mice treated alone with the herbal extract ($p < 0.01$ and $p < 0.05$). It reduced virus yields in the skin and brain stronger than acyclovir alone. It exhibited a stronger anti-HSV-1 activity in the brains than in the skin, in contrast to acyclovir treatment alone. The combination was not toxic to mice.

Antimutagenic activity

Tannin fractions and gallic acid from the dried pulp of *T. chebula* were evaluated for their antimutagenic potential. They all were highly significant active against S9-dependent mutagen 2AF. The effect corresponds with the nature of the fractions; the monomeric gallic acid was the least effective (20).

The water extract, and not the chloroform extract of dried *T. chebula* fruits inhibited the direct acting mutagens sodium azide and 4-nitro-o-phenyldiamine in the strains TA100, TA1535, TA97a, TA98 of *Salmonella typhi murium* and S9-dependent mutagen 2-aminofluoren in TA97, TA98 and TA100 strains. Autoclaving the water extract reduced the effect not significantly (14).

In the VITOTOX Test for detection of DNA damages in prokaryotic and eucaryotic cells extracts from *T. chebula* were not genotoxic. This result is consistent with another Ames Test. But in the COMET assay the extracts increased DNA damages with a content above 500 ppm (2).

Anticancer activity

In several human malignant cell lines a 70 % methanolic extract of *T. chebula* fruits decreased the cell viability, inhibited the cell proliferation and induced the cell death in a dose-dependent manner. In lower concentrations some apoptosis was induced, but at higher concentrations necrosis was the major mechanism of the cell death.

The following IC₅₀ values could be revealed:

Chebulinic acid: 53.2 ± 0.16 μ M, tannic acid 59.0 ± 0.19 μ M, ellagic acid 78.5 ± 0.24 μ M, respectively (32).

In an Indian investigation program for cytotoxic agents from the bark of *T. arjuna* four novel cytotoxic agents (arjunic acid, arjungenin, arjunetin and arjunoglucoside 1) were isolated. Arjunic acid was significantly active against several human cancer cell lines. Palmitoyl arjunic acid, a semi-synthetic ester showed two times more activity against the liver cancer cell lines HepG-2 and WRL-68 (34)

Antioxidant and cytoprotective effects

The aqueous extract of *T. chebula* fruits was tested for its cytoprotective activity.

In cultured rat primary hepatocytes and rat livers the extract reversed an oxidative injury; induced by tert-butyl hydro peroxide and lactate dehydrogenase leakage significantly.

The in vivo pre-treatment with 500 or 1000 mg 5 day before; a single dose of 0.01 mM/kg i.p. significantly lowered the serum levels of the hepatic enzyme markers aspartate aminotransferase and alanine transferase and reduced the indicators of oxidative stress in the liver, such as glutathione disulfide content and lipid peroxidation in a dose dependent manner. The histopathological examination of the rat livers showed a reduction of the liver lesions and repaired necrosis. The authors speculate that the extract has the potential to prevent the oxidative damages in living systems (23).

The aqueous extract of *T. chebula* was tested for its antioxidant activity after gamma radiation in rat liver microsomes and mitochondria. It inhibits xanthine oxidase activity. It is an excellent scavenger of DPPH radicals. A HPLC analysis showed the presence of ascorbate, gallic acid and ellagic acid. The extract seems to be able to protect cell organelles from radio-induced damages (28).

The water extract of *T. chebula* fruits was tested for its radio protective ability, therefore. The free radical neutralizing ability was comparable to that of ascorbate (100 μ M) 93.5 % and gallic acid (100 μ M) 91.5 %, respectively. It protected the plasmid DNA pBR322 from the radiation-induced strand breaks.

The administration of 80 mg/kg i.p. prior to whole body irradiation of mice (4 Gray) reduced the peroxidation of membrane lipids in the mice liver from radiation-induced DNA damages. Human lymphocytes also were protected from DNA damages exposed in vitro by 2 Gray (11). In preparations of liver microsomes, of mitochondria and of red blood cells from Wistar rats, arjunic acid revealed as a strong antioxidant and as a free radical scavenger more potent than ascorbic acid (42).

“Triphala”, a combination of equal proportion of the plants *T. chebula*, *T. bellerica* and *Emblca officinalis* is extensively used in the Indian medicinal system.

The extracts alone, or combined, were tested for their inhibition activity of lipid peroxidation and scavenging hydroxyl and superoxide radicals in vitro. The 50 % inhibition of lipid peroxidation, induced with Fe^{2+} /ascorbate were 85.5, 27, 74, and 69 μ g/mL. The concentrations needed for inhibition of the hydroxyl radical scavenging were 165, 71, 155.5, and 12.5 μ g/mL.

The oral administration of the extracts (100 mg/kg) reduced the blood sugar level in normal and alloxan (120 mg/kg) diabetic rats significantly within 4 h. A continued daily administration sustained the effect (31).

Antiplasmodial extracts of *T. avicennoides* were analysed by HPLC and nuclear magnetic resonance methods. That revealed the presence of known hydrolysable tannins and of some related compounds like castalagin, ellagic acid, flavogallonic acid, punicalagin and terchebulin.

Toxicity assays with mouse fibroblasts showed IC50 values \geq 1500 μ g/mL. The integrity of human erythrocyte membranes was not affected at these IC50 values (38).

Pharmacological effects

Activity against anaphylactic shock

The effect of the water soluble fraction of a portioned methanol extract from *T. chebula* fruit was tested in an anaphylactic shock model in vivo. The results were tested by the death of Spague-Dawley rats (200-300 g) and ICR mice (20-30 g).

Doses of 0.01-1.0 g/kg of the extract, administered 1 h before the experiment inhibited the anaphylactic shock with 100 %. Administration 5-10 min after decreased the mortality dose-dependently. Oral application reduced the cutaneous anaphylaxis with 63.5 \pm 7.8 %. From the rat mast cells the release of histamine was hindered in a dose dependent manner (37).

Antispasmodic activity

The crude extract of *T. bellerica* fruits caused the relaxation of spontaneous contractions in the isolated rabbit jejunum at a concentration of 0.1 - 3.0 mg/mL. In the guinea pig ileum it produced a rightward parallel shift of acetylcholine curves. On rodents it protected from castor oil-induced diarrhoea and carbachol-mediated bronchoconstriction.

The authors conclude that the extract possesses a combination of anticholinergic and Ca^{2+} - antagonistic effects which may explain its folkloristic use (13).

Gastrointestinal activity

In the Ayurvedic medicine *T. chebula* is a commonly used agent for improving gastrointestinal motility. With Charles Foster rats gastric emptying was measured.

Rats given *T. chebula* (100 mg/kg/day) increased their gastric emptying with 86.57 \pm 6.65 % ($p < 0.01$) compared with normal rats (51.6 \pm 7.79 %). From this study *T. chebula* can serve as an alternative to prokinetic drugs available today (43).

Indomethacin-induced stomach ulcerations of rats were healed by an ethanolic extracts of *T. bellerica* in an accelerated mode compared with the autohealing and with that of misoprostol (6).

The antidiarrhoeal effects of aqueous root extract from *T. avicennoideis* were studied on the isolated rabbit jejunum for gastrointestinal motility, and for castor oil-induced diarrhoea in mice.

The extract inhibited the spontaneous pendular movement of the isolated rabbit jejunum and attenuated the acetylcholine induced contractions. The extract (100, 200, 400 mg/kg) also caused a dose-dependent decrease of the gastrointestinal transit and markedly protected the mice against castor oil-induced diarrhoea. The intraperitoneal LD50 value of mice was 871.4 - 917.4 mg/kg intraperitoneally.

The phytochemical screening revealed the presence of tannins, saponins and flavonoids (1).

Immunosuppressive effects

Gallic acid and chebulagic acid, isolated from fruits of *T. chebula* (the so called kashi) inhibited the killing activity of CD8 and CTL clones at IC50 values of 30 and 50 μ M, respectively. Granule exocytose in response to anti-CD3 stimulation was also blocked by both substances at the equivalent concentrations (15).

Chebulagic acid from immature seeds of *T. chebula* was found as a potent suppressor of the T cell activity.

In DBA/1J mice arthritis was induced by subcutaneous immunization with bovine type II collagen on days 0 and 21. Chebulagic acid was administered intraperitoneally for 3 weeks, either as prophylaxis (10 or 20 mg/kg) before disease onset or as a therapy (20mg/kg) after disease onset. In both the prophylactic and either in the therapeutic model, all clinical scores, like serum levels of total and anticollagen IgG and levels of interleukin-10 and interleukin-6 were reduced.

The serum levels of the transforming growth factor beta were markedly elevated. The number of the granulocytes was reduced, but the proportion of CD4+, CD25+ T cells was greater in the knee joints of the chebulagic acid-treated mice.

Authors conclude that chebulagic acid significantly suppressed the onset and progression the disease in mice (24).

Antidiabetic activity

Because of the antidiabetic use of *T. chebula* in the Ayurvedic medicine the chloroform extract of the seed powder was investigated on streptozotocin-induced diabetic rats in short term and long term studies.

In the long term study the extract (300 mg/kg) was given the diabetic rats for 8 weeks. Blood glucose was measured weekly for 4 weeks. The extract reduced dose-dependently the blood glucose of diabetic rats in the long term study, and in a short term study comparably with the standard drug glibenclamide. A significant renoprotective activity was observed in the *T. chebula* treated rats. These results lend support for the traditional use (30).

Furthermore the aqueous extract of *T. chebula* fruits has been evaluated for its antidiabetic activity on streptocin induced mild diabetic rats and compared with the known drug tolbutamide. The oral dose of 200 mg/kg produced a fall of 55.6 % ($p < 0.01$) in the oral glucose tolerance test. The oral administration of the extract, daily once for two months reduced the elevated blood glucose to 43.2 % ($p < 0.01$) and reduced the increase in the glycosylated haemoglobin ($p < 0.01$).

The hepatic and skeletal muscle glycogen content decreased to 75 % and 62.2 % in the diabetic controls. In the in vitro investigation the pancreatic islets showed that the insulin release was nearly two times more than that in untreated diabetic animals.

The treatment did not bring any unfavourable effects on the other blood parameters of the liver and the kidney function tests. The LD50 value was above 3 g/kg. There were no deaths of animals even at this dose (27).

Chebulagic acid, isolated from *T. chebula* proved to be a reversible and non-competitive inhibitor of maltase with a KI value of 6.6 μM . The inhibitory influence of chebulagic acid on the maltase-glucoamylase complex was more potent than on the sucrase-isomaltase complex. The magnitude of the inhibition is greatly affected by its origin (12).

Cardiotonic activity

The fruits of *T. chebula* are claimed to be useful in the treatment of heart diseases. Different extracts from the dried pulp without kernels have been tested on isolated frog hearts, therefore. For each extract ten-to fifteen experiments were performed, the results are the average of them.

All extracts exhibited cardiotonic activity. The benzene and chloroform extracts showed a moderate cardiotonic activity, though at high doses because they were not completely soluble in the experimental Ringer solution. Ethylacetate, butanone, butanol and aqueous extracts exerted fairly potent cardiotonic activities. These all gave easily dispersible solutions, produced dose-dependent positive inotropic effects and an increase in the cardiac output. There was no appreciable change in the heart rate. Propranolol could not block the activity of the rabbit heart. The extracts being tested here stimulated the isolated perfused frog heart without inducing depression. Chebulin, isolated from the fruits of *T. chebula* was found to depress the isolated perfused Thus the cardiotonic effects of the various extracts appear to be due to some principles present in them (29).

The fruits of *T. chebula* are claimed to be useful against other maladies especially against heart diseases. They are included in the composition of many indigenous remedies. Besides the known effects of extracts on isolated frog hearts in this investigation extracts are applied on (Na^+ , K^+ and Mg^{2+}) ATP ases of a whole homogenate prepared from ventricular portion of frog heart. The extracts exerted the following inhibition:

Butanolic extract 13.5 % and 57.4 % with doses of 0.5 and 1.0 mg

Aqueous extract 31.22 %, 40.68 %, and 49.18 % with doses of 0.1, 0.5, and 1.0 mg.

The inhibition of the ATPase system with the dose of 1 mg is enormous. It is higher than that caused by ouabain, which is a specific inhibitor of this ATPase (47).

The ethanolic extract of *T. arjuna* was tested on anaesthetized dogs and cats for its cardiovascular action. Intravenous administration of an aqueous solution of the dry extract (1, 2, 5 mg/kg) induced a dose dependent decrease in the blood pressure and the heart rate. The peaks of the hypotensive and bradycardiac effect appeared within 5 min after its administration. The cardiovascular effect persisted for 90 min.

In anaesthetized dogs 2 mg dry extract in 0.1 ml saline total dose was injected intracerebroventricularly. The hypotensive peak (60 % decrease) and bradycardiac effect (18 % decrease) was observed two minutes after the injection and lasted approximately for and half an hour (39).

In rats with isoprotenerol (200 mg/kg) induced myocardial damage an ethanolic extract of *T. chebula* fruits (500 mg/kg) was tested. In them the level of lipid peroxidase increased significantly in the serum and the heart. The activity of the myocardial marker enzymes decreased with a concomitant increase in the activity of the serum. The myocardial necrosis was confirmed by histopathological examination. Pre-treatment with the extract ameliorated the effect of isoprotenerol on the lipid peroxide formation and retained the activities of the diagnostic marker enzymes (40).

Preventive activity against atherosclerosis

Rabbits fed cholesterol experimentally showed hypercholesterolaemia and atherosclerosis. The drug *T. bellerica* reduced the levels of lipids in hypercholesterolic animals. In the drug-treated rabbits the liver and heart lipids decreased ($p < 0.05$) (36).

Activity against intoxication of cardiac tissue with arsenic

Arsenic is a harmful metalloid and is ubiquitous in many environments.

Mice orally administered 10 mg NaAsO₂ for two days accumulated the toxin in the cardiac tissue and reduced the cardiac antioxidant enzymes, namely superoxide dismutase, catalase, glutathione-S-transferase, glutathione reductase, and glutathione peroxidase. The gift of arsenic increased the total cholesterol level and reduced the high density lipoprotein cholesterol content in the sera. Arjunolic acid, given at a dose of 20 mg/kg for 4 days prior to the intoxication, protected the cardiac tissue from the arsenic-induced oxidative impairment and prevented the hyperlipidemia (26).

Wound healing

The alcoholic extract of leaves from *T. chebula* was topically administered on dermal wounds of rats. The treated wounds healed much faster, indicated by improved rates of contraction and a decreased period of epithelisation. The granulation tissue increased in total protein DNA and collagen content. The levels of hexosamine and uronic acid in these tissues also increased up to day 8 post-wounding. In addition, the extract was active against *Staphylococcus aureus* and *Klebsiella*.

These results document the beneficial effects of *T. chebula* extract for the healing process (41).

Antioxidative activity against hepatotoxicity

A purified compound, consisting of chebulic acid and its minor isomer neochebulic acid with a ratio of 2:1 was isolated from the ethanolic extract of *T. chebula* fruits by consecutive extraction. The components were verified by spectroscopic analysis, NMR and MS. These compounds exhibited in vitro a free radical scavenging activity in isolated rat hepatocytes and a ferric reducing activity. The treatment of rat hepatocytes with chebulic acid significantly reduced the tert-butyl hydroperoxide (t-BHP)-induced cell cytotoxicity, the intracellular reactive oxygen species level and the ratio of GSSH oxidized form of glutathione (GSH) to the over total GSH (GSH + GSSH) (4.42 %), as compared to that with t-BHT alone (8.33 %) (42).

An ethanolic (95 %) extract of *T. chebula* fruits prevented the hepatotoxicity caused by rifampicin, isoniazid and pyrazinamide within 12 weeks. Chebuloside was the marker of the extract. The hepatoprotective effect can be attributed to this substance, because of its antioxidative and membran stabilizing property, therefore (42).

Ethnoveterinary practice

In Kaduna State of Nigeria indigenous knowledge exists for treating trypanosomiasis of domestic animals. According to questionnaires and interviews of livestock farmers and traders, several plants are used alone or together. Among these the stem bark of *Terminalia avicennoides* is employed. Fulani herdsman boil the bark (vernacular name “wake” in Fulde, “baushe” in Hausa) with water, mix it with local cheese or palm oil and give it to the animals for drinking. But there are no reports about the results of this technique (3)

Results of clinical studies

Plant derived medicines are part of the Indian traditional health care system. Therefore a concentrated extract of *T. chebula* was tested in dentistry.

A mouth rinse of 10 % was prepared by dilution with sterile distilled water and was assessed by testing 50 salivary samples collected from people with high risk of caries.

Salivary pH, buffering capacity, and microbial activity were assayed before rinsing, immediately after, 10 min, 30 min, and 1hr after rinsing. There was an increase in the pH and buffering capacity and decrease in microbial count.

The aqueous extract of *T. chebula* used as mouth rinse seems to be an effective anticaries agent (7).

Further clinical results were not available.

Toxicity

In mice > 3 g/kg lethal

Evaluation

In *T. chebula* and its related plants tannins are the main biologically active substances. They are present in different molecular forms, like dimers, tetramers and polymers, depending from the mode of extraction. In aqueous or ethanolic extracts the lower molecules are prevalent. From a medicinal view most of them bring good results. They are effective against bacteria, viruses, parasites and cancer cells. They protect animals and organs with their antioxidant property. They are nearly not toxic.

But because there are no dosages known for the use in humans, they can not be recommended for the internal use with humans.

Terminalia chebula (fruits)

for mouth rinsing against caries	* * *
as an additive in tooth paste	* * *
as aqueous extracts for wound healing	* *
as tea against diarrhoea	* * *

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