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Sacred basil – an Ayurvedic adaptogen

By Hans Wohlmuth

Sacred basil (*Ocimum tenuiflorum*, syn. *O. sanctum*) is considered a sacred plant by the Hindus and is dedicated to Krishna.¹ Known also as holy basil in English and as *tulsi* or *tulasi* in Hindi, the plant grows wild in India but is also widely cultivated in home and temple gardens.

Sacred basil has a long history of medicinal use, and is mentioned in ancient Ayurvedic texts such as *Charak Samhita*. More contemporary texts, such as *Indian Medicinal Plants* by Kirtikar and Basu (1975), mention sacred basil for treatment of a variety of conditions including pain, fever, vomiting, bronchitis, earache and diseases of the heart and blood,² but it has also been used in the treatment of diabetes, arthritis and asthma.³

Fresh leaves taken with black pepper have been used as a prophylactic against malaria, and a decoction of the root has been recommended for malarial fevers.⁴ The leaf juice has been used for chronic fever, haemorrhage, dysentery and dyspepsia and also as an anthelmintic and topically for ringworm and skin diseases.⁴

The traditional form of preparation is an aqueous extract of the leaves.^{5,6}

Ayurveda is not the only system of medicine to honour and make use of sacred basil, the plant also figures in the ancient medical systems of the Greek, Roman, Sidha and Unani.⁵

Botany

Sacred basil is a member of the family Lamiaceae (Labiatae) and is closely related to the common basil (*Ocimum basilicum*). It is an upright, 30-60 cm tall plant covered with soft hairs. The stems are square in transection, and the leaves are opposite, elliptical-oblong with relatively long petioles and serrated leaf margins. The flowers appear in racemes arising in whorls on the terminal part of the stems and are labiate, bilaterally symmetrical and purplish in colour. Sacred basil is found throughout India and in many parts of the Old World tropics and also occurs in the warmer parts of Australia.

Chemistry

Sacred basil contains a volatile oil consisting of about 70% eugenol as well as methyl eugenol and caryophyllene.^{3,7} Other constituents with likely pharmacological activity include the triterpenoid ursolic acid, rosmarinic acid, alkaloids, saponins, flavonoids (including apigenin and luteolin and glycosides thereof), phenylpropane glucosides and tannins.^{1-3,8-10}

The seeds of sacred basil contain a fixed oil containing five fatty acids, including about 17% linolenic acid and just over 50% linoleic acid.^{11,12}

Sacred basil as an adaptogen

Traditional use has attributed a wide variety of properties to sacred basil. These include rejuvenating, tonic and vitalising properties that would contribute to longevity and a healthy life, as well as anti-septic, anti-allergic and anti-cancer effects.^{6;13}

In view of pharmacological evidence showing sacred basil to possess multiple pharmacological effects including immuno-modulating, anti-stress, hepatoprotective, chemopreventive, and anti-inflammatory, the plant can appropriately be classed as an adaptogen.

The term adaptogen was coined by the Russian scientist Lazarev in 1947 to describe substances that increase the body's non-specific resistance to stress. According to Lazarev, an adaptogen is an agent that allows the organism to counter adverse physical, chemical or biological stressors by raising non-specific resistance towards such stress, thus allowing the organism to 'adapt' to the stressful circumstances.^{1;14}

The concept of adaptogenic action was further elaborated by Brekhman and Dardymov some 20 years later.^{1;14} They put forward specific criteria that a substance should meet in order to be regarded as an adaptogen, namely that the substance should (1) produce a non-specific response and therefore increase resistance against a variety of stressors, (2) have a normalising (amphoteric) action on physiological function irrespective of the pathological state, and (3) be innocuous.

The mode(s) of action of adaptogens is not fully understood, but considerable amounts of evidence suggest the involvement of effects mediated by the pituitary and the pituitary-adrenal axis.¹ Specific pharmacological actions frequently found in adaptogens include antioxidant, anti-cancerogenic, immuno-modulatory, hypocholesterolaemic and hypoglycaemic.¹⁵

Medicinal plants commonly regarded as possessing adaptogenic action include Korean and American ginseng (*Panax ginseng*, *P. quinquefolius*), Siberian ginseng (*Eleutherococcus senticosus*), *Schisandra chinensis* and ashwagandha (*Withania somnifera*).¹

Pharmacology

Pharmacological studies have shown that animals treated with sacred basil extract withstand both physical and chemical stress of different kinds significantly better than controls (see below).¹ A leaf extract has been shown to stimulate the release of ACTH from pituitary cells *in vitro*.¹ This evidence, coupled with the non-toxic nature of the plant and its extract, makes sacred basil an excellent example of an adaptogenic medicinal plant.

Anti-stress activity

Several studies have demonstrated that sacred basil improves resistance to different types of stress. Increased resistance has been demonstrated in animal models against stressors such as behavioural despair, induced gastric ulcers, and exposure to hepatotoxins.^{16;17}

Two studies have shown an ethanolic extract of sacred basil to prevent endocrine stress responses to noise-induced stress.^{18;19}

One of these studies showed that elevation of plasma corticosterone levels induced by loud noise was prevented in rats treated with sacred basil extract.¹⁸

The other study found that sacred basil treatment prevented several noise-induced stress responses in the rat, namely an increase in plasma corticosterone level, leukopenia and enhanced neutrophil function.¹⁹

Thus a variety of studies using different animal models of stress suggest that sacred basil can ameliorate the physiological responses to stress, thus in effect enabling the body to better cope with stress without becoming 'stressed out'.

Antioxidant activity

A number of studies have demonstrated, either directly or indirectly, that sacred basil possesses good antioxidant activity.

Sacred basil demonstrated protective effects against copper sulphate toxicity in rats.²⁰ Copper sulphate caused the development of free hydroxyl radicals and subsequent increased lipid peroxidation and led to rises in levels of antioxidant enzymes such as superoxide dismutase and catalase. Administration of sacred basil restored the various parameters to near normal values.

Several studies have shown sacred basil leaf extract to be radioprotective, i.e. to protect against the damaging effects of ionising radiation. Free radical scavenging and antioxidant activity is the likely mechanism involved in this radioprotective effect.^{21-23 21-23}

Two flavonoids, orientin and vicenin, isolated from the leaves of sacred basil, have been shown to increase survival time in lethally irradiated mice. When animals were pre-treated with either of the flavonoids, a significant decrease in chromosome aberration following gamma irradiation was seen, with vicenin providing the best protection.⁸

Six phenolic compounds isolated from sacred basil, including eugenol, rosmarinic acid, apigenin and three other flavonoids showed good to excellent antioxidant activity *in vitro*.⁹

Ursolic acid isolated from sacred basil protected against lipid peroxidation in liver microsomes *in vitro*.¹⁰

Chemoprevention refers to protective activity against chemically induced malignant tumours.

Oral treatment with very high doses of sacred basil leaf extract for 15 days resulted in significantly elevated activities of enzymes (cytochrome P-450, cytochrome b₅, aryl hydrocarbon hydroxylase and glutathione S-transferase) involved in the detoxification of carcinogens and mutagens.²⁴ Sacred basil extract was also found to elevate hepatic and extrahepatic levels of glutathione. Glutathione is an important part of the body's protective mechanism against free radicals.

Sacred basil extract has been shown to protect against chemically induced oral cancer and the development of skin papillomas in rodents.²⁵

Chemopreventive activity has also been demonstrated for sacred basil seed oil, which contains fatty acids including linolenic acid. Antioxidant activity was deemed to be partly responsible for the chemopreventive effect.²⁶

Anti-cataract activity

Sacred basil leaf was found to have both prophylactic action and be able to arrest the progress of cataract formation in animal models.²⁷ Oxidative damage by free radicals is believed to be the major cause of cataracts, and sacred basil's anti-cataract effect is undoubtedly closely associated with its antioxidant activity.

Immuno-modulating activity

Pharmacological studies in rats have indicated that both aqueous and methanolic extracts of sacred basil leaves stimulate humoral and cellular immunity.^{6,13} Increased humoral immune response was demonstrated by increased antibody titre in response to challenge with typhoid antigen, while raised cellular immunity was evidenced by increased lymphocyte count.⁶

A steam distilled oil from the fresh leaves modulated various aspects of humoral immunity *in vitro* and *in vivo*.¹³ Antibody titre, including IgE titre was enhanced *in vivo*, and the oil also significantly inhibited histamine release from peritoneal mast cells and antagonised the spasmogenic effects of histamine, serotonin and acetylcholine *in vitro*.

The authors of this study suggested that sacred basil might have an anti-allergic action resembling that of sodium chromoglycate, a widely used anti-allergic drug that suppresses the release of histamine.

Anti-inflammatory, analgesic and anti-pyretic activity

Leaf extracts of sacred basil inhibited both acute and chronic inflammation in animal models, and also had analgesic and anti-pyretic activity.⁵ All of these effects may, at least in part, be attributed to the inhibition of prostaglandin biosynthesis.

That sacred basil indeed contains compounds with the potential to inhibit prostaglandin biosynthesis was confirmed by a recent study, which showed that several compounds isolated from sacred basil (eugenol, rosmarinic acid, and the flavonoids cirsilineol, cirsimaritin, isothymonin and apigenin) inhibited the key enzyme involved in the biosynthesis of prostaglandins, cyclooxygenase.⁹

The fixed seed oil of sacred basil has been found to have both anti-inflammatory and anti-ulcer activity and appears to exert these effects through dual inhibition of arachidonic acid metabolism, i.e. by inhibiting both the cyclooxygenase and lipoxygenase pathways.^{11;12;28;29}

Psychopharmacological effects

A leaf extract of sacred basil was found to produce effect similar to those produced by low doses of barbiturates in pharmacological studies, but at the same time produced some effects reminiscent of amphetamines.³⁰ These results suggest that the effects of sacred basil on the central nervous system might involve dopaminergic neurones.

Anti-diabetic actions

Several studies have shown sacred basil (both as an extract and as a dietary component) to have hypoglycaemic action in animal models of diabetes.^{7;31;32}

A reduction of serum lipid levels (total lipids, total cholesterol, triglycerides and phospholipids), uronic acid and total amino acids, all relevant to the metabolic dysfunction of diabetes, has also been observed in diabetic animals fed a diet including 1% sacred basil leaf powder.⁷

Clinical trial in NIDDM

A randomised, placebo-controlled, single-blind, crossover trial in patients diagnosed with noninsulin-dependent diabetes mellitus (NIDDM) was conducted to examine the effects of sacred basil (dried leaf 2.5 g daily) on fasting and postprandial blood glucose and serum cholesterol levels.³

Forty patients, twenty of whom were receiving oral hypoglycaemic drugs and twenty of whom were newly diagnosed without a history of anti-diabetic drug use, took 2.5 g of sacred basil leaf or placebo (spinach) powder in water on an empty stomach upon rising. Subjects taking anti-diabetic medication were advised to stop doing so at least 7 days prior to the trial. Following a 5-day run-in period, subjects were randomised to take sacred

basil or placebo for four weeks, followed by the other treatment for four weeks. Investigators were blinded to the sequence of treatments.

The results showed that sacred basil treatment caused a significant decrease in both fasting and postprandial blood glucose levels compared with placebo. Fasting blood glucose fell by 21.0 mg/dL (95% CI -31.4- -11.2; $p < 0.001$) and postprandial blood glucose fell by 15.8 mg/dL (95% CI -7.0 - -5.6; $p < 0.02$). This represented reductions in fasting and postprandial blood glucose levels of 17.6% and 7.3%, respectively. A mild reduction in total cholesterol levels was also observed with the sacred basil treatment. No adverse effects were recorded during the study.

The mechanism responsible for the hypoglycaemic activity of sacred basil is not known. It has been speculated that the herb may improve beta cell function and enhance insulin secretion.³

Safety

Sacred basil has a long history of safe traditional use in India.

Anti-fertility effects, including abortifacient and anti-spermatogenic effects, have been described in rats, but only following the inclusion of sacred basil leaf in the diet at high levels.^{33;34} The doses producing these effects are in the order of 1000 mg per kilo bodyweight or more daily, equivalent to a daily dose of 50 g or more in humans.

There is no indication of safety concerns about sacred basil in the literature.

The LD₅₀ for the oral administration of an ethanolic extract of the whole plant is 4508±80 mg in mice.¹⁶ This very high value supports the innocuous nature of the extract.

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Trikatu — a traditional Ayurvedic formula

By Hans Wohlmuth

Trikatu is a traditional Ayurvedic herbal formulation consisting of three herbs in equal amounts, Black pepper (*Piper nigrum*), Long pepper (*P. longum*) and Ginger (*Zingiber officinale*).

‘Trikatu’ is a sanskrit word meaning ‘three acrids’, referring to the pungent qualities of the three ingredient herbs. The use in Ayurveda of these three herbs is documented in the ancient Ayurvedic materia medica dating back several thousands of years.^{1,2}

In Ayurveda, the ingredients of Trikatu are important components of numerous formulations used for a wide range of disorders.^{1,2}

The importance of Trikatu and its ingredient herbs is illustrated by the fact that no less than 210 of the 370 compound formulations listed in the *Handbook of Domestic Medicines and Common Ayurvedic Remedies* (published by the Central Council for Research in Indian Medicine and Homoeopathy, Delhi 1979) contain either Trikatu or its ingredients.¹

The widespread use of the same herbs in so many formulations for a great variety of complaints has led to the suggestion that these herbs confer some unique property to formulations¹, in other words, that they have adjuvant properties.

In 1900, it was suggested that Black pepper, Long pepper and Ginger were added to formulations ‘often without reason and sometimes only for the sake of rhyme’ (cited in Atal *et al.* 1981), but this seems unlikely, a view supported by both traditional knowledge and more recent work.

According to Ayurvedic philosophy, disease results from imbalance between the three humours of the body, *kapha*, *vata* and *pitta*. It has been suggested that the acrid or pungent ingredients of Trikatu act to restore the balance of these humours (cited in Johri & Zutshi 1992), a hypothesis that offered an explanation for the widespread application of these herbs. In terms of Ayurveda, Trikatu is also described as rejuvenating digestive fire (*agni*) and burning away toxic build-up in the digestive tract (*ama*), thus facilitating proper digestion, assimilation and metabolism as well as elimination.

In 1928, Bose, while studying the anti-asthmatic properties of *Adhatoda vesica*, noted that Long pepper, when added to *Adhatoda* leaves, would increase their efficacy (in Atal *et al.* 1981). This effect of increasing the bioavailability of other substances has subsequently been studied further and will be discussed in more detail below.

Composition and constituents

As mentioned above, Trikatu consists of equal parts Black pepper (*Piper nigrum* dried fruit), Long pepper (*P. longum* dried fruit) and Ginger (*Zingiber officinale* dried rhizome).

Both Black and Long pepper contain as their major active constituent the alkaloid piperine, which is chiefly responsible for the pungency of these peppers (Fig. 1).

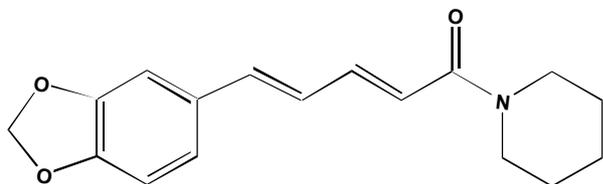


Fig. 1. Piperine

Black pepper contains 5-9% of the alkaloids piperine and piperettine and 1-2.5% of volatile oil, the major constituents of which are alpha- and beta-pinene, limonene and phellandrene.^{3;4}

In one study, the essential oil of Black pepper was found to comprise 33.7% beta-caryophyllene.⁵

Long pepper was found to contain about 1.25% piperine as well as about 1% volatile oil, the major constituents of which were beta-caryophyllene (17%), pentadecane (17.8%) and beta-bisabolene (11.16%).⁶

Long pepper also contains an amide, which has demonstrated coronary vasorelaxant activity.⁷

The major pungent compound in dried Ginger rhizome is [6]-shogaol, the dehydration product of [6]-gingerol, which is the primary pungent compound in fresh Ginger.

[6]-Shogaol is more pungent than [6]-gingerol. Ginger also contains a volatile oil, which shows considerable variation depending on geographical origin. Ginger from India typically yields a volatile oil containing high levels of zingiberene and ar-curcumene.^{8;9}

Piperine

Piperine (1-piperoylpiperidine) is an alkaloid and the main pungent principle in both Black and Long pepper.

In pharmacological studies in animals, piperine has been shown to stimulate digestive enzyme activity, including that of pancreatic lipase, amylase, trypsin and chymotrypsin¹⁰, as well as intestinal lipase, sucrase and maltase.¹¹

In one pharmacological study, piperine was found to protect against gastric ulceration; it also inhibited gastric acidity and pepsin A activity.¹²

Piperine has been found to affect the cytochrome P-450 family of metabolising enzymes, and both stimulation and suppression of specific enzymes have been demonstrated in different models.¹³⁻¹⁷ Piperine has also been shown to inhibit another metabolic step, glucuronidation, in isolated intestinal cells.¹⁸

Despite the contrasting findings in terms of the effect of piperine on the cytochrome P-450 enzymes, most human and animal studies indicate that piperine inhibits, rather than stimulates, drug metabolism in most cases, thus increasing the bioavailability and effect of some drugs.

As will be further discussed below, piperine is chiefly responsible for the effect of Trikatu and peppers of increasing the bioavailability of many other compounds.

In animals, piperine has demonstrated anti-convulsive activity^{19;20}, as well as both CNS stimulating and depressant activity, as well as anti-pyretic, analgesic and anti-inflammatory effects.¹

In addition, piperine has been shown to interact with the serotonergic system and deplete substance P in the spinal cord, and neuromuscular transmission and sensory receptors are reported to be affected by the compound.¹

Anti-fertility action but also pro-fertility effects of piperine have been observed in various animal models.²¹⁻²⁵

Piperine is almost completely (97%) absorbed from the gastrointestinal tract following oral administration in rats, and after 24 hours only traces remained in serum, kidney and spleen. In rats, the metabolism of piperine appears to involve glucuronidation and sulfation pathways, and metabolites include vanillic and piperonal acid, piperonylic acid and piperonyl alcohol.^{1;26}

Long pepper



Long pepper (*Piper longum*) is a dioecious creeper native to India, where it is also sometimes cultivated. The medicinal fruits are small, dark red berries.

In Ayurveda, Long pepper fruit (*pippali*) is considered acrid, hot and light, and a digestive, appetiser, aphrodisiac and tonic. It is employed in the treatment of many complaints, including cough, dyspnoea, leprosy, tuberculosis, diabetes, colic, indigestion, haemorrhoids, skin disorders, anaemia, chronic fever, typhoid, anorexia and intestinal worms.^{27;28}

Long pepper was found to significantly decrease the frequency and severity of asthma attacks in a group of 20 asthmatic children, and facilitated the regeneration of hepatocytes following toxic liver damage.²⁸

Long pepper fruits have shown activity against experimental *Giardia lamblia* infection in mice at doses ranging from 250-900 mg/kg.²⁹ The same study found evidence for both specific and nonspecific immunostimulatory activity of long pepper, as measured by haemagglutination titre, plaque forming cell counts, macrophage migration index, and phagocytic index.

Long pepper is used in traditional preparations for intestinal complaints and has demonstrated efficacy against caecal amoebiasis (*Entamoeba histolytica*) in rats.³⁰ Pure piperine was also found to be effective. Hypoglycaemic activity of Long pepper has been demonstrated in diabetic rats.³¹

Black pepper



Black pepper (*Piper nigrum*) is a woody climber widely cultivated in India and elsewhere. The dried fruit is used as a spice world wide and also comprises the medicinal part.

In Ayurveda, Black pepper is described as being acrid, bitter, light and hot, and as having alterative, carminative, anthelmintic and appetite stimulating properties. It is used traditionally in the treatment of many and varied conditions, including respiratory complaints such as asthma, heart complaints, diabetes, colic, worms, haemorrhoids, eczema, intermittent fevers and dysentery.²⁷

Ginger



Ginger (*Zingiber officinale*) is a so-called cultigen — a cultivated plant, the wild ancestor of which is unknown. In the case of Ginger, it is thought to have originated in India or Southeast Asia.

Ginger is a monocotyledonous plant with a fleshy rhizome, which is the medicinal part.

In Ayurveda, both the fresh rhizome (*ardraka*) and the dried rhizome (*shunthi*) are used. It is the dried rhizome that forms one of the three ingredients of Trikatu.

Ginger is described as acrid, hot, promoting digestive power, anodyne, antirheumatic, carminative, cooling, diuretic and aphrodisiac. It is used in the Ayurvedic tradition for the treatment of numerous conditions including vomiting, cough, dyspnoea, anorexia, fever, anaemia, flatulence, colic, constipation, diarrhoea, dyspepsia, cholera, diabetes and swelling.²⁷

A considerable amount of research has been carried out on Ginger and its pungent constituents, the gingerols (fresh rhizome) and the shogaols (dried rhizome). Among the pharmacological effects demonstrated are inhibition of cyclooxygenase and

5-lipoxygenase, anti-platelet, anti-oxidant, anti-tumour, anti-rhinoviral and anti-hepatotoxic activity, and clinical studies have found ginger effective in postoperative nausea, vomiting in pregnancy and in the prevention of motion sickness.³²

A recent *in vitro* study found Ginger to stimulate markers of humoral immunity.³³

Effects on bioavailability

Several studies have demonstrated that Trikatu (as well as some of its ingredients, see below) can significantly affect the bioavailability of other compounds, including herbal and pharmaceutical drugs. Most of these studies appear to suggest that Trikatu and its components can increase the bioavailability of other substances.

The constituent responsible for this bioavailability enhancing effect is piperine.^{2;34}

As mentioned above, an early study found that adding Long pepper to *Adhatoda vesica* leaves increased their efficacy in asthma (in Atal *et al.* 1981).

Enhanced bioavailability as a result of co-administration with either piperine, Black pepper or Long pepper, or Trikatu has been observed for several drugs including vasicine (from *Adhatoda vasica*), sparteine (from *Spartium junceum* but also found in broom, *Cytisus scoparius*), phenytoin, propranolol, theophylline, pentobarbitone, sulphadiazine and tetracycline.^{1;2;34;35}

For example, piperine administered at a dose of 30 mg/kg together with sparteine to rats more than doubled the bioavailability of sparteine.²

A study on human volunteers found that the bioavailability of theophylline (150 mg) or propranolol was increased by the concurrent administration of 20 mg piperine daily for 7 days, as evidenced by higher C_{max} and AUC for both compounds and longer elimination half-life for theophylline.³⁵

In the case of the anti-tuberculosis drug, rifampicin, several studies have yielded inconclusive results. The bioavailability of rifampicin has been found to increase in patients with pulmonary tuberculosis when co-administered with piperine, while Trikatu had been found to decrease the bioavailability of rifampicin in healthy volunteers.³⁴

The primary mechanism by which piperine (and Trikatu) affects the bioavailability of other compounds seems to be via the nonspecific and noncompetitive inhibition of microsomal liver metabolism involving the cytochrome P-450 enzyme system.^{1;13;16;34;36;37}

Piperine has been shown to inhibit certain hydroxylation, demethylation, deethylation and glucuronidation metabolic processes, and *in vitro* studies with hepatic microsomal suspensions have found that piperine inhibited a variety of mixed function oxygenases.^{1;34}

It is also possible that Trikatu enhances absorption from the digestive tract, an idea that would fit the common view in Western herbal medicine of pungent herbs such as ginger as remedies that facilitate the absorption of other herbs and nutrients.

This idea is supported by a study in rabbits showing enhanced gastrointestinal blood flow immediately following the oral administration of Trikatu or piperine with increased glucose absorption as a result (cited in Johri & Zutshi 1992).

It has also been suggested that piperine could interact with intestinal epithelial cells with increased absorption as a result, and *in vitro* studies have shown piperine to stimulate gamma-glutamyl transpeptidase activity and increase amino acid uptake by rat jejunum epithelial cells. These findings suggest that piperine may cause increased permeability of intestinal cells.¹

Safety

The acute, subacute and chronic toxicity of piperine, Black pepper and Long pepper has been studied in animals. At pharmacological doses, no adverse effects were observed in terms of mortality, general growth pattern or clinical pathology.^{1;38}

The mutagenic potential of piperine was studied in four different test systems. The results showed piperine to be non-mutagenic.³⁹

In very large doses, long pepper caused an increase in sperm motility and in the weight of the lungs, spleen and reproductive organs of treated animals.³⁸

The potential for drug interactions has been discussed above.

Indications for Trikatu

Trikatu works primarily in the digestive tract, where it assists proper digestive function through stimulation of digestive enzyme activity. Trikatu also acts on the respiratory system.

Trikatu would not normally be used by itself, but incorporated into formulations with other herbs.

Indications for Trikatu include:

- Indigestion
- Flatulence
- Colic
- Weak digestion
- Poor absorption
- As an adjuvant to increase the bioavailability of other herbs
- Intestinal infection
- Common cold
- Cough

Contraindications and cautions

Trikatu is for professional use only.

Because of its pungency, Trikatu is not suitable for children.

Since Trikatu may affect the bioavailability of other compounds, it should not be administered to people who are taking prescription drugs, without close monitoring by the prescribing practitioner.

Similarly, Trikatu may affect (most likely increase) the bioavailability of other therapeutic substances, including herbal medicines and nutritional supplements, and the dose of these may need to be adjusted accordingly.

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