REVIEW ARTICLE

Trikatu - A combination of three bioavailability enhancers

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Abstract

Trikatu, as per Ayurveda's *Bhaisajyaratnawali* is a compound herbal formulation containing three bitter herbs mixed together in equal quantities. Dried fruits of *Piper nigrum* (Maricha) and *Piper longum* (Peepli) and dried rhizomes of *Zingiber officinale* (Sunthi) are used to prepare this miraculous formulation. It is prescribed in Ayurvedic system of medicine for treatment of tastelessness, digestive impairment, and diseases of nose and throat such as chronic rhinitis/sinusitis, skin diseases, asthma, cough, frequent urination, obesity, and Filariasis. Trikatu is also added in various Ayurvedic formulations with a view to restore the disturbed "*tridoshas- vatta, pitta and kapha*." It calms down the increased *Vata* and *Kapha* and increases the *Pitta*. It has pungent (*katu*) taste, hot (*ushna*) potency, light (*laghu*) and dry (*ruksha*) quality, and digestive (amapachaka) therapeutic effect. Modern pharmacological studies also revealed that Trikatu possesses the capability to enhance the bioavailability of various phytoconstituents and synthetic drugs if incorporated with them thereby helping in achieving the therapeutic goals. Apart from traditionally known health benefits, Trikatu also possesses immunomodulatory, antiviral, expectorant, carminative, hypolipidemic, hypoglycemic, antiemetic, and anti-inflammatory potential. Simply it is concluded that Trikatu is a miraculous combination which is needed to be explored more exhaustively to solve the bioavailability issues of allopathic, ayurvedic, and other traditional systems of medicines.

Key words: Ayurvedic, bioavailability, *Piper longum*, *Piper nigrum*, trikatu, *Zingiber officinale*

INTRODUCTION

Trikatu as the name itself indicates its meaning, "tri" in Sanskrit stands for three and "*katu"* stands for acrids. The three acrid herbs including *Maricha* (Black pepper), *Peepli* (Long Pepper), and *Sunthi* (Ginger), when combined in equal quantities, forms the miraculous formulation Trikatu. Trikatu is an Ayurvedic formulation mentioned in Ayurveda for a number of ailments. In *Bhaisajyaratnawali*, Trikatu is mentioned as:

पिप्पली मरिचं शुण्ठी त्रयमेतद्विमिश्रितम ।
त्रिकटु त्र्यूषणं व्योषं कटुत्रिकमथोच्यते ।।१६ ।।

The *shloka* completely defines the procedure for preparation of Trikatu and method of its use along with the indications in which it is to be used.

Ayurvedic system of medicine prescribes Trikatu for the management of tastelessness (*Arocaka*) disturbed digestion (*Agnimandya* and *Amadosa*), diseases of nose (*Pinasa*) and upper respiratory tract (*Gala* and *swasa roga, Kasa*), excess and frequent urination (*Meha*), edema (*Gulma)*, obesity (*Sthaulya*), Filariasis (*Slipada*), and skin diseases (*Tvakroga)*. Trikatu acts primarily by its effect on stomach, liver, and pancreas. In stomach, it increases production of digestive juices thereby stimulating digestion. In liver, it acts as Cholagogue and increases production of bile salts by stimulating gallbladder functioning. Trikatu also has its influence on pancreatic functioning. In a nutshell, Trikatu affects overall digestive system along with its curative effects on respiratory, urinary, immunity, skin, and metabolic systems of our body.

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Trikatu is also added in various Ayurvedic formulations with a view to restore the disturbed "*tridoshas-vata, pitta, and kapha*." It calms down the increased *Vata* and *Kapha* and increases the *Pitta*. It has pungent (*katu*) taste, hot (*ushna*) potency, light (*laghu*) and dry (*ruksha*) quality, and digestive (*amapachaka*) therapeutic effect [Figure 1].[1]

METHOD OF PREPARATION

Equal quantities of all the three acrid herbs, dried fruits of *Piper longum* Linn.(Long Pepper), *Piper nigrum* (Black Pepper), and dried rhizomes of *Zingiber officinale* are finely powdered separately in a mortar pestle or grinder. The fine powders of individual herbs are weighed in equal quantities and mixed together properly. This mixture of powders is then sieved through sieve no. 80 to get extra fine powder which has more therapeutic value due to more surface area. The fine powder of Trikatu is then stored in moisture free airtight containers.[1]

Dosage

Ayurvedic texts prescribe 1–3 g of Trikatu churna to be consumed with honey to mask the bitter taste or warm water for maximum therapeutic benefits. Trikatu is added in many Ayurvedic polyherbal formulations in such a quantity that it will be sufficient to enhance the bioavailability of the main ingredients of that formulation by acting through various mechanisms. When added in formulations, the actual pharmacological activity of Trikatu is not exhibited because its dose is not the therapeutic dose.[1]

Chemistry of Trikatu

Trikatu contains the three herbs *P. longum*, *P. nigrum,* and *Z. officinale*. The component herbs *P. longum* and *P. nigrum* contain Piperine as the main chemical as well as a biological marker along with other constituents in minor quantities. *Z. officinale* contains chemical constituents such as Gingerols, Gingiberene, Shagols, and other chemical components.

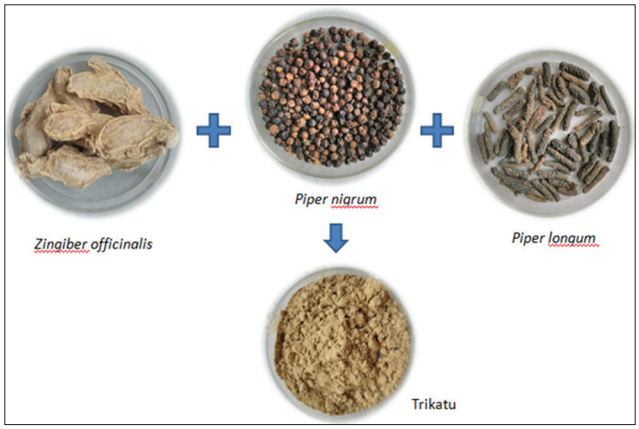

Figure 1: Formulation of Trikatu

Chemical composition of *P. longum*

Piperine is the major and active constituent of long pepper. The piperine content is 3–5% (on dry weight basis) in *P. longum*. The fruit of *P. longum* contains a large number of alkaloids and related compounds, the most abundant of which is piperine, methyl piperine, iperonaline, piperettine, pellitorine, piperlongumine, piperlonguminine, asarinine, piperundecalidine, refractomide A, pipercide, piperderidine, longamide and tetrahydropiperine, terahydro piperlongumine, dehydropipernonaline piperidine, pregumidiene, brachystamide, brachystamide-A, brachystine, terahydropiperlongumine, and trimethoxy cinnamoyl-piperidine. Lignans Sesamin, pulvuatilol, fargesin, and others have also been isolated from the fruit of *P. longum*.

Volatile oil of the fruit *P. longum* is a complex mixture. Major components of essential oil are caryophyllene and pentadecane (both about 17.8%) and bisaboline (11%) along with volatile piperine. Other components include thujine, terpinoline, p-cymene, p-methoxy acetophenone, and dihydrocarveol.[2]

Chemical Composition of *P. nigrum*

P. nigrum contains lignans, alkaloids, flavonoids, amides, and other aromatic compounds along with approximate 3.5% of volatile oil. Components of essential oil include sabinene, pinene, linalool, limonene, and phellandrene. Piperine is an alkaloid and the chemical marker of *P. nigrum*. Chavicine which is an isomer of piperine is also present. Piperine and Chavicine are not responsible for the aroma of the black pepper. Piperine is responsible for pungency of the black pepper.[3]

Chemical Composition of *Z. officinalis*

Exhaustive chemical screening of ginger reveals that it contains over 450 compounds. The major composition of ginger rhizomes is carbohydrates (50–70%), lipids (3–8%), terpenes, phenolic compounds, amino acids, raw fiber, ash, protein, phytosterols, vitamins, and minerals. Volatile terpenoidal constituents of *Z. officinale* include zingiberene, β-bisabolene, α-farnesene, α-curcumene, and β-sesquiphellandrene. Phenolic compounds include gingerol, paradols, and shogaol. Gingerols and shagols are responsible for pungency of Ginger. These gingerols and shogaol are found in higher quantities of up to 20–25%. Other gingerol- or shogaol-related compounds (1–10%), which have been reported in ginger rhizome, include 6-paradol, 1-dehydrogingerdione, 6- gingerdione and 10-gingerdione 4- gingerdiol, 6-gingerdiol, 8-gingerdiol, and 10-gingerdiol, and diarylheptanoids. The characteristic odor and flavor of ginger are due to a mixture of volatile oils such as shogaols and gingerols.[4]

Bioavailability Enhancers

- Bioavailability enhancers are drug facilitators.
- They are molecules which by themselves do not show typical drug activity.

- However, when used in combination, they enhance the activity of the drug molecule in various ways.

Simply, a bioavailability enhancer is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined without any typical pharmacological activity of its own at the dose used.

Need of Bioavailability Enhancers

Many allopathic and herbal formulations despite their impressive *in vitro* findings demonstrate less or negligible *in vivo* activity due to following reasons:

- Poor lipid solubility.
- Improper molecular size.
- Resulting in poor absorption.
- And hence poor bioavailability.

Here, the need arises for a natural and safe solution for combating these bioavailability problems. Trikatu fits best to manage these bioavailability issues with allopathic and herbal formulations. There are numerous pharmacological findings that support the use of Piperine and Gingerols to enhance the bioavailability.

Piperine is the biomarker of both *P. longum* and *P. nigrum*. Piperine acts by a number of mechanisms to enhance the bioavailability.

- Increases bioavailability of the drug across the membrane.
- Potentiates the drug molecule by conformational interactions.
- Reduction in HCl secretion and increase in gastrointestinal tract (GIT) blood supply.[5]
- Acts as receptors for drug molecule making target cells more receptive to drugs.
- Inhibition of gastrointestinal transit, gastric emptying time, and intestinal motility.[6,7]
- Modifications in GIT Epithelial cell membrane permeability.[8,9]
- Chalagogous effects.[8]
- Bioenergetics and Thermogenic properties.[8,10]
- Suppression of First Pass Metabolism and inhibition of drug metabolizing enzymes.[10]
- Stimulation of gamma-glutamyl transpeptidase activity which enhances uptake of amino acids.[11]

PHARMACOLOGICAL STUDIES DEMONSTRATING BIOAVAILABILITY ENHANCING ACTIVITY OF PIPERINE AND GINGER

The effect of simultaneous administration of Piperine on plasma concentration of Carbamazepine given twice daily in epileptic patients undergoing carbamazepine therapy was evaluated, and it was observed that piperine significantly enhanced the bioavailability of carbamazepine. The mechanism of action was possibly by increased absorption and reduced elimination of the carbamazepine.[12] Antidepressant effects of curcumin were investigated with coadministration with piperine. It was observed that the combination of piperine with curcumin showed significant potentiation of its anti-immobility, neurotransmitters (serotonin and dopamine) enhancing, and monoamine oxidase inhibitory effects as compared to curcumin effect when taken alone.[13] Another similar study revealed that there was potentiation of antidepressant activity of curcumin when administered with piperine.[14] While evaluating the effects of tiferron alone and in combination with piperine against beryllium-induced biochemical alterations and oxidative stress, it was found that the combination reversed all the variables significantly toward the control.[15] In a randomized, crossover and placebo-controlled study of the influence of piperine on the pharmacokinetics of nevirapine (an antiretroviral drug) under fasting conditions. The piperine or placebo was administered to healthy adult males for 6 days. On the 7th day, Piperine or placebo was administered with nevirapine. Post-dosing blood samples showed enhanced bioavailability of nevirapine with piperine.[16] Study of effect of oral curcumin with piperine on the pain and the markers of oxidative stress in patients with tropical pancreatitis for 6 weeks revealed that there was a significant reduction of the erythrocyte malonyldialdehyde levels in combination therapy as compared to placebo treatment with significant increase in glutathione levels.[17] 1.3 times more plasma bioavailability of epigallocatechin-3-gallate was observed in CF-1 mice when taken with piperine as compared to epigallocatechin-3-gallate alone. The mechanism involved inhibition of glucouronidation and GIT transit.[18]

Ginger is one of the components of Trikatu which also possess significant bioavailability enhancement activity. It has a powerful effect on mucous membrane of the gastrointestinal tract. It regulates the intestinal functions to facilitate absorption. Ginger when used in the dose of 10–30 mg/kg body weight acts as bioenhancer. Pharmacological studies show that it dramatically enhanced the bioavailability of various medicines especially antibiotics such as amoxicillin, azithromycin, erythromycin, cephalexin, cefadroxil, and cloxacillin.[19]

Ayurvedic formulations containing Trikatu[1]

S. No.	Formulation	Indication
1.	*Sarasvata churna*	Epilepsy,[20] Brain disorders
2.	*Astangavleha*	Cough and Asthma
3.	*Eranda paka*	Edema and Pain in Urinary system
4.	*Panchnimba churna*	Skin diseases
5.	*Puga khanda*	Dyspepsia and Bleeding haemorrhoids
6.	*Vyagriharitaki*	Cough and Rhinitis
7.	*Arkadi kwatha churna*	Lock jaw and Cold cough

8.	*Punarnava gugglu*	Gout and Scrotal swelling
9.	*Ashwagandhadi churna*	*Tridosha*
10.	*Dadimashtaka churna*	Malabsorption syndrome

Other Pharmacological Activities of Trikatu

Different extracts and fractions of Trikatu possess Antioxidant,[21] Antihyperlipidemic,[22] Antianorectic,[23] Antitumor,[24] Hepatoprotective,[25] Antimicrobial,[26-28] Anthelmintic,[29] Analgesic,[28] Antifungal,[28] Immunomodulatory,[30,31] Antiallergic,[32] Antiarthritic,[33] and Anti-inflammatory[34,35] activities.

Therapeutic Indication

Trikatu Churna is helpful in following health conditions.[36]

- Constipation with mucous or sticky stool.
- Loss of appetite.
- Indigestion.
- Gas or flatulence.
- Bloating.
- Abdominal distension.
- Irritable bowel syndrome.
- Common cold (acute phase during running nose).
- Cough with thin white phlegm.
- Asthma (chest congestion due to phlegm).
- Weight loss (obesity).
- Body aches with feeling of heaviness in the body.
- High cholesterol levels.
- Atherosclerosis.
- High blood pressure due to hypercholesterolemia.
- Gout.

Caution

However, Trikatu churna contains herbs and spices, which we use in our daily kitchen, but the excess intake can cause some unwanted effects. In the dosage <1 g/day, it is safe to use.[36]

Side Effects

The most common side effect of Trikatu is heartburn and acidity. The excess dosage may cause the following side effects.[36]

- Burning aftertaste.
- Heartburn.
- Burning sensation in the throat.
- Heat sensation in the body.
- Mouth ulcer (rare).
- Sweating (rare).
- Redness in eyes or burning sensation in eyes (very rare).

Contraindications[36]

- Acid dyspepsia.
- Heartburn.
- Burning sensation in any part of the body such as in the throat, abdomen, feet, or hands.
- Vomiting.
- Red eyes.
- Skin diseases with burning sensation as a symptom.
- Constipation with dry and hard stool or bleeding in stool.
- Bleeding disorders.
- High-risk pregnancies.
- Threatened abortion.

CONCLUSION

Trikatu being an herbal formulation will be the best solution for bioavailability related issues with allopathic, Ayurvedic and formulations of other traditional systems of medicines. It has got the tremendous potential to increase the bioavailability of drugs and nutrients. The scientific findings further strengthen the claims of the traditional ancient texts about Trikatu's health benefits.

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