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## PHYTOCHEMISTRY AND PHARMACOLOGY OF TRIKATU

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**Abstract:** *Trikatu* is a very well known 'Rasayana' in Ayurveda and widely used as a polyherbal ayurvedic formulation in India. It consists of three well known plants, viz., *Piper longum* Linn., *Piper nigrum* Linn. and *Zingiber officinale* Rosc. in equal ratio. It is mentioned in the ancient books of Ayurveda used for the treatment of fever, asthma, cold and cough, diabetes, nasal diseases, obesity, anorexia, digestive, respiratory system and normal urinary tract function. Phytochemical investigations indicate that 3 compounds reported from the polyherbal formulation and also it contains various chemical category viz. alkaloids, phytosterol, triterpenes, flavonoids and various other phenolic compounds. Pharmacological activities of *Trikatu* reported include hepatoprotective, antioxidant, analgesic, anti-anorectic, anti-inflammatory, antimicrobial, antifungal, anthelminthic, anti-arthritic, adaptogenic, antihyperlipidemic and antitumor activity. In the present review the literature data on the phytochemical and biological investigations on the *Trikatu* are summarized up to March 2015.

**Keywords:** *Trikatu*; adaptogenic; antimicrobial; anthelminthic; anti-anorectic.

**Introduction:** The ancient documented Ayurvedic Materia Medica which dates back to 6000 years BC mentioned these herbs used in *Trikatu* as essential ingredients of numerous prescriptions and formulations used for a wide range of disorders [1]. Out of the 370 formulations listed in the Handbook of Domestic Medicine and Common Ayurvedic Remedies, 210 contain either *Trikatu* or its individual components [2]. As per Ayurvedic pharmacology, '*Trikatu*' means '*Katu-Tikta rasa*' (bitter-pungent or acrid taste), '*Usna*' (hot), '*Virya*' (potency), '*Madhura rasa*' (sweet taste) and '*Vata-kapha Nasaka*' (air and mucus destroyer under the disease conditions) [3]. The Ayurvedic system of medicine has described various herbal formulations in the treatment of diseases, which play an important role in modern health care and curing various ailments and diseases. The uses of herbal medicines are increasing as dietary supplements to fight or prevent common diseases. In Ayurvedic Formulary of India it is used in various diseases like, *Arocaka* (Tastelessness), *Agnimandya* (Digestive impairment), *Amadosa* (Products of impaired digestion and metabolism / consequences of Ama), *Gala Roga* (Diseases of throat), *Pinasa*

(Chronic rhinitis/sinusitis), *Kustha* (Diseases of skin), *Swasa* (Dyspnoea/Asthma), *Kasa* (Cough), *Tvakroga* (Skin disease), *Gulma* (Abdominal lump), *Meha* (Excessive flow of urine), *Sthaulya* (Obesity), *Slipada* (Filariasis) [4]. *Trikatu* is one of the Ayurvedic preparations used from the period between 7<sup>th</sup> century B.C. and the 6<sup>th</sup> century A.D., for the treatment of a variety of ailments. It is a combination of black pepper (*Piper nigrum* Linn.), long pepper (*Piper longum* Linn.), and ginger (*Zingiber officinale* Rosc.). *Trikatu* was formulated by taking equal weight ratio of the three crude drugs for therapeutic purposes. *Trikatu* enhances the metabolic process by rapid absorption of nutrients [5, 6]. Which contains an alkaloid as active component "Piperine", which enhances the bioavailability of drugs and nutrients [7]. These plant materials are also used worldwide as spices. They are also used as important ingredients in Ayurvedic, Siddha and Unani (ASU) drugs and folklore medicine. The consumption of *Trikatu churna* exert several health benefits by the virtue of their innumerable therapeutic potentials, such as in fever, asthma, cold and cough [6], diabetes, nasal diseases, obesity, anorexia [8], digestive, elephantiasis, carminative, skin disorders, abdominal

distention, respiratory system diseases<sup>[5]</sup>, dyspepsia and in urinary tract infection. *Trikatu* is highly useful for vasodilatation and immune-potentiating activity<sup>[9]</sup>. *Trikatu* and its active principles like piperine, 6-shogaol and 6-gingerol showed promising anti-inflammatory effect in both rheumatoid arthritis and acute gouty arthritis<sup>[10, 11]</sup>. Decoction of sesame seeds (*tila*) mixed with ghee, jaggery, Bharangi (*Clerodendrum serratum* Linn.) root powder and *Trikatu* powder is used as the best remedy for amenorrhoea and uterine tumor<sup>[12]</sup>. It helps in the improvement of gastric function<sup>[6]</sup>.

### Pharmacology

**Toxicity Study:** Acute and sub-acute toxicity study of *Trikatu* was performed in Charles Foster rats for study of safety profiling. Results showed that in acute toxicity experiment *Trikatu* (2000 mg/kg, b.w.) was well tolerated by the animals under study and no significant changes were observed in morbidity, mortality, gross pathology, vital organ weight, gain in weight, haematological count and other necessary parameters. Biochemical parameters such as serum creatinine, SGPT, SGOT, serum lipid profile and tissue biochemical parameters such as reduced glutathione and malonaldehyde content as oxidative stress markers were found normal<sup>[13]</sup>. Acute toxicity studies of *Trikatu mega Ext* revealed that LD<sub>50</sub> is 300mg/kg body weight in mice<sup>[14]</sup>.

**Pharmacokinetics:** Pharmacokinetic profile of indomethacin along with *Trikatu* was performed in rabbits. The results showed that *Trikatu* enhanced the absorption of indomethacin which was supposed due to the increase in gastrointestinal blood flow as well as an increased rate of transport across gastrointestinal mucosa<sup>[15]</sup>. Concomitant administration of *Trikatu* and diclofenac sodium decreased significantly the bioavailability of diclofenac sodium<sup>[8]</sup>. *Piper longum* (long pepper) increased the blood levels of vasicine by nearly 233%. Piperine, the active principle of Piper species, increased blood levels of sparteine more than 100%. The effect of *Trikatu* on the bioavailability and pharmacokinetics of isoniazid was studied in rabbits. In a crossover study, ten rabbits were administered either single dose (orally) of isoniazid (14 mg/kg) alone or in combination with *Trikatu* (piperine, 10mg/kg). The study was carried out by collecting blood sample at different time interval and assayed for isoniazid by fluorimetric technique. Results indicate that *Trikatu* decreases the bioavailability

of isoniazid<sup>[16]</sup>. The effect of single and multiple doses of *Trikatu* on the bioavailability and pharmacokinetics of rifampicin were studied in rabbits. Rabbits were administered a single dose of rifampicin (24 mg/kg, p.o.) alone or in combination with a single dose of *Trikatu* (500 mg/kg, p.o.). In the other experiment, six rabbits were administered a single dose of rifampicin (24 mg/kg, p.o.) before and after multiple doses of *Trikatu* (500 mg/kg, p.o.) for seven consecutive days. In both studies, blood samples were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 9 and 12 h after drug administration and assayed for rifampicin. In animals groups treated with single dose of *Trikatu* there was a significant decrease in the peak plasma concentration (C<sub>max</sub>) of rifampicin. Multiple doses of *Trikatu* also reduced the C<sub>max</sub> and delayed the T<sub>max</sub> of rifampicin although not to a statistically significant level. Other pharmacokinetic parameters of rifampicin were not significantly altered. Co-administration of *Trikatu* does not influence the extent of bioavailability but reduces the rate of bioavailability (C<sub>max</sub>) of rifampicin<sup>[17]</sup>. Several studies have reported enhancement of blood levels of drugs like vasicine, sparteine, phenytoin, propranolol, theophylline, sulphadiazine and tetracycline when co-administered with *Trikatu* or piperine<sup>[18,19]</sup>. *Trikatu* has been shown to enhance the bioavailability of number of drugs by nonspecific and noncompetitive inhibition of the cytochrome P<sub>450</sub> enzyme system. The enhanced bioavailability of drugs is a result of a non specific and noncompetitive inhibition of drug metabolising enzymes by *Trikatu* (piperine). It has been shown to inhibit arylhydrocarbon hydroxylation, ethylmorphine-N-demethylation, and 7-ethoxycoumarin-o-deethylation and 3-hydroxybenzopyrene glucuronidation in a nonspecific and noncompetitive manner *in vitro*. It appears that the *Trikatu* group of drugs increases bioavailability either by promoting rapid absorption from the gastrointestinal tract, or by protecting the drug from being metabolized /oxidized in its first passage through the liver after being absorbed, or by a combination of these two mechanisms<sup>[20, 21, 8]</sup>.

**Antioxidant Activity:** *In vitro* antioxidant activity of petroleum ether, benzene, chloroform, ethyl acetate, 70% ethanol and aqueous extract of *Trikatu* was performed. *Trikatu mega Ext* exhibited significant scavenging effects on 2, 2-diphenyl-2-picryl hydroxyl (DPPH) free radicals, super oxide anion. The scavenging effect of

sample was found lower than that of ascorbic acid. The sample possess statistically significance DPPH free radical scavenging activity at a concentration of 100 µg/ml, inhibited the production of superoxide anion radical by 89.74% showing strong superoxide radical scavenging activity<sup>[22]</sup>.

**Antihyperlipidemic Activity:** The effect of *Trikatu* on lipid profile of *Rattus norvegicus* fed with atherogenic diet and standard diet was performed. Towards this goal an indigenous preparation of *Trikatu* was fed to normal and cholesterol fed male *Rattus norvegicus* to ascertain its efficacy as a hypolipidaemic agent. Its effects on body weight and lipid profiles were measured. It was found that '*Trikatu*' by virtue of its ability to reduce triglycerides and LDL cholesterol and to increase HDL cholesterol can reduce the risk of hyperlipidaemia and atherosclerosis. Hence '*Trikatu*' can be used as a potent hypolipidaemic agent and it can reduce the atherosclerosis associated with a high fat diet<sup>[23]</sup>.

**Antianorectic Activity:** The anti-anorectic activity of the hydro-alcoholic extracts of the *Trikatu* was evaluated to determine its effects in anorexia induced rats. Anorexia was induced in rats by physical stress arising by immobilization of animals for 60 min., intraperitoneal injection of *Escherichia coli* lipopolysaccharide (LPS, 100 µg/kg body weights), intraperitoneal administration of fluoxetine (8 mg/kg body weight). Similar doses of the extracts were tested on freely feeding rats and on rats that had been deprived of food for 20 h. Results indicates that hydro-alcoholic extract of *Trikatu* reduces the marked anorexia induced by stress in a dose-dependent manner. Pretreatment with *Trikatu* extract at doses of 200 and 400 mg/kg significantly reversed the anorectic effect induced by restraint stress and by administration of Fluoxetine hydrochloride (FLU). The components of *Trikatu* failed to reverse the inhibition of feeding individually. In contrast, pretreatment of *Trikatu* reversed stress-, fluoxetine-induced anorexia. The study provides strong evidence of the synergistic action of *Trikatu* to reduce stress-induced anorexia<sup>[24]</sup>.

**Antitumor Activity:** Anti-tumor activity of mercaptopurine in combination with aqueous extract of *Trikatu* and *Gomutra* was conducted. 20-methylcholanthrene a polycyclic aromatic hydrocarbons was used to induce tumor in albino mice. Haematological and endogenous antioxidant parameters were evaluated in the

study. Individual treatment with mercaptopurine (5 mg/kg) and *Trikatu* (100 mg/kg) significantly restored the altered haematological and antioxidant parameters to normal values. Even mercaptopurine (2.5 mg/kg) at its sub therapeutic dose showed equivalent effects as that of therapeutic dose of mercaptopurine (5 mg/kg) when it was co administered along with *Trikatu* [100 mg/kg] compared to the positive tumor control group<sup>[25]</sup>.

**Hepatoprotective Activity:** Protective and curative effect of ethanolic extract of *Trikatu* against carbon tetrachloride induced hepatotoxicity in rats was examined. Carbon tetrachloride (1 mL/kg<sup>-1</sup>) given through intraperitoneal route caused liver damage in rats manifested by significant rise in serum enzymes levels, declines in reduced glutathione level and elevations in malondialdehyde levels. The oral administration of ethanolic extract of *Trikatu* in a dose of 150 mg/kg<sup>-1</sup> to carbon tetrachloride intoxicated rats. The degree of protection was measured using biochemical parameters such as serum glutamate oxalate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), bilirubin and total protein. The ethanol extract at an oral dose of 150 mg/kg exhibited a significant protective effect by lowering serum levels of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase and total bilirubin. Liv-52 syrup was used as positive control<sup>[26]</sup>.

**Antimicrobial Activity:** The antibacterial activity of the aqueous, ethanol, acetone and methanolic extract of *Trikatu* was evaluated by disc diffusion method. *Trikatu* extracts showed strong antibacterial activity against *S. aureus*, *S. epidermidis*, *P. vulgaris*, *E. coli*, *P. aeruginosa*, *B. subtilis* and *K. pneumoniae*. Ampicillin was used as positive control (10 mcg/ disc). The antibacterial activities of aqueous, ethanol, methanol and acetone extracts of *Trikatu* were performed against enteric bacterial pathogens such as *E. coli*, *S. aureus*, *P. aeruginosa*, *P. vulgaris*, *S. epidermidis*, *S. typhi*, *S. typhimurium* and *E. aerogenes*. Ethanol extract of *Trikatu* showed moderate antibacterial activity against all the bacterial pathogens while methanol extract showed strong antibacterial activity against *S. epidermidis* and *S. aureus*, moderate antibacterial activity against *P. vulgaris*, *P. aeruginosa*, *S. typhi*, *E. coli*, *K. pneumoniae*, *S. typhimurium* and *E. aerogenes*. Acetone extract of *Trikatu* showed strong antibacterial activity against *S.*

*epidermidis*, *S. aureus*, *P. vulgaris*, *S. typhi*, *E. coli*, *K. pneumoniae* and *E. aerogenes* whereas moderate antibacterial activity against *P. aeruginosa* and *S. typhimurium* [27, 28].

In another experiment antibacterial activity of ethanol extracts of *Trikatu* had been performed against *E.coli* and *S. aureu* using agar well diffusion method. Ethanolic extract of *Trikatu* showed moderate activity ( $17 \pm 0.11$ ,  $16 \pm 0.12$ ) against tested microbes as compared to antibiotic streptomycin sulphate used as positive control was found to be  $20 \pm 0.12$ ,  $19 \pm 0.01$  respectively [29].

**Anthelmintic Activity:** Anthelmintic activities of aqueous and ethanolic extract of *Trikatu* were performed using adult earthworm *P. posthuma*. Piperazine citrate was used as standard in the study. Results indicated that ethanolic extract of *Trikatu* was found more active as compared to aqueous extract. Both aqueous and ethanolic extract of *Trikatu* showed almost equal activity as compared to standard drug piperazine citrate [30]. In another experiments it was found that aqueous extract of *Trikatu* showed higher anthelmintic activity as compared to the standard drug albendazole [31].

**Analgesic Activity:** Analgesic effect of ethanol extract of *Trikatu* was performed in albino mice of either sex by using hot plate. At a dose of 250 mg/kg, b.w., *Trikatu* extract exhibited significant analgesic activity as compared to standard drug analgin [29].

**Antifungal Activity:** *In vitro* antifungal activity of ethanol extract of *Trikatu* had been tested against *Aspergillus niger*, and *mucor species* using agar well diffusion method. Ethanol extract showed highest activity ( $6.2 \pm 0.01$ ,  $7.0 \pm 0.05$ ) against tested fungus as compared to antifungal agent Nystatin ( $9.0 \pm 0.12$ ,  $10 \pm 0.11$ ) used as standard drug [29].

**Immunomodulatory Activity:** The immunomodulator activity of the *Trikatu* mega Ext (Pet. Ether, Benzene, Chloroform, Ethyl acetate, 70% ethanol and water) was evaluated by carbon clearance assay, Delayed Type Hypersensitivity tests in oral administration of mice at a dose of 100-200 mg/kg body weight. The megaExt Showed significant ( $p < 0.001$ ) increased in phagocytic index when compared to control group indicates stimulation of the reticulo-endothelial system and Potentiated the delayed type hypersensitivity reaction induced by sheep red blood cells. The results obtained in this study indicate that *Trikatu* possesses potential immunomodulatory activity and has therapeutic

potential for the prevention of autoimmune diseases [32] in another study. In the present study, *Trikatu*, (1000 mg/kg/b.wt.) was evaluated for its immunomodulatory properties in comparison to indomethacin (reference drug) in rats. The results obtained in our study showed a significant decrease in cell mediated immune responses, humoral immune responses (haemagglutination titre and plaque forming assay) and macrophage phagocytic index of *Trikatu* compared to control implying its immunosuppressive property [33].

**Adaptogenic Activity:** Adaptogenic activity of megaext of *Trikatu* was evaluated by Swim endurance test and anoxic tolerance test in mice. The evaluation of adaptogenic potential by oral administration of mega Extract of *Trikatu* (100-200 mg/kg) evoked a significant increase in the swimming time (min.) ( $p < 0.001$ ) and also increases in anoxic tolerance time ( $p < 0.001$ ) in physical and anoxic stress models as compared to control thus confirming its adaptogenic nature [14].

**Anti-allergic activity:** The topical preparation of ethanolic extract of *Trikatu* did not show additional effects for relieving mosquito bite reaction as compared with the reference product containing camphor, menthol, and eucalyptus. However, both preparations can reduce papule size and relieve erythema intensity, edema and pruritis symptoms from mosquito bite reaction. Thus *Trikatu* preparation containing *Trikatu* extract, menthol, camphor, and eucalyptus did not provide additional anti-inflammatory effect compared to the reference product containing camphor, menthol, and eucalyptus [34].

**Anti-arthritic Activity:** The anti-arthritic effect of oral administration of oral administration of *Trikatu* (1000 mg/kg body weight) and indomethacin (3 mg/kg body weight, intraperitoneal) on Freund's adjuvant (0.1 mL) into the foot pad of the right hind paw. The thickness of the hind paw was monitored by using a vernier scale periodically which was markedly reduced on treatment with 1000 mg/kg body weight *Trikatu* and 3 mg/kg body weight indomethacin. The results evidenced a significant lowering of all the biochemical and immunological parameters to near normal levels in arthritic rats as evidenced by the radiological and histopathological assessments. Thus results suggest that *Trikatu* could be a promising alternative drug for the control and management of rheumatoid arthritis [35].

**Anti-inflammatory Activity:** The anti-inflammatory activity of the *Trikatu* was

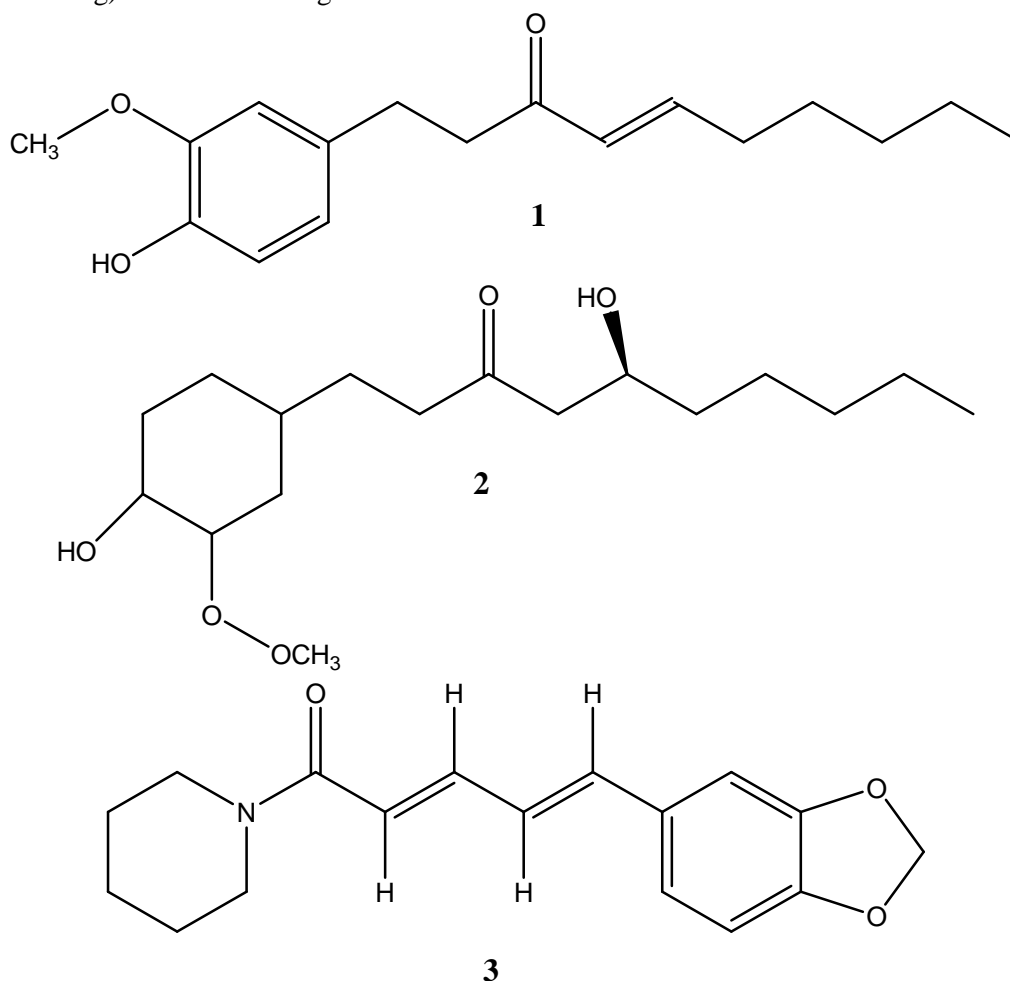
evaluated by carageenan-induced paw tests to determine its effects on acute and chronic phase of inflammation models in rabbits. *Trikatu* showed Percent edema inhibition at the third hour elicited by the combination of diclofenac sodium and *Trikatu* (59.37%) was significantly lower as compared to diclofenac alone (74.42%). It is also observed that *Trikatu* by itself also induced a significant reduction in edema formation (62.85%) and the degree of inhibition is comparable with that of diclofenac sodium with *Trikatu*. Result indicate that the extent to which edema was inhibited by the combination of diclofenac and *Trikatu* was similar to that shown by *Trikatu* alone, but significantly less than that produced by the sole administration of diclofenac. Likewise, *Trikatu* significantly decreased the plasmatic concentrations of diclofenac<sup>[8]</sup>.

In another study, *Trikatu*, (1000 mg/kg/b.w.) was evaluated for anti-inflammatory activity in comparison to indomethacin (reference drug) in rats. A significant anti-

inflammatory effects was observed in *Trikatu* treated adjuvant induced arthritic rats by a reduction in the levels of circulating immune complexes and inflammatory mediators (TNF-alpha and Interleukin-1beta)<sup>[33]</sup>.

The anti-inflammatory activity of methanolic extract of *Trikatu* was evaluated by carageenan-induced paw edema to determine its effects on acute and chronic phase of inflammation models in rats. Methanolic extract of *Trikatu* showed maximum inhibition (71.18%) at a dose of 400 mg kg<sup>-1</sup> b.w. after 5 h of drug administration in carageenan-induced paw edema, whereas indomethacin produced 68.86% of inhibition<sup>[11]</sup>. In another study, methanolic extract of *Trikatu* showing effective against Carragenan- induced paw oedema in wistar rats. Aspirin (150 mg/kg p.o.) used as suspension for standard drug<sup>[36]</sup>.

**Phytochemistry:** Phytochemical investigation on *Trikatu* led to the isolation of 6-Shogaol (**1**), 6-gingerol (**2**), *Piperine* (**3**)<sup>[3]</sup> from its powder.



**Conclusion:** It is strongly believed that detailed information as presented in this review on the

phytochemical and various biological properties of the polyherbal formulation *Trikatu* might

provide detailed evidence for the use of this formulation in different medicines and diseases. Extracts and fractions of the formulation possess anti-arthritic, mosquito bite, immunomodulatory, adaptogenic, antifungal, anthelmintic, bioavailability, toxicity studies, anti-anorectic, hepatoprotective, antioxidant, analgesic, anti-inflammatory, antihyperlipidemic, antimicrobial and antitumor activity.

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