Multi-dimensional action of “Trikatu”
(Piper nigrum, Piper longum and Zingiber officinale)

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Abstract

“Trikatu”- an Ayurvedic formulation comprising of a 1:1:1 ratio of dried fruits of Piper nigrum, Piper longum and dried rhizomes of Zingiber officinale is widely used to enhance the bioavailability of drugs, like vasicine, indomethacin, etc. The enhanced biological response might lead to alteration of therapeutic regimens of commonly prescribed drugs. Some research work has been carried out on bioavailability of Trikatu. Pharmacokinetic and Pharmacodynamic studies on interaction of “Trikatu” with diclofenac sodium indicates that Trikatu pretreatment might decrease the bioavailability of certain drugs probably through a drug-herb interaction there by adversely affecting the therapeutic efficacy of these drugs. Researches shown that piperacine enhances bioavailability of certain drugs and has been demonstrated to sustain a higher level of plasma concentration of some drugs when orally co-administered with them. There is evidence to that, it inhibits the major drug metabolizing enzyme CYP3A4 and the drug transported P-glycoprotein. The present work aimed to the probable mode of action by analyzing each ingredient Pippali (Piper longum), Marica (Piper nigrum), Śuṇṭi (Zingiber officinale) with the help of active ingredients Piperine, Zingiberone etc.

Key words: Trikatu, Diclofence sodium, CYP3A4 enzyme, Piperine, Zingiberone.
INTRODUCTION

Herbs and plants have been in use as a source of therapeutic compounds in traditional medicinal system since ancient time. Medicinal plants play an important role in traditional health care systems. The medicinal value of these plants lies in some chemical substances that produce a definite physiological action on the human body. The most important of these bioactive constituents of plants are alkaloids, tannins, flavonoids and phenolic compounds. "Trikatu" an Ayurvedic formulation comprising of 1:1:1 ratio of dried fruits of Piper nigrum, Piper longum and dried rhizomes of Zingiber officinale is widely used to enhance the bioavailability of drugs. Trikatu is an herbal bioenhancer compound having Indian long pepper, black pepper and ginger. It provides a natural and safe support system for impaired gastric function associated with gaseous distension. Trikatu is a safe digestive, carminative, anti-flatulent and is effective in dyspepsia. It also improves gastric function. The present work aimed to the probable mode of action on Trikatu by analyzing the each ingredient Pippali (Piper longum), Marīca (Piper nigrum), Śuṇṭī (Zingiber officinale) with the help of active ingredients Piperine and Zingiberone etc.

RESEARCH FINDINGS

Ginger (Zingiber officinale)

Ginger (Figure:1) is an important plant with several ethnomedicinal and nutritional values. Therefore, used extensively worldwide as a spice, flavouring agent and herbal remedy.

In the fresh ginger rhizome, the gingerols were identified as the major active components and gingerol [5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one] is the most abundant constituent in the gingerol series (Figure:2). Traditionally, Z. officinale is used in Ayurveda, Siddha, Chinese, Arabian, African, Caribbean and many other medicinal systems to cure a variety of diseases viz., nausea, vomiting, asthma, cough, palpitation, inflammation, dyspepsia, loss of appetite, constipation, indigestion and pain. The plant is reported for antimicrobial activity, anticancer activity, antioxidant activity, antidiabetic activity, nephroprotective activity, hepatoprotective activity, larvicidal activity, analgesic activity, anti-inflammatory activity and immunomodulatory activities.

Black pepper (Piper nigrum Linn)

Black Pepper (Figure:3) is a dried fruit of Piper nigrum L., which is used in many herbal formulations and also used in food in view of its spicy taste. The main chemical constituent of Piper nigrum L., is the alkaloid piperine (Figure:4) (a trans-trans isomer of 1-piperoyl piperidine), which has many pharmacological properties.

Figure 1: Dried ginger

Figure 2: Gingerol series

Figure 3: Black pepper

Figure 4: Piperine

It is used for the treatment of diarrhoea and constipation in ancient times till present. Recent studies revealed that it has many other effects of pharmacological importance including, antimicrobial, antioxidant, and mainly as bioenhancer which promotes the absorption of many drugs and nutritional supplements. The bio enhancing activity
is due to its inhibitory activity of drug metabolizing enzyme CYP3A4. Midazolam is a short-acting benzodiazepine and has the anxiolytic, sedative, hypnotic, anti-convulsant, muscle relaxant and amnesic effects. Midazolam is extensively used as hypnotic, pre-anaesthetic medicine and as post-operative medicine for its amnesic property. Midazolam is extensively metabolized in both the liver and the intestine via CYP3A4 and CYP3A5 to 1-hydroxyMidazolam and 4-hydroxyMidazolam which undergo rapid conjugation with glucuronic acid and then excreted into the urine within 24 hr. Many drugs and herbs have been reported to cause pharmacokinetic drug interaction with Midazolam by the inhibition of CYP3A4, such as curcumin, itraconazole, DHA, green tea, andrographis paniculata, diltiazem and verapamil, which can modulate efficacy of Midazolam and may increase the risk of side effects such as drowsiness, confusion, memory loss, hypotension or respiratory depression.

Long pepper (Piper Longum)

Dried unripe fruits of long pepper (Figure: 5) are used as a tonic in alternative medicine. Decoction of immature fruits and roots is used in chronic bronchitis, cough and cold.

![Figure 5: Long pepper.](image)

Piperine is the major and active constituent of long pepper (Piper longum). The piperine content is 3-5% (on dry weight basis) in P. longum. The essential oil of the fruits showed insecticidal and insect-repellent activity. Bio-assay-guided isolation of chloroform extract of the fruits of P. longum is used in an invitro DGAT inhibitory assay, lead to isolation of a new alkamide together with four known alkamides. Pharmacological inhibition of acyl CoA: diacylglycerol acyl transferase by alkamides emerged as a potential therapy for the treatment of obesity and type 2 diabetes. An amide namely dehydropipernonaline having coronary vaso-relaxant activity was isolated from the fruit of Piper longum. Methanolic extract from dried fruits, roots and nutgalls of Piper longum, Piper sarmentosum, Quercus infectoria respectively, were examined for their spasmylytic activities using isolated rat or guinea pig ileum and compared with a reference anti-diarrheal drug such as loperamide and an L– type calcium channel blocker such as verapamil. The ethanol extracts inhibited platelet aggregation induced by U46619 in a concentration-dependent manner and by thrombin weakly. It was concluded that P. longum contains a constituent(s) that inhibits platelet aggregation as a noncompetitive thromboxane A2 receptor antagonist. Four acid amides, piperine, pipernonaline, piperoctadecaline, and piperoniumine, isolated from the fruits of P. longum showed dose-dependent inhibitory activities on washed rabbit platelet aggregation induced by collagen, arachidonic acid, and platelet-activating factor (PAF), except for that induced by thrombin. Piperlongumine, in particular, showed stronger inhibitory effects than other acid amides to rabbit platelet aggregation induced by collagen, AA and PAF. Piperine was found to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics due to its easy partitioning and increase in permeability of other drugs such as vasicine, indomethacin, diclofenac sodium etc. It was suggested that piperine might be inducing alterations in membrane dynamics and permeation characteristics, along with induction in the synthesis of proteins associated with cytoskeletal function, resulting in an increase in the small intestine absorptive surface, thus assisting efficient permeation through the epithelial barrier. The study showed that piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects.

CONCLUSION

Our Acharyas incorporated Trikatu in numerous yogas (Medicinal formulations) keeping in view on its multi-dimensional action. Trikatu is reported for antimicrobial activity, anticancer activity, antioxidant activity, anti-diabetic activity, nephroprotective activity, hepatoprotective activity, larvicidal activity, analgesic activity, anti-inflammatory activity and immunomodulatory activities. Trikatu as a bioavailability enhancer can be explored in various formulations. Piperine was found to enhance the bioavailability of structurally and therapeutically diverse drugs, possibly by modulating membrane dynamics due to its easy partitioning and increase in permeability of other drugs such as vasicine, indomethacin, diclofenac sodium etc.
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