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Review Article

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"YOGAVAHI REVISITED: A CRITICAL REVIEW OF PIPPALI, TRIKATU AND PIPERINE AS BIOAVAILABILITY ENHANCERS, FROM CLASSICAL CONCEPT TO CLINICAL PHARMACOKINETICS"

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ABSTRACT
Pippali (*Piper longum*) and the classical combination Trikatu (Pippali, Maricha and Shunthi) are added to many Ayurvedic formulations, and modern authors often describe them as bioenhancers in line with the classical idea of yogavahi, a substance that carries and amplifies the effect of what it is combined with. Piperine, the principal alkaloid of long and black pepper, has been studied for this property since the 1980s. This review traces the concept from classical texts to modern pharmacology and appraises the human evidence. Mechanistic studies show that piperine inhibits hepatic drug metabolism, the efflux transporter P-glycoprotein and the enzyme CYP3A4. In healthy volunteers, piperine increased exposure to phenytoin, propranolol and theophylline. A small study reported a 2000% increase in curcumin bioavailability with 20 mg of piperine, but that figure rested on a curcumin-only control below the detection limit, and a larger crossover trial found no significant advantage of a piperine formulation over a standard extract. Piperine also enhanced rifampicin activity against *Mycobacterium tuberculosis* in vitro, but its clinical value as an adjunct remains unproven. The evidence supports the classical intuition that pepper alters what accompanies it, but the effect is variable, depends on the co-administered substance, and is not selective, so the same mechanism that enhances an herbal drug can raise levels of a conventional drug with a narrow therapeutic index. We propose that Ayurvedic bioenhancement be studied with whole classical preparations, realistic doses and formal pharmacokinetic designs.

KEYWORDS: Yogavahi, Pippali, Trikatu, piperine, bioavailability, bioenhancer, P-glycoprotein, CYP3A4, Dravyaguna

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INTRODUCTION

Classical Ayurveda describes certain substances as yogavahi: carriers that take on the properties of what they are combined with and enhance them. Honey is the classical example.[1] Pippali (*Piper longum*) and Trikatu, the combination of Pippali, Maricha (*Piper nigrum*) and Shunthi (*Zingiber officinale*), are not called yogavahi in the same words, but they are added to a very large number of formulations, often in small proportions, in a way that suggests a similar role.[2] Pippali is also a rasayana in its own right, given in progressively increasing doses (vardhamana pippali), while Charaka warns against its excessive use.[1]

Modern research gave this practice a mechanistic interpretation. Work at the Regional Research Laboratory in Jammu in the 1980s showed that piperine, the main alkaloid of long and black pepper, increases the blood levels of several drugs, and the term bioenhancer entered the literature.[2,3] Since then, piperine has been combined commercially with curcumin and other supplements, and many Ayurvedic authors present it as scientific confirmation of the yogavahi concept. This review appraises that claim: the mechanisms, the human pharmacokinetic evidence, the limits of the best-known results, and the implications for practice.

METHODS

This is a critical narrative review. We searched PubMed, publisher websites and regulatory documents for mechanistic studies and human pharmacokinetic studies of piperine, Pippali and Trikatu as enhancers of co-administered substances, and for reviews of the classical concept.

MECHANISMS

Three mechanisms are well supported. First, piperine inhibits hepatic drug metabolism: early work showed that it is a potent inhibitor of drug-metabolising enzymes in rodents.[3] Second, it inhibits the intestinal and hepatic efflux transporter P-glycoprotein; in Caco-2 cell monolayers piperine inhibited the transport of digoxin and cyclosporine with half-maximal inhibitory concentrations of 15.5 and 74.1 μM.[4] Third, it inhibits CYP3A4, the enzyme responsible for the first-pass metabolism of many drugs, in human liver microsomes.[4] Because P-glycoprotein and CYP3A4 act together in the gut wall and liver, inhibiting both can substantially increase the oral bioavailability of shared substrates.[4,5] Effects on gastrointestinal transit, glucuronidation and membrane permeability have also been proposed.[2]

These mechanisms explain why the effect is not selective. Piperine does not recognise whether a co-administered substance is a desirable herbal constituent or a conventional drug; it acts on any substrate of the pathways it inhibits.

HUMAN EVIDENCE

Table 1 summarises the main human studies.

Table 1. Human pharmacokinetic evidence for piperine as a bioavailability enhancer.

Co-administered substance	Study	Finding	Comment
Phenytoin	Bano et al., 1987;[6] Velpandian et al., 2001[7]	Increased absorption; pepper in food delayed elimination	Single-dose; 5–6 volunteers; very low certainty[8]
Propranolol, theophylline	Bano et al., 1991[9]	Increased bioavailability	Healthy volunteers; small
Curcumin	Shoba et al., 1998[10]	Up to 2000% increase in AUC with 20 mg piperine and 2 g curcumin	Curcumin-only control below detection limit; 8 participants; 6-hour sampling[11]
Curcuminoids	Fança-Berthon et al., 2021[12]	Piperine formulation not significantly different from standard extract	Randomised crossover; 30 adults; 24-hour sampling

Conventional drugs

In healthy volunteers, piperine increased the absorption of phenytoin after a single dose,[6] and black pepper added to food altered both its absorption and elimination.[7] Increased bioavailability of propranolol and theophylline was also reported.[9] A 2026 systematic review graded these phenytoin studies as low or very low certainty because of their size and design but still recommended monitoring phenytoin levels when piperine is co-administered.[8] These studies show that bioenhancement in humans is real for some drugs;

they also show that it is a mechanism of interaction.

Curcumin: a cautionary example

The most widely quoted result in the field is that 20 mg of piperine increased the bioavailability of 2 g of curcumin by 2000% in human volunteers.[10] A review by the United Kingdom Committee on Toxicity noted that the study involved eight participants and six hours of sampling, that the curcumin-only control was below the limit of detection, and that it was unclear how undetectable values were handled in calculating the area under the curve.[11] A randomised crossover trial in 30 adults comparing five turmeric formulations over 24 hours found that the piperine formulation did not differ significantly from a standard extract and absorbed less well than a colloidal formulation.[12] The Committee noted that other studies found at most about a two-fold increase with piperine.[11] Curcumin is in any case an unstable and poorly bioavailable molecule with a doubtful record as a drug lead.[13] The striking 2000% figure should therefore not be cited as established.

Antitubercular drugs

Piperine has been studied as an adjunct to antitubercular drugs. In vitro it reduced the minimum inhibitory concentration of rifampicin against *Mycobacterium tuberculosis*, including multidrug-resistant isolates, increased its bactericidal activity and prolonged its post-antibiotic effect, possibly by inhibiting the efflux pump Rv1258c.[14] These are preclinical findings; robust clinical evidence that piperine-containing combinations improve treatment outcomes is lacking.

A DRAVYAGUNA PERSPECTIVE

The modern findings support the classical intuition that Pippali and Trikatu change the action of what accompanies them. They do not, however, support every modern claim made on their behalf. Three points deserve emphasis.

First, classical use concerns whole drugs in specific formulations and doses, not isolated piperine. Trikatu contains several alkaloids, essential oils and gingerols, and its effects may not equal those of piperine alone.[2] Almost no human pharmacokinetic study has tested a classical preparation containing Pippali or Trikatu with a defined co-administered drug.

Second, classical texts treat Pippali as potent. Charaka cautions against its excessive use,[1] and the vardhamana regimen increases and then decreases the dose under supervision. A drug that alters the fate of others in the body is exactly the kind of drug that requires such care. The concept of yogavahi implies amplification of what is present, which in a patient taking conventional medicines includes those medicines.

Third, enhancement is not a uniform property. The same mechanism produced a clear effect on phenytoin but a disputed effect on curcumin. Whether Pippali enhances a given co-administered substance depends on whether that substance is limited by the pathways piperine inhibits. This is consistent with the classical view that the action of a combination depends on its specific constituents rather than on a general rule.

IMPLICATIONS AND RECOMMENDATIONS

- Do not assume that adding Pippali or piperine improves the efficacy of a herbal product; demonstrate it for each combination.
- Treat Pippali, Trikatu and piperine supplements as potential causes of interaction with drugs that have a narrow therapeutic index, such as phenytoin, theophylline, cyclosporine and tacrolimus.[4,6,9]
- Conduct crossover pharmacokinetic studies of classical preparations with and without Pippali or Trikatu, using adequate sampling periods and validated assays sensitive enough to quantify the control arm.[11]
- Characterise the piperine and other alkaloid content of the preparation tested.[15]
- Use physiologically based modelling to predict which co-administered drugs are likely to be affected.[5]

LIMITATIONS

This review is narrative and relies on a small number of human studies, several of which are old, small and accessible only in abstract. Studies of whole Pippali or Trikatu in humans are almost absent, so conclusions about classical preparations are extrapolated from piperine.

CONCLUSION

Piperine inhibits hepatic metabolism, P-glycoprotein and CYP3A4, and it increases exposure to several conventional drugs in humans. This gives a pharmacological basis to the classical use of Pippali and Trikatu as carriers of other drugs. The effect is variable, its best-known demonstration with curcumin has not been reproduced, and it is not selective, so it can raise levels of conventional drugs as readily as

herbal ones. The yogavahi concept is best understood not as a guarantee of enhanced efficacy but as a reminder, already present in the classics, that the action of a drug depends on its company.

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