

REVIEW ARTICLE SIGNIFICANCE OF PHARMACOKINETICS AND
PHARMACODYNAMICS OF *PIPER NIGRUM L.* [MARICH]Dr. Vishesh Duggal^{*1}, Dr. Omprakash Sharma² and Dr. Naresh Garg²¹PG Scholar Department of Dravyaguna Vigyan.²Professor and HOD Department of Dravyaguna Vigyan, SriGanganagar College of Ayurvedic Science and Hospital, Tanta University, SriGanganagar – 335001, India.***Corresponding Author: Dr. Vishesh Duggal**
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ABSTRACT

The dry fruit of Marich (*Piper nigrum L.*) is an ingredient of more than 3500 Ayurvedic formulations. Its bioavailability enhancing activity on accompanying ingredients and its imperative 'pharmacological actions rationalize this. Piper nigrum has been proved to possess bioavailability-enhancing activity with various structurally and therapeutically diverse drugs. Various mechanisms responsible for the action are reviewed in this paper. Taking into consideration the exclusive principles behind Ayurvedic pharmaceuticals; the significance of its pharmacokinetics and pharmacodynamics as a part of a formulation is immense. It is possible to carry out the bioavailability study of an Ayurvedic formulation containing Marich using piperine as a marker. Various researchers have elaborated important its pharmacological actions viz anti-inflammatory, anti-metastatic, anti-peroxidative [cancer preventing], anti-oxidant, anti-depressant, anti-diarrheal actions. This supports the rationale of its being a part of most rejuvenating, anti-inflammatory, digestive, and anti-diarrheal Ayurvedic formulations.

KEYWORDS: Marich, Piper nigrum, piperine, Ayurvedic formulation, Shwasakuthara Rasa, bioavailability.

INTRODUCTION

Marich [*Piper nigrum L.*] is a branching climbing perennial shrub, mostly cultivated in hot and moist parts of India. Black pepper consists of dried, fully developed unripe fruits of the climber, which is used, in Ayurvedic drugs. It is also used as a spice in Indian subcontinent. It is nearly globular in shape, about 4- 5 mm in diameter with a characteristic coat with deep-set wrinkles. In Ayurveda Marich has been well documented for its therapeutic potentials. Ayurvedic texts describe the following properties of Marich. Dry fruit of Marich is tissue penetrating [teekshna], hot [ushna], ununctous [ruksha] and digestive stimulant, carminative and has anti-asthmatic properties. It's not too hot; and is pungent, both in rasa [taste] and vipaka. It alleviates kapha and vayu and aggravates pitta. The chief activity of Marich is of being pramath. This means that it has a potential to clear congestion in the body channels [srotasas] by penetration into the congestion itself.

***Piper nigrum L.* as an ingredient of Ayurvedic drugs**

Marich i. e. black pepper is an ingredient of more than 3500 Ayurvedic formulations⁹. In most of the formulations it is in a very small amount whereas in some formulations like Vasantakalpas, Shwasakuthara rasa etc it is a major ingredient by proportion.

An Ayurvedic combination known as Trikatu churna.^[10,11] contains dried powder of Piper nigrum, Piper Longum and Zingiber officinale suggestive of synergism. In this preparation, the three herbs enhance properties of each other; as all of them are having quite similar characteristics. Trikatu too, is one of the ingredients of many Ayurvedic formulations. It has been suggested that its use in the Indian system of medicine could be due to its bioavailability enhancing action on other medicaments.^[12] due to the sharp tissue penetrating activity.^[5]

In the formulation titled Suvarnamalini Vasant,^[13] Marich is a major herbal ingredient. The other ingredients are Suvarnabhasma, Mauktikapishiti, detoxified Darada [cinnabar], detoxified Kharpara, cow's butter and lemon juice. Except Marich, all ingredients are of sheeta virya and promote anabolism. At the same time, they are a little heavy for absorption. When these are combined with Marich having ushna veeya and catabolising properties, targeted antagonism is achieved. This assists the activity of increasing metabolism at micro-level [dhatwagnideepan] for which this drug is famous.

Some of the formulations in the table are purely herbal formulations whereas some are 330 herbomineral. It is

observed that various dosage forms have been reported to get the desired effect and raise the potency and efficacy of drugs. As indicated, above combinations in Ayurvedic formulations are based on certain fundamental principles.^[14] The combinations consist of completely un-fractionated herbs put together by employing processes like mardana [titration]. Some herbs enhance action of the combination while others avoid or minimize possible side effects. Thus, therapeutic

effect produced is the cumulative effect of formulation due to the rational combination not always attributed to an active ingredient. Just as one active principle in a herb balances the others' action by synergism or antagonism, one ingredient balances the action of others in the formulation. E.g. whenever Vatsanabh [Aconitum chasmanthum] is an ingredient of any drug; Tankana [borax] has to be there, as it is an antidote of the former.

Table elaborating basic principle of synergism-antagonism in ayurvedic drugs.

Formulations	Role of marich (bioavailability)	Role of other ingredient
Suvarnamalini vasant	Antagonistic to other ingredient, catabolising action	Anabolising action heavy for absorption
Trikatu	Synergistic to other ingredient	Synergistic
Shwaskuthara rasa	Vata kapha alleviating pramathi action	Vata kapha alleviating anti asthmatic
Marichadigulika	Catabolising	Catabolising action
Laghumalinivasant	Catabolising	Anabolising agent

In the herbomineral preparation called Shwasakuthara rasa; Marich is the key-ingredient. This drug is used mainly in management of bronchial asthma or vata kapha dominant shwasa disease. This formulation is prepared by triturating together detoxified [i.e. shodhi~ Parada (Hg), Gandhaka (S), Manasheela (As₂S₂), Tankana (borax), Vatsanabh, Trikatu and Marich. We came across four different references of Shwasakuthara Rasa in which concentrations and manufacturing processes of each formulation varies with respect exclusively to Marich. The proportion of Marich changes from equal amount to eight times of the others, whereas the preparation procedure is constant.^[15,16] Pharmaceutical practice is to triturate all raw drugs at the same time as against the guideline in Yogaratnakara to mix and triturate each black pepper one by one. This exclusive process is rationalized by propounding its share in increasing effectiveness of the drug. Marich is known for pramathi activity and hence its role is important in treatment of diseases such as bronchial asthma.

Moreover, Marich (*Piper nigrum* L) is shown to possess bioavailability-enhancing activity with various structurally and therapeutically diverse drugs. It has also been reported to have several pharmacological actions. A review of researches on *Piper nigrum* is essential to know its role as an ingredient of most Ayurvedic formulations.

The known active principle from the key ingredient can serve as a tracer to study pharmacokinetics or dynamics of any Ayurvedic formulation. Here, the active constituent of black pepper is an alkaloid named piperine [C₁₇H₁₉O₃ N, m.p. 129-30°: [1-[5-[1, 3-benzodioxol-5-yl]-1-oxo-2, 4, pentadienyl] piperidine]^[17] The sharp tasting alkaloid constitutes approximately 5 to 9 percent of commercial black pepper. It was first isolated in 1820, and its structure was established by laboratory syntheses in 1882 and 1894.^[18] It is absent in the leaves and stem of pepper plant.

Other pungent alkaloids occurring in the pepper plant in smaller amount are chavicine, piperidine and piperretin.^[19] The sharp flavor of freshly ground pepper is attributed to the compound chavicine, a geometric isomer (having the same molecular formula but differing in structure) of piperine. The loss of pungency of pepper on storage is associated with slow transformation of chavicine into piperine.^[20]

Various researches on *Piper nigrum* and piperine highlight the following points.

***Piper nigrum* L. as a bioavailability enhancer**

In vitro experiments have showed that piperine enhanced the uptake of radio labelled L-leucine, L-isoleucine and L-valine, and increased lipid peroxidation in freshly isolated epithelial cells of rat jejunum suggesting that piperine may interact with the lipid environment to produce effects which lead to increased permeability of the intestinal cells.^[21] Co-administration of piperine, from *Piper nigrum* L. enhanced bioavailability of beta lactam antibiotics, amoxicillin trihydrate and cefotaxime sodium significantly in rats,^[22] and that of propranolol and theophyllin in healthy volunteers.^[23] Piperine derived from black pepper increased the plasma levels of coenzyme q10 following oral supplementation.^[24] Piperine enhanced the bioavailability of the tea polyphenol(-)-epigallocatechin-3-gallate in mice.^[25] and phenytoin.^[26] and aflatoxin B1 in rat tissues.^[27] It enhanced the serum concentration, extent of absorption and bioavailability of curcumin [from *Curcuma longa* L.] in both rats and humans with no adverse effects in the doses used [20 mg/kg in rats and 20 mg in humans].

Black pepper as a nutraceutical and its bioenhancing dose: According to a US patent, as a daily supplement taken with a nutrient or nutrients by an average healthy adult, piperine is effective and safe in a broad dose range. A preferred effective dose range of piperine for

oral use to enhance nutrient bioavailability is 0.0004-0.15 mg/kg/day. The recommended dose of piperine for a healthy individual for oral use is approximately 5 mg/person/ day. The recommended dose in cases of clinically diagnosed nutritional deficiencies is up to 15 mg/ person/day in divided doses. i.e. 5 mg every six hours (in the morning, at noon, and in the evening). Black pepper contains approximately 5-9% piperine and is listed by the FDA as an herb which is generally recognized as safe (GRAS) for its intended use as spice, seasoning, or flavoring. The bioenhancing dose of piperine as used in the 331 invention is a maximum of approximately 15 mg/ person/day, or no more than 20 mg/day in divided doses, which corresponds to from several thousands to up to 40,000 times less than the LDs dose of piperine, as established in various experiments on rodents.^[29] Possible Mechanisms for the.

Bioavailability enhancing Activity of *Piper nigrum* L

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.^[29] The increased bioavailability could be attributed to the effect of piperine on microsomal metabolizing enzymes or enzymes system.^[30] Piperine may act as an apolar molecule and form apolar complex with drugs and solutes. It may modulate membrane dynamics due to its easy partitioning thus helping in efficient permeability across the barriers.^[31] A study hypothesized that piperine bioavailability enhancing property may be attributed to increased absorption, which may be due to alteration in membrane lipid dynamics. and change in the conformation of enzymes in the intestine. In conclusion, it was suggested that piperine may be inducing alterations in membrane dynamics and permeation characteristics, along with induction in the synthesis of proteins associated with cytoskeleton function, resulting in an increase in the small intestine absorptive surface, thus assisting efficient permeation through the epithelial barrier.^[32] The effectiveness of an extract from the fruit of black pepper, consisting of a minimum of 98.0% pure alkaloid piperine, was evaluated for its ability to improve serum response of beta-carotene. Study suggests that the serum response during oral betacarotene supplementation is improved through the non-specific, thermogenic property(s) of piperine, described in the paper as thermo-nutrient in action.^[33] In all the studies, *Piper nigrum* proved to be bio-enhancer on co-administration with other main drugs. This explains the inclusion of Marich or Trikatu in 3500 formulations. However, Ayurvedic preparations containing *Piper nigrum* as main ingredient may not have been designed only due to its bio-enhancing property but owing to its pharmacological action. The significance of pharmacological activity of Marich as the main ingredient of a formulation needs to be searched.

Pharmacokinetics of Piperine

Studies, on the metabolism of piperine were conducted to study its absorption, tissue distribution and excretion of urinary conjugates in rats. Upon administration to male albino rats at a dose of 30 mg (85 mg/kg) intraperitoneally, about 97% was absorbed irrespective of the mode of dosing. Three per cent of the administered dose was excreted as piperine in the feces. Piperine was not detectable in urine. When averted sacs of rat intestines were incubated with 200-1000 mcg of piperine, about 47-64% of the added piperine disappeared from the mucosal side. Only piperine was present in the serosal fluid and also the intestinal tissue, indicating that piperine did not undergo any metabolic change during absorption. Examination of the passage of piperine through the gut indicated that the highest concentration in the stomach and small intestine was attained at about 6 h. Only traces < 0.15% of piperine were detected in serum, kidney and spleen from 30 min to 24 h. About 1-2.5% of the intraperitoneally administered piperine was detected in the liver during 0.5-6 h after administration as contrasted with 0.1-0.25% of the orally administered dose.^[34] After oral administration of piperine (170 mg/ kg) to rats, the metabolites in bile and urine were examined by thin-layer chromatography, high performance liquid chromatography and combined gas chromatography-mass spectrometry. Four metabolites of piperine, viz. piperonylic acid, piperonyl alcohol, piperonal and vanillic acid were identified in the free form in 0-96 h urine whereas only piperic acid was detected in 0-6 h bile. Based on these results, a pathway for the biotransformation of piperine in rats is proposed.

Pharmacological Actions

Piperine was isolated from *Piper nigrum* Linn for the evaluation of anti-inflammatory activity in rats. Different acute and chronic experimental models were employed simultaneously & biochemical estimations were made to elucidate the underlying mechanism of the action. It acted significantly on early acute changes in inflammatory processes and chronic granulative changes.^[36] A study indicated that supplementation with black pepper or the active principle piperine can reduce high-fat diet induced oxidative stress to the cells.^[37] In vitro studies indicate that piperine is shown to possess antioxidant activity.^[38] It is also shown to possess antidepressant like activity.^[39] This goes in support of pepper being a part of many rejuvenating formulations described in Ayurvedic texts. The effect of piperine on the inhibition of lung metastasis induced by melanoma cells was studied in mice. The results of this study demonstrate the antimetastatic activity of piperine.^[40] Chemoprevention has emerged as a very effective measure against carcinogenesis. Oral supplementation of piperine effectively suppressed lung carcinogenesis in benzopyrene induced mice. It was observed that piperine shows chemo-preventive effect by modulating lipid peroxidation and augmenting anti oxidant defense system.^[41] Piperine was found to suppress

benzo(a)pyrene (B(a)p) induced lung cancer in Swiss albino mice.^[42] Being a potential inducer of detoxication system, the possible chemo preventive role of black pepper in chemical carcinogenesis is suggested.^[43] A study has suggested unique association between anti-oxidative effect of piperine and ultimately the capability of piperine to prevent cancer.^[44] This proves that pepper has potential activity on lungs supporting the objective of its being an ingredient of most Ayurvedic formulations advocated in treatment and prevention of respiratory disorders. Researchers have investigated the effect of piperine on castor oil-stimulated fluid accumulation in the mouse small intestine. These results suggest that piperine reduces castor oil-induced fluid secretion with a mechanism involving capsaicin sensitive neurons. Anti-diarrhoeal activity of piperine against castor oil, MgSO₄ and arachidonic acid was studied and proven in mice. The results validate the rationale for its use in traditional anti-diarrhoeal formulations.^[46]

CONCLUSIONS

1. The dry fruit of Marich (*Piper nigrum* L.) is a minor ingredient of more than 3500 and major ingredient of approximately 10 commonly used Ayurvedic formulations. Imperative pharmacological actions and bioavailability enhancing activity on accompanying ingredients rationalize inclusion of Marich in such a large number of formulations.
2. Various researchers have elaborated its important pharmacological actions, which support the rationale of its being a part of most anti-inflammatory, rejuvenating, digestive, antidiarrheal Ayurvedic formulations.
3. Toxicological studies prove safety of piperine, the chief active constituent of *Piper nigrum* L ; as the estimated amount of piperine in Ayurvedic drugs is much less than its toxic dose.
4. Marich predominant formulations like *Suvarnamalini Vasant*, *Madhumalini Vasant*, *Laghumalinivasant*, *Marichadi gulika* should be studied employing new technologies to generate evidence base for Ayurvedic formulations.

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