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Bioavailability Enhancement by Piperine: A Review

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Abstract
Oral absorption of drug is very important issue especially when the drug is poorly bioavailable, given for long periods and expensive. Poorly bioavailable drugs remain sub-therapeutic because a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may also lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug. Several approaches have been used to maximize oral bioavailability, but with the discovery of the first bioavailability enhancer piperine in 1979, a new class of drug and a new concept was introduced in to the science. Bioenhancers or bioavailability enhancers are mostly the plant based molecules which promote the biological activity or bioavailability or the uptake of drugs in combination therapy. This review article concludes the bioavailability enhancing property of piperine.

Keywords: Piperine, bioenhancer, bioavailability, *Piper nigrum*, combination therapy.

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INTRODUCTION

Drug discovery is no longer a game of chance or just limited to the availability of new technology. Better understanding of various approaches and key learning from the past with the appropriate strategy for the future is essential to make a significant difference.[1] During the past few years a large number of approved new drug applications have originated from the biotechnology industry and analysts expect a continuation of pharmaceutical-biotechnology alliances to help expand pipelines.[2] Similarly, natural products have contributed nearly half of all small molecules approved in this decade. It has been suggested that the current drug discovery approach of finding 'new entity drugs', if shifted to 'combining existing agents' may be helpful. Therefore natural product drug discovery based on ethnopharmacology and traditional medicines may also be considered as attractive strategic options.[3,4]

Recently the combination of therapeutic agents with natural compounds possessing absorption improving activities has gain great interest for enhancing the bioavailability of poorly bioavailable drug. Natural compounds such as piperine, quercetin, sinomenine, glycyrrhizin, gentistein, naringin, niazeridine and lysergols were evaluated for their bioenhancing effect, along with modern medicines.[5]

Plants have been the source of medicines since thousands of years. Members of the botanical family piperaceae were among the first cultivated plant and the species of the genus Piper are the important medicinal plants used in various systems of medicine.[6] Black pepper (Piper nigrum) and long pepper (Piper longum) are the best known spices in the family and are probably among the most recognized spices in the world. Both the peppers have been used medicinally for centuries. Black pepper alone accounts for about 35% of the world's total spice trade.[7,8]

Generally the fruits of P nigrum and P longum contain 1.0–2.5% volatile oil, 5–9% alkaloids, of which the major ones are piperine, chavicine, piperidine, and piperetine. Most of the pharmacological properties of P nigrum and P longum fruits are attributed to a piperidine alkaloid; piperine which is present in the fruits in amounts of 1.7–7.4%.[9]

HISTROY AS BIOENHANCER

The term bioavailability enhancer or bioenhancer was first coined by Indian scientists C.K. Atal, the Director of the Regional Research laboratory, Jammu, who discovered and scientifically validated Piperine as the world's first bioavailability enhancer in 1979. Bioenhancers are molecules, which do not possess drug activity of their own at the dose used but promote and augment the biological activity or bioavailability or the uptake of drugs in combination therapy.[10]

C.K. Atal, the Director of the institute scrutinized a list of ancient Indian Ayurvedic formulations used in the treatment of a wide range of diseases. He found that one of the groups of herbals which has been documented very frequently as essential part of about 70% of Ayurvedic prescriptions, is `Trikatu`, that comprises three acrids viz. long pepper, black pepper and dry ginger in equal proportions. He observed that a majority of Ayurvedic formulations contained either Trikatu or else one of the ingredients of Trikatu, namely Piper longum (210 formulations out of 370 reviewed) used in a large variety of diseases. In subsequent experiments using various drugs and extracts with trikatu and its ingredients they found that mainly piperine enhances the bioavailability of most of the drugs used in experiments and the role of ginger is to regulate intestinal function to facilitate absorption.[11,12,13]

ISOLATION AND EXTRACTION OF PIPERINE FROM PIPER SPECIES

Piperine was discovered by Hans Christian Ørsted in 1819. It is known as one of the main components of pepper. [14] Piperine is responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine). [15] It can be isolated from the fruits of P. nigrum or P. longum. The powdered fruits of the plant are extracted with dichloromethane at room temperature with stirring for 12 hours. The extract is filtered, concentrated in vacuum, and then the residue is purified on an alumina column. Pure piperine can also be obtained by crystallization from ethanol, which may be required for food and/or medicinal usages. Piperine is obtained directly from the crude residue in lesser amounts by extraction in alcohol, filtration and successive crystallization. Piperine can be synthesized from the interaction of piperyl chloride (formed from piperic acid and phosphorus pentachloride) and piperidine. [16]

PROPERTIES OF PIPERINE

PHYSICAL AND CHEMICAL PROPERTIES OF PIPERINE

Piperine is a nitrogenous pungent substance.[17] The chemical structure of piperine places it in the group of cinnamamides.[18] The congeners of cinnamamides possess sedative, hypnotic, anticonvulsant, antidepressant, and skeletal muscle relaxing properties. Highly pure piperine is needle-shaped or short rod-shaped light yellow or white crystalline powder. It yields salts only with strong acids. The solution of piperine in alcohol has a pepper-like taste. [19]

S No	IUPAC Name	1-[5-(1,3-Benzodioxol-5yl)-1-oxo-2,4-pentadienyl]piperidine
1	Chemical name	1- piperoyl piperidine
2	Molecular formula	C17H19NO3
3	Molecular mass	285.34 gm mol^{-1}
4	Percentage composition	C= 71.55%, H=6.71%, N=4.91% and O=16.82%
5	Taste	Tasteless at first, but burning aftertaste
6	Melting point:	130°C
7	Density	1.193 gm cm^{-3}
8	pK (18°)	12.22
9	Solubility	Insoluble in water, soluble in benzene and acetic acid
10	Stereoisomer	isopiperine, isochavicine and chavicine
11	UV absorption maxima (methanol)	332 nm

Table 1: Properties of Piperine[20,21,22,23]

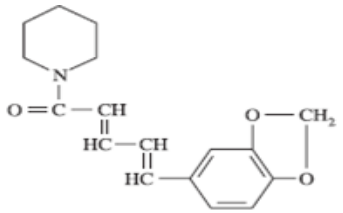

Figure 1: Chemical structure of Piperine[24]

PHARMACOKINETICS OF PIPERINE IN RAT

Piperine is rapidly absorbed through the GIT and could be detected in plasma as early as 15 min after administration to rat.[25] 97% of piperine was absorbed after oral administration of piperine at a dose of 170 mg/kg to the male albino rats. 3% of the administered dose was excreted up to 4 days as piperine in the feces and it is not detectable in urine. Piperine did not go undergo any metabolic change during absorption from intestine but letter it is metabolized rapidly by liver and other tissue and maximum plasma concentration was attained at about 6 hr. Urine is the major excretion route for piperine metabolites in rats as no metabolite could be detected in faces. Half life ($t_{1/2}$) was found to be 18.24 hr.[26] About 36% of the orally administered piperine was excreted as conjugated phenols in urine and 62% as methylenedioxyphenyl metabolites.[27] 4 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. Metabolism of piperine would involve an amidase which splits piperine at the --CO--N-- bond followed by the oxidation of the side chain and scission of the methylene-dioxy group.[28]

TOXICITY

The LD_{50} of piperine in mice and rats were found to be 330 mg Kg^{-1} and 514 mg Kg^{-1}, respectively. In sub acute toxicity studies, piperine at the dose rate of 100 mg Kg^{-1} for 7 days was reported to be non toxic.[29]

BIOENHANCING PROPERTY OF PIPERINE

BIOENHANCING DOSE OF PIPERINE

The effective bioenhancing dose of piperine for drugs varies but lots of studies indicate that a dose of approximately 10% (wt/wt) of the active drug or a daily dose of at least 15-20 mg/day could be regarded as an appropriate bioenhancing dose for most drugs. This bioenhancing dose of piperine corresponds to form several thousands to up to 40,000 times less than the LD_{50} dose of piperine, as established in various experiments on rodents.[10, 29, 30].

ADVANTAGES OF USING PIPERINE AS BIOENHANCER

There are various advantages of using bioenhancer in combination therapy. These are follows –

- Efficacy of drug is increase due to increase in bioavailability.
- Combination of bioenhancer with drug reduces the dosage and dangers of drug resistance can be minimized.
- Adverse drug reaction/side effect and toxicity of drug will be minimized because of reduced dosage. This is especially true of anticancer drugs like Taxol.
- There are ecological benefits too eg. Toxol used to treat ovarian cancer or breast cancer is derived from bark of Pacific yew tree, one of the slowest growing trees in the world. At present to treat one patient, six trees, 25-100 years old need to be felled with bioenhancers fewer trees will be destroyed.
- They can reduce inter-individual variability as well as intra-individual variability as they increase the bioavailability of drug.[30]

PROPOSED MECHANISM FOR BIOENHANCING EFFECT

By action on drug metabolizing enzyme

One of the reasons for bioenhancing effect of piperine is attributed to the interaction of piperine with enzymes that participate in drug metabolism, such as mixed function oxidases found in the liver and intestinal cells or may be due to inhibition of hepatic and non hepatic drug metabolizing enzymes.

Piperine may also interact with the process of oxidative phosphorylation, or the process of activation/deactivation of certain metabolic pathways, thus slowing down the metabolism and biodegradation of drugs. This action of piperine results in higher plasma levels of drugs, rendering them more available for pharmacological action.

Glucuronyl transferase activity also inhibited by piperine through the lowering of the endogenous UDP glucuronic acid contents and decreased transferase activity. Furthermore the aryl hydrocarbon hydroxylase (AHH) and 7-ethoxycoumarin deethylase (7 ECDE)) activities inhibited by piperine both under *in*

vitro and in vivo conditions. Researcher showed that Methylenedioxyphenyl ring in piperine has been found to be responsible for inhibition of drug metabolizing enzymes and piperine mediated inhibition of AHH activity. [31,32]

Piperine can reduce the biotransformation in gut by inhibiting CYP3A activity in gut epithelial cells. Inhibition of CYP3A by piperine in gut epithelial cells will lead to total increase in drug bioavailability in serum. Fewer drug molecules will be metabolized by phase I enzymes in the gut and will not be available for the phase II conjugation enzymes. This will lead to increased concentration of untransformed drug passing from gut in to blood and on to other tissue in the body. Piperine may reduce CYP3A drug biotransformation by acting as an inhibitor of CYP3A activity.[33]

Piperine is a potent inhibitor of UDP-GDH and it exerts stronger effects on intestinal glucuronidation than in rat liver.[34]

By affecting blood supply to GIT and membrane fluidity

The mechanism of enhancing the drug bioavailability can be explained by following possible explanations: a) increased blood supply to the gastrointestinal tract, b) effect on membrane fluidity with concentration dependency.

Piperine interacts with proteins embedded in the cell membrane by stimulating leucine amino peptidase and glycyl-glycine dipeptidase activity. This suggests that piperine could modulate the cell membrane dynamics related to passive transport mechanism due to its apolar nature by interacting with surrounding lipids and hydrophobic domain of cellular proteins. The improved bio availability of nutrients by the piperine is perhaps due to its thermo nutrient action or thermogenic action. Bioavailability enhancing action of drugs is partly due to enhancement of blood supply in enteric vessels as a result of local vasodilatation.[35,36]

By enhancing drug transport

A resent work concluded in Regional Research Laboratory, Jammu has shown that piperine acts as modulator of cell membrane dynamics and help the transport of drugs across these barriers. Piperine form complex with drugs and help them reach the target site rather than spread out non – specifically. It 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 of drugs across the barriers.[37]

Piperine may inhibit the capability of pathogen to reject the drug. It is very useful in case of antibiotic resistant strain of pathogen. Piperine may increase the entry of drug to pathogen either by modulating the signaling process so that accessibility of drug to pathogen is increased or by enhancing the binding of drug to receptors like DNA or protein of the pathogen.[30]

BIOAVAILABILITY ENHANCEMENT BY PIPERINE

Pattanaik S, *et al.*, (2009) evaluated the effect of piperine (20 mg p.o.) on the pharmacokinetics of carbamazepine (300 or 500 mg bid) in epilepsy patients. The comparison of pharmacokinetic parameters from blood samples at regular interval, after the administration of carbamazepine and carbamazepine along with piperine showed that piperine significantly increased the mean plasma concentrations of carbamazepine in both dose groups. There was a significant increase in AUC, average C(ss) and a decrease in K(el) in both the dose groups. C_{max} and t_{max} were increased significantly following piperine administration in the 500 mg dose group. They concluded that piperine could significantly enhance the oral bioavailability of carbamazepine, possibly by decreasing the elimination and/or by increasing its absorption.[38]

Jin MJ, *et al.*, (2010), investigated the enhanced oral exposure of fexofenadine (10 mg/kg) in rats in the presence and absence of piperine (10 or 20 mg/kg, given orally). Results of study indicated that combination of piperine increases the oral exposure (AUC) of fexofenadine by 180% to 190% and bioavailability approximately by 2-folds. They concluded that this effect of piperine likely due to the inhibition of P-glycoprotein-mediated cellular efflux during the intestinal absorption.[39]

Janakiraman K, *et al.*, (2011) aimed to include Piperine (bioenhancer) as a formulation additive in oral formulations of Ampicillin Trihydrate. Physical mixture of Ampicillin Trihydrate and Piperine (1:1) was tested for their compatibility and stability study. The above studies proved that Piperine can be used as a formulation additive for bioenhancing effect in oral formulations of Ampicillin Trihydrate.[40]

Shoba G, *et al.*, (1998) studied the effect of piperine on the bioavailability of curcumin in rats and healthy human volunteers at a dose 20 mg/kg and 20 mg and 2 g/kg to rats and 2 g respectively. Concomitant administration of piperine increases the t_{max} while elimination half life and clearance significantly decreased and the bioavailability was increased by 154%. On the other hand in humans the increase in bioavailability was 2000%. The study shows that piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects.[41]

Kasibhatta R, *et al.*, (2007) conducted a crossover, placebo-controlled pilot study in eight healthy adult males. Blood samples were collected from 1 to 144 hours post-dose of the subjects received piperine 20mg

or placebo each morning for 6 days, and on day 7, nevirapine 200mg plus piperine 20mg or nevirapine plus placebo in a crossover fashion. Analysis of pharmacokinetic data showed there was increase in mean maximum plasma concentration (Cmax), area under the plasma concentration-time curve. The last measurable concentration (C(last)) [AUC(t)], AUC extrapolated to infinity (AUC(infinity)) and C(last) values of nevirapine was increased by approximately 120%, 167%, 170% and 146%, respectively.[42]

Singh A, *et al.*, (2010) found an increase of 57% and 88.53% in peak plasma levels and AUC respectively of metronidazole when given with piperine to male New Zealand white rabbits (2.0-2.5 kg body weight).Three groups of rabbits were formed from which one group was considered as control and received only vehicle (distilled water) orally. Remaining two groups were treated with metronidazole (20 mg/ kg) and combination of metronidazole (20 mg/ kg) and piperine (10 mg/kg) respectively.[43]

Pooja S, *et al.*, (2007) evaluated the analgesic activity of *Piper nigrum* (10 mg/kg) extract and its interaction with diclofenac sodium (5 mg/kg) and pentazocine (5 mg/kg) in albino mice (25-30 grams). Peripheral analgesic activity was evaluated by acetic acid induced writhing test, using diclofenac sodium, *Piper nigrum* extract and their combination orally. Similarly central analgesic activity was studied by tail flick method using pentazocine and *Piper nigrum* extract and their combination orally. Results showed significant decrease in writhes 78.43% and significant increase in tail flick latency in case of combination with respect to control. The findings suggest that the *Piper nigrum* extract significantly increased the analgesic activity of diclofenac sodium and pentazocine.[44]

Badmaev V, *et al.*, (2000) found the nonspecific bioenhancing effect of piperine (5 mg) when it was increase the plasma levels of supplemental coenzyme Q10 in a clinical study using a double-blind design. The relative bioavailability of 90 mg and 120 mg of coenzyme Q10 administered in a single-dose experiment or in separate experiments for 14 and 21 days with placebo or with 5 mg of piperine was determined by comparing measured changes in plasma concentration. The results of the single-dose study and the 14-day study indicate smaller, but not significant, increases in plasma concentrations of coenzyme Q10 but supplementation of 120 mg coenzyme Q10 with piperine for 21 days produced approximately 30% greater, area under the plasma curve than was observed during supplementation with coenzyme Q10 plus placebo.[45]

Badmaev V, *et al.*, (1999) evaluated the effectiveness of piperine (5 mg) to improve serum response of beta-carotene (15 mg) during oral supplementation using a double-blind, crossover study design. The results indicate that supplementation with beta-carotene plus piperine for 14-days produced a 60% greater increase in area under the serum beta-carotene curve (AUC) as compared to beta-carotene plus placebo. They suggest that the improved serum response is non-specific and due to thermogenic property(s) of piperine.[46]

Supriya Veda, *et al.,* (2009) found significantly enhanced intestinal uptake of β-carotene as a result of consumption of pungent spices black pepper, red pepper, ginger, piperine and capsaicin. Study showed higher *in vitro* absorption of β-carotene in all spice-fed animals. Dietary piperine, ginger, capsaicin and black and red pepper increased the uptake of β-carotene by 147%, 98%, 50% and 59% and 27% respectively. Results suggested that specific dietary spices may alter the ultra structure and permeability characteristics of intestines and which could form a food based strategy to possibly reduce vitamin A deficiency.[47]

Boddupalli B M, *et al.*, formulated gastroretentive microspheres of omeprazole along with piperine and estimated the pharmacokinetics parameters in rabbits. They found hat there was a significant increase in the area under curve from 3.441±1.093 mg·h/mL to 14.422±0.708 mg·h/mL along with an increase in Cmax. This clearly shows the increased absorption and decreased metabolism of omeprazole when administered along with piperine.[48]

Desai SK, *et al.*, (2008) evaluated the dose dependent potentiation of hepatoprotective activity of hydroalcohalic extact of roots of *Boerhavvia diffusa* by piperine (10 and 20mg). Hepatotoxicity was induced by CCl_4 and rifampicin – isoniazid combination and effect of piperine evident by reduction in serum glutamate pyruvate transaminase, serum glutamate oxaloacetate transaminase, and alkaline phosphatase in both cases.[49]

Bano G, *et al.*, (1991) examined the effect of piperine (20 mg) on the bioavailability and pharmacokinetics of propranolol (40 mg) and theophylline (150 mg) in a crossover study for 7 days. Result showed an earlier t_{max} and a higher C_{max} and AUC in the subjects who received piperine and propranolol and a higher C_{max}, longer elimination half-life and a higher AUC in case of theophylline with piperine.[50]

Johnson JJ, *et al.*, (2011) examined the effect of piperine (10 mg/kg) on pharmacokinetic parameters of resveratrol (100 mg/kg) in mice. Serum levels of resveratrol and resveratrol-3-*O*-β-D-glucuronide were analyzed at different times and they found that AUC of resveratrol was enhanced to 229% and the maximum serum concentration (C_{max}) was increased to 1544% with the addition of piperine.[51]

Janakiraman K, *et al.*, (2008) found that co-administration of Piperine (20mg/kg) enhanced oral

bioavailability of Ampicillin and Norfloxacin in animal model. This is reflected in various pharmacokinetic measurements like C_{max}, T_{max}, AUC and t½ of the above antibiotics in animal model.[52]

Hiwale A R, *et al.*, (2002) found that co-administration of piperine enhanced bioavailability of beta lactam antibiotics, amoxycillin trihydrate and cefotaxime sodium significantly in rats. The improved bioavailability is reflected in various pharmacokinetic parameters viz. t_{max}, C_{max}, t(1/2) and AUC, of these antibiotics. The increased bioavailability could be attributed to the effect of piperine on microsomal metabolising enzymes or enzymes system.[53]

Lambert JD, *et al.*, (2004) reported that the piperine (70.2mol/kg) increases the C_{max} and AUC of Epigallocatechin-3-gallate (EGCG) (163.8 mol/kg) by 1.3-fold compared to mice (intragastric administration) treated with EGCG alone. They demonstrated that Piperine (100mol/L) inhibited EGCG glucuronidation in mouse small intestine (by 40%) and also inhibited production of EGCG-3_-glucuronide in human HT-29 colon adenocarcinoma cells. The appearance of EGCG in the colon and the feces of piperine-cotreated mice was slower than in mice treated with EGCG alone.[54]

Khan I A, *et al.*, (2006) found that piperine in combination with ciprofloxacin markedly reduced the MICs and mutation prevention concentration of ciprofloxacin for *Staphylococcus aureus*, including methicillin resistant *S*. *aureus*. The enhanced accumulation and decreased efflux of ethidium bromide in the wild-type and mutant (CIPr-1) strains in the presence of piperine suggest its involvement in the inhibition of bacterial efflux pumps.[55]

Pattanaik S, *et al.*, (2006) explore the effect of a single dose of piperine (20 mg) in patients with uncontrolled epilepsy on the steady-state pharmacokinetics of phenytoin (150 mg or 200 mg twice daily). Blood samples were collected and analyzed at regular interval. There was a significant increase in AUC, C_{max}. The results showed that piperine enhanced the bioavailability of phenytoin significantly, possibly by increasing the absorption of the phenytoin.[56]

Gupta SK, *et al.*, (1998) found that the plasma concentration of nimesulide (10 mg/kg) was increased from 8.03± 0.99 ug/ mL to 11.9±0.23 ug/mL after the coadministration of nimesulide with piperine (10 mg/kg). This indicates that piperine inhibits the biotransformation and metabolism of nimesulide which leads to higher levels of drug in the systemic circulation. [57]

Mujumdar AM, *et al.*, (1990) studied the effect of piperine on pentobarbitone induced hypnosis in rats. Piperine potentiated the pentobarbitone sleeping time, as compared to the controls. They concluded that it is possible that, piperine inhibits liver microsomal enzyme system and thereby potentiates the pentobarbitone sleeping time.[58]

Patel S, *et al.*, (2011) studied the influence of co-administration of piperine (15 mg/kg) on pharmacokinetic profile of single dose of gatifloxacin (10 mg/kg body weight) in layer birds. The study revealed that piperine significantly enhances the bioavailability of gatifloxacin from 74.52 ± 1.021% to 85.74 ± 0.956% as compared to control group. The results thus obtained were the combined effect of piperine on the absorption kinetics and the inhibition of the metabolism of gatifloxacin.[59] Devada SS, *et al.*, (2011) observed **s**imilar effects in broiler birds where piperine enhances the bioavailability of same drug from 72.96 ± 1.10 % to 81.95 ± 1.56 % compared to gatifloxacin alone treated group.[60]

Singh A, *et al.*, (2011) treated the male New Zealand white rats with atenolol (100 mg/kg) and combination of atenolol and piperine (10 mg/kg). They found that bioavailability of atenolol was significantly enhance in the presence of piperine.[61] Singh A, *et al.*, (2012) found similar bioenhancing effect when they treated male New Zealand white rats with Losartan potassium (100 mg/kg) and combination of Losartan potassium and piperine (10 mg/kg).[62]

Bhardwaj RK, *et al.*, (2002) investigated the influence of piperine on P-glycoprotein-mediated, polarized transport of digoxin and cyclosporine in monolayers of Caco-2 cells and also the effect of piperine on CYP3A4-mediated formation of the verapamil metabolites D-617 and norverapamil by using human liver microsomes. Piperine inhibited digoxin and cyclosporine A transport in Caco-2 cells with IC50 values of 15.5 and 74.1 _M, respectively. CYP3A4-catalyzed formation of D-617 and norvera3pamil was inhibited in a mixed fashion, with *K*i values of 36 ± 8 (liver 1)/49 ± 6 (liver 2) and 44 ± 10 (liver 1)/77 ± 10 _M (liver 2), respectively. They showed that piperine inhibits both the drug transporter P-glycoprotein and the major drug-metabolizing enzyme CYP3A4. [63]

Venkatesh S, *et al.*, (2011) studied the influence of piperine (10 mg/kg) on ibuprofen induced antinociception and its pharmacokinetics. Piperine was significantly increase the plasma concentration and dose-dependent antinociceptive activity of ibuprofen evaluated by both acetic acid writhing and formalin test, when it was administered with ibuprofen. From this study it can be concluded that piperine can be used as a bioenhancer along with ibuprofen.[64]

MARKETED PRODUCT OF PIPERINE AS BIOENHANCER WITH DRUG

Risorine is a formulation developed by Indian Institute of Integrative Medicine, Jammu, and marketed in India in November 2009 in public–private partnership with Cadila Pharmaceutical Ltd, Ahmedabad. Risorine has

been approved for marketing by Drug Controller General of India, after successful completion of all the phased clinical trials. It contains rifampicin (200 mg), isoniazid (300 mg), and piperine (10 mg). It has been found to be bioequivalent with commercially available rifampicin preparations. This is due to enhanced uptake of the drug by body cells, and also because the drug remains available in blood for longer durations. Combining piperine with rifampicin decreases the dose of rifampicin from 450 to 200 mg. [65]

CONCLUSION

Black pepper contains approximately 5-9% piperine and listed by FDA as an herb which is generally recognized as safe for its intended use as spice. Concept of bioenhancer is based on traditional system of Indian medicines. The biological properties of piperine have been extensively studied only in recent years. The bioenhancing dose of piperine is approximately 15 -20 mg/person/day in divided dose which is very less than the LD_{50} dose of piperine. The successful use of piperine to increase bioavailability of certain drugs has created interest in the area of nutrient and food absorption and more ever based on these findings several other reputed plants are evaluated for bioavailability/bioefficacy or bioenhancing activity. But piperine still remains the most effective bioenhancer for drugs, plant extracts and also for nutraceuticals. The development of plant based bioenhancer is to be targeted for the drugs that are given for longer period of time, highly toxic and expensive. Although piperine enhances the bioavailability of many drugs but extensive research and effective formulation strategy is needed to formulate the best bioavailable combination of drug with piperine.

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