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PREFORMULATION AND FORMULATION STUDY OF ANTICANCER PRINCIPLE OF PIPERINE

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ABSTRACT

Piperine increases bioavailability of many drugs and nutrients by inhibiting various metabolising enzymes. Piper nigrum L and its active constituent ‘’Piperine’’ exhibits diverse pharmacological activities like antihypertensive, antiplatelet, antioxidant, antitumor, anti-asthmatics, analgesic, anti-inflammatory, anti-diarrheal, antispasmodic, antidepressants, immuno-modulatory, anticonvulsant, anti-thyroids, antibacterial, antifungal, hepato-protective, insecticidal and larvicidal activities etc. Piperine's 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. The approach is novel as the abundantly available natural product piperine is utilized as precursor for the synthesis of new potential anticancer agents. This review article concludes the bioavailability enhancing property, Preformulation and formulation study and anticancer property of piperine.

KEYWORDS: Piperine, Anticancer, Liposomes, Preformulation, Bio-enhancer, Bioavailibity.

INTRODUCTION

Piperine is discovered by Hans Christian Orsted in 1819. It is known as one of the main components of pepper. Piperine is responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine). It can be isolated from the fruits of P. nigrum or P. longum. Piperine, a major alkaloid of black pepper (Piper nigrum Linn.) and long pepper (Piper longum Linn.), has been used in folk medicine for the treatment of various

diseases, including seizure disorders. Pharmacological studies have shown that piperine possesses various activities including anti-inflammatory and analgesic, anticonvulsant, anti-ulcer, anti-depressant, cytoprotection, antioxidant and cognitive enhancing effect.[1,2,9,10]

Piperine is an alkaloid responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine). It has also been used in some forms of traditional medicine and as an insecticide. Piperine forms monoclinic needles, is slightly soluble in water and more so in alcohol, ether or chloroform: the solution in alcohol has a pepper-like taste.[1,2,9] Piperine has been reported to inhibit lung metastasis induced by B16F10 melanoma cells, and the anti-invasive effects of piperine on fibro-sarcoma cells also have been demonstrated. The therapeutic properties of piperine with other antitumor drugs were tested in various cell types. But there is little known about the anticancer activities of piperine on mammary cancer cells and the underlying mechanism. The 4T1 tumors closely mimics human breast cancer in its anatomical site, immunogenicity and growth characteristics. After sc inoculation in the abdominal mammary fat pad, the primary tumor grows into a nodule with the histology of a high grade breast cancer and sheds spontaneous systemic metastases. Metastatic growth in the lungs is usually the main cause of death of mice. The pattern and histological appearance of such metastases are similar to what is seen in humans, therefore, this model is suitable for testing the effects of experimental therapies on metastatic disease. The effects of piperine on the tumor growth and metastasis of 4T1 breast cancer in vitro and in vivo. And the possible mechanism for the inhibitory effect of piperine on tumor cell growth and migration were investigated. The antitumor efficacy makes piperine a potential candidate for future cancer therapy.[3,4]

PHARMACOLOGICAL ACTIVITY OF PIPERINE

Anticancer Activity of Piperine

The anticancer activity of piperine against many cancer cell lines has been reported earlier. Therefore, the mechanisms of anticancer activity of piperine against both androgen independent and dependent cells of prostate cancer were investigated. The proliferation of LNCaP, 22RV1, PC-3, and DU-145 prostate cancer cells was found to be dose dependently inhibited by piperine. Piperine treatment was also found to induce apoptosis, by the activation of caspase-3 and by the cleavage of PARP-1 proteins in different prostate cancer cells like PC-3, DU-145 & LNCaP prostate cancer cells.[4] Treatment with piperine also found to disrupt the androgen receptor expression in LNCaP prostate cancer cells and cause significant

diminutionin the level of Prostate Specific Antigen in LNCaP cells. The expression of phosphorylated STAT-3 and Nuclear factor-κB transcription factors were reduced in LNCaP, PC-3 and DU-145 prostate cancer cells after treatment of with piperine. These results suggested that there was a significant reduction in the androgen dependent and independent growth of tumor in naked mice model of Xeno-transplanted with prostate cancer cells after treatment of piperine. Piperine is non-genotoxic and found to possess anti-mutagenic and anti-tumor influences.[9,10,11,12]

Anti-Inflammatory Activity of Piperine

The piperine was evaluated for the anti-inflammatory, analgesic, and anti-arthritic activities. The in vitro anti-inflammatory activities were evaluated on interleukin 1β stimulated fibroblast like synoviocytes obtained from rheumatoid arthritis, while anti-arthritic including analgesic activities were evaluated on carrageen an induced acute paw model of pain and arthritis in rats. The prostaglandin E2, cyclooxygenase 2, interleukin 6 and matrix metallo-proteinase levels were evaluated by ELISA and RT-PCR methods of analysis. Piperine treated groups were found to reduce the synthesis of prostaglandin E2 in a dose dependant comportment at the concentrations of 10-100 μg/mL. It significantly inhibited the synthesis of prostaglandin E2 even at 10μg/mL. The expression of interleukin 6 and matrix metallo-proteinase 13 were also inhibited. The migration of activator protein1into the nucleus in interleukin 1β treated synoviocytes was inhibited by piperine while migration of nuclear factor κB was not affected by piperine. The pain and arthritic symptoms in rats were significantly reduced by piperine. It was concluded that piperine showed anti-inflammatory, analgesics and anti-arthritic activities in arthritis model of rats.[9,10,11,12]

Antioxidant Activity of Piperine

Free radicals cause many diseases. Different free radicals attack on membranes causing oxidation of lipids, loss of different enzyme activities and may cause cancer. Antioxidants completely stop or delay the process of oxidation. Antioxidant protection system includes enzymes like Ascorbate, Catalase, Peroxidase and Superoxide dismutase which scavenge both radicals and related non radical oxygen species. Plants are important source of antioxidants. Some in vitro studies revealed that Piperine inhibited free radicals and reactive oxygen species, therefore known to possess protective effects against oxidative damage. Piper nigrum or piperine also found to decrease lipid peroxidation in vivo. Piper nigrum reported to possess antioxidant activity that might be due to the presence of flavonoids and

phenolic contents. Piper nigrum was found to prevent the oxidative stress by inhibiting lipid peroxidation, human lipoxygenase and arresting hydroxyl and superoxide free radicals, decrease lung carcinogenesis in animal studies. The memory enhancing and antioxidant proprieties of the methanolic extract of Piper nigrum L. fruits at a doses of 50 and 100 mg/kg, orally, for 21 days in amyloid beta (1-42) were investigated in Alzheimer's disease model in rats . The memory-enhancing effects of the extract were studied by means of in vivo (Y-maze and radial arm-maze tasks) approaches.

While, the antioxidant activity was evaluated by measuring activities of glutathione peroxidase, catalase, superoxide dismutase, and by measuring the total content of reduced glutathione, malondialdehyde, and protein carbonyl levels in the hippocampus. The amyloid beta (1-42)-treated rats showed the diminishing of spontaneous starvariation percentage within Y- maze task and enhancement of work memory and reference memory errors within radial arm-maze task. Administration of the methanolic extract of Piper nigrum significantly improved memory performance and exhibited antioxidant potential. These studies suggest that methanolic extract of Piper nigrum ameliorates amyloid beta (1-42)-induced spatial memory deterioration by depletion of the oxidative stress in the hippocampus of rats. The antioxidant effect of three Piper species viz P. nigrum, P. guineense and P. umbellatum was evaluated for the protection of renal, cardiac, and hepatic antioxidant status in atherogenic diet fed hamsters. Animals were fed atherogenic diet addition with different doses of Piper species viz P. nigrum, P. guineense and P. umbellatum at a dose of 1 g/kg and 0.25 g/kg for 12 weeks. Piper species significantly inhibited the atherogenic diet induced increased lipid profile and alteration in antioxidant enzymes activities. This study showed an antioxidant protective role of the extracts of Piper species against atherogenic diet induced oxidative stress in renal, cardiac and hepatic tissues.[9,10,11,12]

Antidepressant Activity of Piperine

The antidepressant-like effect of piperine and its possible mechanisms was evaluated in corticosterone-induced model of depression in mice. Depression-like behavior in mice was developed after 3 weeks corticosterone injections. The depression was revealed by the significant reduction in sucrose utilization and augmentation in immobility time in the forced swim test and tail suspension test. Further, the brain-derived neurotrophic factor protein and mRNA levels in the hippocampus were also significantly decreased in corticosterone-treated mice. Corticosterone induced the behavioral and biochemical changes were significantly

diminished after treatment to animals with Piperine. These results showed that piperine produces an antidepressant-like effect in corticosterone-induced model of depression in mice.[9,10,11,12]

LIPID BASED NOVEL FORMULATION FOR PIPERINE

Liposomes

Liposomes are the spherical bilayer vesicles with an aqueous interior formed by the self association behavior of amphiphilic phospholipids with cholesterol molecules. This self associating behavior of phospholipids originates from their tendency to shield their hydrophobic groups from aqueous environment while interacting with the aqueous phase with their hydrophilic groups. Depending upon their bilayer structure and size, liposomes can be categorized as multilamellar, large unilamellar, or small unilamellar. Alternatively, depending upon the driving force for drug release, they can be classified as conventional liposomes, pH sensitive liposomes, cationic liposomes, immunoliposomes and long circulating liposomes. These lipid based particulate carriers can significantly enhance the solubility of poorly water soluble chemopreventives. Different drugs based upon their lipophilic character can distribute either in the phospholipid bilayer, in the interior aqueous phase, or at the bilayer water interface. The lipophilic natures of many chemopreventives including piperine, curcumin, make them suitable candidates for liposomal drug delivery where lipophilic core of these liposomes provide an optimum environment for drug entrapment.[6,7,12]

Some advantages of liposome

- Provides selective passive targeting to tumor tissues (Liposomal doxorubicin).
- Increased stability via encapsulation.
- Reduction in toxicity of the encapsulated agents.

METHODS OF LIPOSOMES PREPARATIONS

1. General Method of Preparation And Drug Loading

Liposomes are manufactured in majority using various procedures in which the water soluble (hydrophilic) materials are entrapped by using aqueous solution of these materials as hydrating fluid or by the addition of drug/drug solution at some stage during manufacturing of the liposomes. The lipid soluble (lipophilic) materials are solubilized in the organic solution of the constitutive lipid and then evaporated to a dry drug containing lipid film followed by its hydration. These methods involve the loading of the entrapped agents before

or during the manufacturing procedure (Passive loading). However, certain type of compounds with ionizable groups, and those which display both lipid and water solubility, can be introduced into the liposomes after the formation of intact vesicles (remote loading).[6,7,12]

2.Reverse Phase Evaporation Method

First water in oil emulsion is formed by brief sonication of a two phase system containing phospholipids in organic solvent (diethyl ether or isopropyl ether or mixture of isopropyl ether and chloroform) and aqueous buffer. The organic solvents are removed under reduced pressure, resulting in the formation of a viscous gel. The liposomes are formed when residual solvent is removed by continued rotary evaporation under reduced pressure. With this method high encapsulation efficiency up to 65% can be obtained in a medium of low ionic strength for example 0.01M NaCl. The method has been used to encapsulate small and large macromolecules. The main disadvantage of the method is the exposure of the materials to be encapsulated to organic solvents and to brief periods of sonication.[6,7,12]

3. SOLVENT DISPERSION METHODS

a) Ether Injection Method

A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to an aqueous solution of the material to be encapsulated at 55-65°C or under reduced pressure. The subsequent removal of ether under vacuum leads to the formation of liposomes. The main drawbacks of the method are population is heterogeneous (70-190 nm) and the exposure of compounds to be encapsulated to organic solvents or high temperature.[6,7,12]

b) Ethanol Injection Method

A lipid solution of ethanol is rapidly injected to a vast excess of buffer. The MLVs are immediately formed. The drawbacks of the method are that the population is heterogeneous (30-110 nm), liposomes are very dilute, it is difficult to remove all ethanol because it forms azeotrope with water and the possibility of various biologically active macromolecules to inactivation in the presence of even low amounts of ethanol.[6,7,12]

CHARACTERIZATION OF LIPOSOMES

1.Particle size and zeta potential

The prepared liposomes were evaluated for their particle size and zeta potential by photon correlation spectroscopy (PCS) using Zeta-sizer. The formulations were diluted to 1:1000

with the aqueous phase of the formulation to get a suitable kilo counts per second (kcps). Analysis was carried out at 25°C with an angle of detection of 90° (45).

2.Liposome Morphology

Transmission Electron Microscopy (TEM) was used to study the Piperine liposome's morphology. The sample was placed on a carbon film coated on a copper grid for TEM. TEM studies were performed at 8 kV. The copper grid was fixed into sample holder and placed in vacuum chamber of the transmission electron microscope and observed under low vacuum and TEM images for recorded. The results were given in results and discussion section (45).

3.Encapsulation efficiency

Separation of unentrapped drug from the prepared liposomes was carried out and analyzed using UV Visible spectrophotometer at a λmax 332nm. Liposomes prepared without drug were treated in similar manner and served as blank for the above study. The formula used to calculate encapsulation efficiency was given below (45)

$$\text{Encapsulation efficiency} = \frac{\text{Entrapped drug (mg)}}{\text{Total amount of drug added (mg)}} \text{ X100}$$

4.In vitro drug release studies

In vitro release studies were performed using dialysis membrane method.The prepared liposomal formulation was placed inside a dialysis membrane immersed in aqueous buffer of volume 100 ml (Phosphate buffer pH 7.4). At predetermined time intervals the sample was withdrawn and the amount of piperine was determined by measuring the absorbance at 332nm using a UV-Visible spectrophotometer. From the absorbance values the cumulative percentage drug release was calculated (45).

❖**TABLE: HERBAL LIPOSOMAL FORMULATIONS**

Formulation	Herbal drug	Biological activity	References
Quercetin Liposome	Quercetin	Anti-oxidant Anti-cancer	Aroonsri P, Jintanaporn W et al, 2008.
Ampelopsin Liposome	Ampe-lopsin	Anti-cancer	He ZF, Liu DY, Zeng S et al, 2008.
Paclitaxel Liposome	Paclitaxel	Anti-cancer	Rane S, Prabhakar B et al, 2009.
Curcumin Liposome	Curcumin	Anti-cancer	Hong W, Chen DW et al, 2008.

❖**TABLE: REPORTED WORK OF PIPERINE**

FORMULATION	DRUGS	APPLICATION	REFERENCES
Nanoparticles	Piperine, curcumin	as a bioenhancer, cancer.	C Moorthi, Kiran Krishnan et al, 2012.
Nanoparticles	Piperine , curcumin	as a bioenhancer	Tu YS , Fu JW, Sun DM et al, 2014.
Solid-lipid Nanoparticles	Piperine	as a bioenhancer, Alzheimer	Yusuf M , Khan M, et al, 2012.
Solid-lipid Nanoparticles	Piperine	Brain targeted, Alzheimer	Mohammad Yusuf, Maria Khan et al, 2012.
PEG-PLGA Nanoparticles	Piperine	breast cancer, as a bioenhancer	Manendra Pachauri , Enna Dogra Gupta et al, 2015.
Gastroretentive capsules	Piperine	as a bioenhancer	Smriti Khatri, Farhan Jalees Ahmed et al, 2015.
Alginate Beads	Piperine	pharmacological studies, drug release studies	Bindu Madhavi, Ravinder Nath, David Banji et al, 2009.
Piperine Cream	Piperine	Vitiligo	Vinod K.R, Santhosh A D et al, 2010.
Nanoparticulate	Piperine curcumin	enhance the bioavailability, anti-cancer	C. Moorthi , K. Kathiresan et al, 2012.

PREFORMULATION STUDY

1.Physical appearance

The sample of piperine was analyzed for physical appearance and compared with the standard.

2.Melting point determination

It is one of the parameters to judge the purity of crude drugs. The melting point of piperine was determined by capillary method. A small quantity of powder was placed into a capillary tube. The tube is placed in the melting point determining apparatus. The temperature at which powder started to melt and the temperature when all the powder melted were noted.

3.Compatibility study

Drug Excipients compatibility by study IR Spectroscopy. The infrared spectrum of the piperine was obtained by KBr pellet technique using FTIR spectrophotometer. To prepare the pellets a few milligrams of the sample were ground together in a mortar with about 100 times the quantity of potassium bromide (KBr). The finely ground powder was introduced into a stainless steel die. The powder was taken pressed in the die between polished stainless steel anvils of a pressure of about 1000 psi.

4. Analytical evaluation

a.Determination of Absorption maxima

The Absorption maxima of drug were determined by uv- visible duble beam spectrophotometer absorption maxima for drug in methanol was found to be 332nm. Determination of absorption maxima is necessary to determine axact concentration of drug in particular media according to their solubility.

b.Preparation of Standard curve of the drug

10mg piperine was dissolved in 10ml methanol and then volume was made upto 100ml with methanol in 100ml volumetric flask to prepare 10000mig/ml conc. 1ml of above stock solution was placed in a 100ml volumetric flask and 100ml volume was made up with methanol. This produced a solution with 10mig/ml concentration. Aliquots of 1,2,3,4 and 5ml of above stock solution were transferred to 10ml volumetric flask and valume was made up to 10ml with methanol and the absorbance was measured at 332nm.

5.Solubility study

The equilibrium solubility of a compound is defined as the maximum quality of that substance which can be completely dissolved in a given amount of solvent. To determine equilibrium solubility 10ml of each solvent was taken in different test tubes. Then accurately weighed drug piperine (10gm) was added in small increment and shaken for 5min every time until precipitate appeared. When precipitate even after shaking remaining drug was reweighed. The quantity of drug dissolved was obtained by subtraction with initial value.

PHYSICAL AND CHEMICAL PROPERTIES OF PIPERINE

Piperine is a nitrogenous pungent substance. The chemical structure of piperine places it in the group of cinnamamides. 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.[2,3,15,18]

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	Taste	Tasteless at first, but burning aftertaste
5	Melting point	130oC

6	Density	1.193 gm cm-3
7	Solubility	Insoluble in water, soluble in benzene and acetic acid and alcohal
8	UV absorption maxima	332 nm

BIOENHANCING PROPERTY AND 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 LD50 dose of piperine, as established in various experiments on rodents.[7,9,22,29,33]

ADVANTAGES OF PIPERINE AS BIOENHANCER

- 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.

Effect of Piperine on metabolism: a bioavailability enhancer

Piperine has shown bioavailability enhancing effects on many therapeutically important drugs and nutrients. Piperine increases the absorption of many drugs and nutrients from the gastrointestinal tract by various mechanisms. It alters the membrane dynamics and increases permeability at site of absorption. Piperine increases the serum half lives of some substances like beta-carotene and coenzyme Q10 and decreases metabolism of many drugs by inhibiting various metabolizing enzymes like cytochrome BS, CYP3A4, NADPH cytochrome, UDPglucuronyl transferase, UDP-glucose dehydrogenase (UDP-GDH), and aryl hydrocarbon hydroxylase (AAH). These enzymatic inhibition by piperine resulted in increased bioavailability of many drugs and nutrients e.g. amoxicillin, ampicillin, acefotaxime,

carbamazepine, ciprofloxacin, norfloxacin, metronidazole, oxytetracyclin, nimesulide, pentobarbitone, phenytoin, resveratrol, beta-carotene, curcumin, gallic acid, tiferron, nevirapine, and sparteine by different types of mechanisms. Therefore, piperine is known as bioavailability enhancer and a potent drug's metabolism inhibitor. Nisar Ahmad, Hina Fazal et al 2013, reported of Biological role of Piper nigrum L. (Black pepper) and piperine.The biological role this speice is explained in different experiments that peppercorn and secondry metabolites of piper nigrum and piperine can be used anticancer, anti-inflammatory, antidepressant and antioxidant activity. Shailendra Wadhwa, Sarita Singhal et al., 2014**,** reported of Bioavailability Enhancement by Piperine. 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. Amritpal singh and Sanjiv duggal et al 2009, as reported of piperine review of advances in pharmacology. Piperine as show the bioenhance properties, antidepressant, anticancer, antioxidant and anti-inflammatry activity. Murlidhar Meghwal and TK Goswami et al 2012, reported of Black pepper and piperine is a spice which can provide natural nutritional and medicinal benefit. It has analgesic, antipyretic, anti-inflammatory, antimicrobial and antidepressant properties.[7,9,22,29,33]

❖**TABLE: Other natural drugs uses in bioavailability enhancers**

Natural drugs	References
Quercetin	Kritika Kesarwani, Rajiv Gupta, 2013.
Genistein	Kritika Kesarwani, Rajiv Gupta, 2013.
Naringin	Kritika Kesarwani, Rajiv Gupta, 2013.
Sinomenine	Kritika Kesarwani, Rajiv Gupta, 2013.
Cuminum cyminum Linn.	Kritika Kesarwani, Rajiv Gupta, 2013.
Zingiber officinale	Kritika Kesarwani, Rajiv Gupta, 2013.
Aloe vera	Kritika Kesarwani, Rajiv Gupta, 2013.

MECHANISM OF ACTION OF PIPERINE

Different mechanisms for the bioenhancer activity of piperine have been proposed including DNA receptor binding modulation of cell signal transduction and inhibition of drug efflux pump. In general, it inhibits drug metabolizing enzymes stimulates absorption by stimulating gut amino acid transporters, inhibits the cell pump responsible for drug elimination from cells and inhibits intestinal production of glocuronic acid. It may increase the absorption of drug in the GIT or inhibit enzymes responsible for drug metabolism, especially in the liver when the drug passws through the liver after absorption from GIT. Oral administration of piperine in rats hydroxylase and UDP- glucuronyl transferase activities. Another study demonstrates that piperine modifies the rate of glucuronidation by lowering the endogenous UDP- glucuronic

acid content and also by inhibiting the transferase activity. Piperine inhibit human p-glycoprotein and cytochrome P350 3A4 (CYP3A4). Both the proteins contribute to a major extent to first- pass elimination of many drugs. Some of the metabolizingenzymes inhibited or induced by piperine include CYP1A1, CYP1A1, CYP1B2, CYP2E1, CYP3A4 etc. most of the drugs metabolized by these enzymes will therefore be influenced by bioenhancers. Some others suggested mechanism include making target receptors more responsive to drug, acting as receptors for drug molicules, increasing GIT vasculature by vasodilation to increase absorption of drugs, modulation of the cell membrane dynamics to increase transport of drugs across cell membranes.[7,9,22,29,33]

CONCLUSION

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 LD50 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. Piperine has analgesic, anticancer, antipyretic, anti-inflammatory, antimicrobial and antineoplastic properties. Piperine is the major alkaloidal constituent of pepper. Systematic pharmacological studies on piperine have revealed its analgesic, antipyretic, anti-inflammatory and central nervous system depressant activities.

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