



BIOAVAILABILITY ENHANCEMENT OF ANTICANCEROUS DRUG FROM MOTHER NATURE: PIPERINE

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Article Received on 20/04/2020

Article Revised on 10/05/2020

Article Accepted on 31/05/2020

ABSTRACT

Alkaloids include a family of naturally occurring chemical compounds containing mostly basic nitrogen atoms. Piperine is an alkaloid present in black pepper (*Piper nigrum*), one of the most widely used spices, in long pepper (*Piper longum*), and other *Piper* species fruits belonging to the family of Piperaceae, and is the carrier of its specific pungent taste, which is responsible for centuries of human dietary utilization and worldwide popularity as a food ingredient. Along with the application as a food ingredient and food preservative, it is used in traditional medicine for many purposes, which has in most cases been justified by modern scientific studies on its biological effects. It has been confirmed that piperine has many bioactive effects, such as antimicrobial action, as well as many physiological effects that can contribute to general human health, including immunomodulatory, hepatoprotective, antioxidant, antimetastatic, antitumor, and many other activities. Bioenhancers or a bioavailability enhancer is a new chapter in medical science first scientifically established in 1979 after the discovery of world's first bioenhancer Piperine. Bioenhancers are defined as substances that increase the bioavailability and bioefficacy of active substances with which they are combined without having any activity of their own at the dose used. Increased bioefficacy means the increased effectiveness of the drug due to increased bioavailability and also due to other mechanism. The approach is novel at 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 of Piperine.

KEYWORDS: Piperine, cancer, bioavailability.

INTRODUCTION

Herbal Medicine

Herbal medicine, or phytotherapy, is the science of using herbal remedies to treat the sick. It therefore covers everything from medicinal plants with powerful action, such as digitalis and belladonna, to those with very gentle action, such as chamomile, mint and many others.^[1] An herb is a plant part used for its scent, flavor, or therapeutics properties. Herbal medicines are one type of dietary supplement. They are sold as tablet, capsules, powders, teas, extracts, and fresh or dried plant. People used herbal medicine to try to maintain or improve their health.^[2] Nature always stands as a golden mark to exemplify the outstanding phenomena of symbiosis. Natural products from plant, animal and minerals have been the basis of the treatment of human disease.^[3] Today estimate that about 80 % of people in developing countries still relays on traditional medicine based largely on species of plants and animals for their primary health care. Herbal medicines are currently in demand and their popularity is increasing day by day. About 500

plants with medicinal use are mentioned in ancient literature and around 800 plants have been used in indigenous systems of medicine.^[4] India is a vast repository of medicinal plants that are used in traditional medical treatments (Chopra et al., 1956). The various indigenous systems such as Siddha, Ayurveda, Unani and Allopathy use several plant species to treat different ailments (Rabe and Staden, 1997). The use of herbal medicine becoming popular due to toxicity and side effects of allopathic medicines.^[5] India has one of the richest plants medical traditions in the world. There are estimated to be around 25,000 effective plant-based formulations, used in folk medicine and known to rural communities in India.^[6]

Bioenhancers

Bioenhancers or bioavailability enhancer is a new chapter in medical science first scientifically established in 1979 after the discovery of world's first bioenhancer piperine. It is a pocket friendly drug technology which reduces the destruction, wastage and elimination of

several orally administered drugs inside the body.^[7] Bioenhancers are defined as substances that increase the bioavailability and bioefficacy of active substances with which they are combined without having any activity of their own at the dose used. Besides several classes of modern drugs like antibiotics, anti-cancer drugs, cardiovascular drugs, anti-inflammatory, central

nervous drugs, etc., they also increase the bioavailability of vitamins and nutrients. Increased Bioavailability means increased levels of drug in the blood stream available for drug action. Increased Bioefficacy means the increased effectiveness of the drug due to increased bioavailability and also due to other mechanisms,^[8]

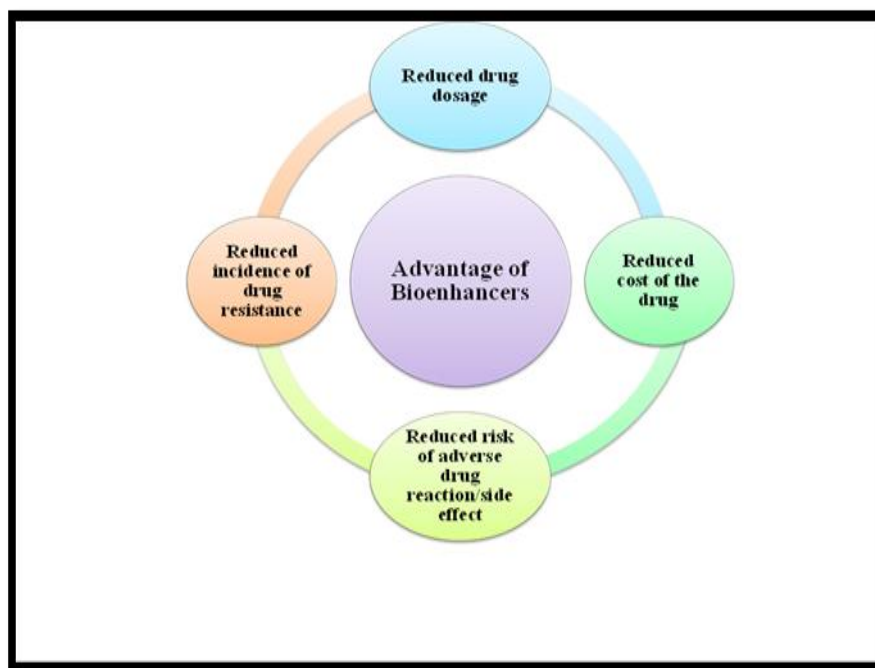


Figure 1: Advantage of bioenhancers.

The rate and extent to which a therapeutically active substance enters systemic circulation and becomes available at the required site of action is termed as bioavailability. Intravenous drugs attain maximum bioavailability, while oral administration yields percentage due to incomplete drug absorption and first-pass metabolism.^[9] Piperine is the world's first bioavailability enhancer coined and scientifically validated by Indian scientists at the Regional Research laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine) in 1979. Earlier it was extensively used in majority of ayurvedic formulations as 'Trikatu', which is a combination of black pepper (*Piper nigrum*), long pepper (*Piper longum*) and ginger (*Zingiber officinale*) for treatment of a large variety of diseases.^[10] The benefits of adding a bioenhancer include reduced drug dosage, reduced cost of the drug, and reduced incidence of drug resistance and reduced risk of adverse drug reaction/side effects, reduced requirement of raw material for drug manufacture.^[11] For example, this is especially beneficial and evident in anti-cancer drugs like Taxol used to treat breast cancer. This drug is obtained from the Yew tree, one of the slowest growing trees in the world, and to obtain taxol for one patient, six trees of 25–100 years need are to be chopped. Simply adding a bioenhancer to Taxol means that fewer trees need to be sacrificed. The great reduction in raw material

is an added, ecological, benefit. With the discovery of the first bioavailability enhancer piperine in 1979, a new class of drug and a new concept was introduced into science. This revolutionary discovery opened up a new field that of increasing drug bioavailability. Piperine still remains the most effective bioenhancer.^[12]

Benefits of using bioenhancers

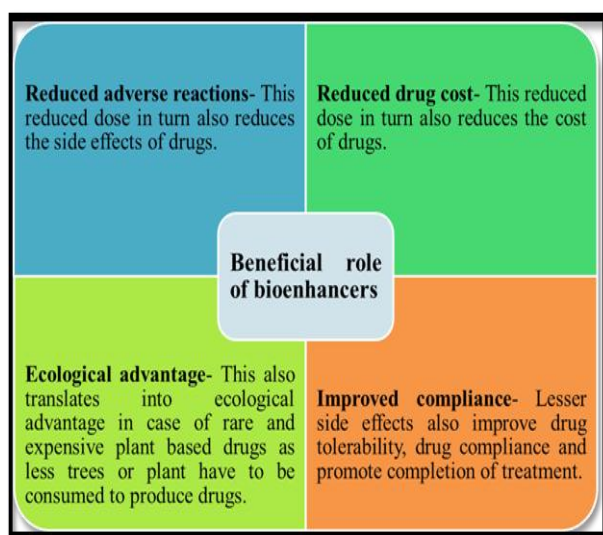
1. As it increases bioavailability drug dose can be reduced
2. Due to reduced dose cost will also reduce
3. It reduces drug resistance
4. Also reduces side effects and adverse drug reactions
5. It increases efficacy of drug
6. In short decreases total treatment cost^[13]

Ideal properties of bioenhancers

1. It must be nontoxic
2. It must be effective at very low concentration
3. Easy to formulate
4. Compatible with API and excipients
5. It should not show any pharmacological activity at the therapeutic dose used
6. It should be free from any toxic /harmful effect on body.^[14]

Table 1: when drug combined with piperine that show increased bioavailability.

S No	Drug	Experimental model	References
1	Nimesulide	Mice	[15]
2	Curcumin	In vivo	[16]
3	Rifampicin	Human	[17]
4	Atenolol	Rats	[18]
5	Ibuprofen	In vitro	[19]
6	Vasicine	Rats	[20]

**Figure 2: Beneficial role of bioenhancers.****History of bioenhancers**

Bioenhancers or bioavailability enhancers as a term and chapter did not exist in any modern scientific literature prior to 1979. The term bioavailability enhancers was first coined in 1979 at Indian Institute of Integrative medicine, Jammu, formerly RRL, Jammu, by Indian scientists (Dr. C. K. Atal, the Director of institute RRL Jammu proposed the hypothesis of increased bioavailability of drugs from a clue during research on traditional medicinal drugs).^[21] Subsequently, the concept of bioavailability enhancers was scientifically researched and scientifically established by him and his research team at RRL Jammu. The institute then discovered and scientifically validated Piperine as the world's first bioenhancer using Sparteine and Vasicine which became the world's first experimentally bioenhanced drugs.^[22] After the discovery of bioenhancer Piperine in 1979, a new chapter was added in medical science. Since then it has generated global interest and research in the field and has led to discovery of many other new bioenhancers. Piperine remains the most potent and extensively researched bioenhancer till date. It is safe, effective, extremely economical and easily manufactured for commercial use. It is also a broad spectrum bioenhancer acting on several classes of modern drugs as noted elsewhere.^[23]

The concept of using bioenhancers

Based on the ayurvedic system of medicine the concept of using bioenhancer is one feasible approach to reduce treatment costs by increasing the drug bioavailability. Global focus today is on methods aimed at reducing drug dosage, and thus drug treatment cost so that medicines become affordable for wide sections of society, including the financially challenged.^[24] The use of bioenhancers seems to be a fruitful method for bioenhancement of an orally administered pharmaceutical compound and leads to improved formulation. Based on a traditional system of Indian medicine, bioenhancers constitute an innovative concept and judicious use of them can lead to reductions in drug cost, toxicity, and other adverse effects. Present day research on expensive, toxic and scarce drugs or drugs that exhibit poor bioavailability demands the use of an ideal bioenhancer which should be safe, effective, economical, easily procured, non-addictive etc.^[25] A new concept was introduced into science in 1979 with the discovery of piperine as a bioenhancer (piperine still remains the most effective bioenhancer), administration of which significantly increased plasma concentrations of rifampicin, phenytoin, spartein, sulfadiazine, tetracycline, propranolol, and theophylline in humans.^[26] The global focus is now on methods aimed at reducing drug dosage, and thus drug treatment cost. Taxol is used to treat breast cancer. This drug is obtained from the Yew tree, one of the slowest growing trees in the world, and to obtain taxol for one patient, six trees of 25–100 years need are to be chopped. Simply adding a bioenhancer to Taxol means that fewer trees need to be sacrificed leading to ecological benefits too. Today compounds like Glycyrrhizin, Cuminum cyminum, Quercetin, Genistein, Carvone, Allicin and Gingerol are also showing increased response in bioenhancement. Bioenhancement may thus be explored as a potent method for the same.^[27]

Classification

Bioenhancers can be classified according to their source of origin, either plant based or animal based or else according to their site of action. Bioenhancers so far almost exclusively discovered in plants, increase the bioavailability of other substances in different^[28] ways:

- Increase of absorption in the intestine
- Inhibition of degradation in the intestine and the liver by inhibition of drug metabolizing enzymes (inhibiting first pass mechanism of destruction of drugs).
- Inhibition of elimination in the drug in gut and through bile by inhibition of efflux pumps.
- Increase of drug permeability of pathogens.
- Inhibition of defense mechanisms of pathogens or tumor tissue (such as efflux of drugs)
- Increasing binding possibilities on binding sites (such as DNA and proteins) of the pathogen
- Improving overcoming of the blood-brain barrier

The use of bioenhancers is familiar concept in Ayurveda as 'Yogavahi' which was used to enhance

bioavailability, tissue distribution and efficacy of drugs especially those with poor availability. One such example is 'trikatu' which is a mixture of Piper longum (long pepper), Piper nigrum (black pepper) and Zingiber officinale (ginger).^[29] Bose, in 1929, first reported the

application of bioenhancer long pepper to increase the antiasthmatic effect of vasaka. Bioenhancers can be classified based on origin and mechanism of action (Table 2 and 3).^[30]

Table 2: Classification based on origin.

Plant origin	Animal origin
Eg: Capsaicin, Ginger, Aloe Vera, Cur cumin, Stevia, Genistein, Naringin, Caraway, Turmeric, Pepper, Peppermint oil.	Eg: Cow urine distillate (Kamdheni ark)

Table 3: Classification based on mechanism of action.

Inhibitors of P-gp efflux pump and other efflux pump	Suppressors of CYP-450 enzyme and its isoenzyme	Regulators of GIT facilitate better absorption
Eg. Caraway, Genistein, Sinomenine, Black cumin, Naringin, Quercetin	Eg. Naringin, Gallic acid and its ester, Quercetin	Eg. Aloe Vera, Niaziridin, Ginger, Liquorices

Bioavailability-enhancing activity of natural compounds from the medicinal plants may be attributed to various mechanisms, such as P-gp inhibition activity by flavones, quercetin, and genistein;^[31] inhibition of efflux transporters, such as P-gp and breast cancer resistance protein (BCRP),^[32] by naringin and sinomenine thus preventing drug resistance; DNA receptor binding, modulation of cell signaling transduction, and inhibition of drug efflux pumps^[33]; by stimulating leucine amino peptidase and glycyl-glycine dipeptidase activity, thus modulating the cell membrane dynamics related to passive transport mechanism as seen with piperine^[34]; nonspecific mechanisms, such as increased blood supply to the gastrointestinal tract, decreased hydrochloric acid secretion, preventing breakdown of some drugs^[35]; and inhibition of metabolic enzymes participating in the biotransformation of drugs, thus preventing inactivation and elimination of drugs and thereby, increasing their bioavailability.^[36]

Hurdles to increase bioavailability

1. One of the challenges is to improve on properties of drug formulations such as longer duration of circulation in blood, enhanced surface area, protection of incorporated drug from degradation, crossing of biological barriers and site specific targeting.
2. Other challenge is large scale production.
3. The challenges of scaling up involve small amount of Nano-materials, agglomeration and the chemistry process.
4. In bio enhancers the advances also bring different challenges for regulatory control.^[37]

New bio-enhancers being developed come with challenges which have to be surmounted. One of the challenges is to improve on properties of drug formulations such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site specific targeting. Another challenge of research and development of herbal

bioenhancers is large scale production.^[38] There is always a need to scale up laboratory or pilot technologies for eventual commercialization. The challenges of scaling up include low concentration of nonmaterial, agglomeration and the chemistry process; it is easier to modify nanomaterial at laboratory scale for performance than at large scale. Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products.^[39] Even though drug delivery using bioenhancer reached at greater degree, not all approaches met with same success.^[40] Still few challenges have to be solved or modified which includes physicochemical character to improve long circulation in blood, drug protection, site specific targeting, crossing biological barriers, increased surface area. Another challenge is development for large scale production, there is need of scale up techniques and pilot techniques for commercialization.^[41] Scaling up challenges include low concentration of nano materials, agglomeration and chemistry processes which can be easily modified at laboratory scale. Regulatory control as a challenge for conventional drug product. There are few standards for physicochemical and pharmacokinetic properties by US-FDA and EMEA in case of products using bioenhancer yet no any standards are set, so regulatory authorities should have take initiative to set standards for such product.^[42]

Bioenhancers in modern medicine

The work done in this area so far explains that tradition of Ayurveda can be the new scope in enhancing the bioavailability of allopathic drug which have proven pharmacotherapeutics action.^[43] Hence the utilization of this phenomenon is done for drug having poor bioavailability.^[44] So the hope in modern science and industrial impact come together to reap the formulating propaganda of drugs for development in human health care.^[45] Drugs in tuberculosis therapy like „Risorine“ by candida Pharma (Nov.2009) which contains rifampicin

and isoniazid it has piperine as a bioenhancer, which shows evidence of increasing bioavailability.^[46]

Bioenhancers in Ayurveda

The term bioenhancer is termed as “Yogvahi” in Ayurveda.^[47] Raw spices and herbs can help through their aroma too, but ayurveda recommends cooking of spices and herbs, because in cooking material is exposed to heat and molecular interaction between medium (oil/ghee) and spices causes interaction of active components it also sanitizes unwanted toxic material present in raw spices and herbs. Cooking helps to access digestive system and other systems. Almost all spices and herbs act as a vehicle for nutrients in food and are called as yogvahi, these help through breakdown of protein, carbohydrates, fat when there is a need.^[48] These are essential in diet but we use them as a flavor in special recipes. The use of bioenhancer may lead to synergistic effect which enhances effect and reduces side effects. This area seems to fit naturally with the complex operation of the human body. It seems reasonable that, to move this whole symphony in a more harmonious direction, it would be most effective with complex substances – with supplements that could affect the whole at once.^[49] Bioenhancers found in plants are piperine, allicin, curcumin, ginger, quercetin, naringin, genistein, caraway, black cumin, niaziridin, lysergol, liquorice, stevia, peppermint oil, aloe, sinnomenium acutum, gallic acid, capsaicin, capmul, ammoniac microflora, gingerol, nitrile glycoside, callistemon rigidus, and ferulic acid.^[50]

Approaches of bioenhancers

The use of bioenhancers seems to be a fruitful method for increasing bioavailability of an orally administered drug and nutraceutical. This approach leads to improved formulation with enhanced oral bioavailability of the active ingredient. Bioenhancers constitute an innovative concept and judicious use of bioenhancers leads to reductions in drug cost, toxicity, and other adverse effects, and have a beneficial influence on the national economy. This patent review article classifies and describes the various bioenhancers and emphasizes their diverse mechanism of action by virtue of which they act as bioenhancers.

Future Scope of bioenhancer

Research on Bioenhancer is going on for Pain Management, Stress, Obesity, Anticancer etc. Unexplored areas of Ayurvedic and other traditional systems of medicines could be an additional area where new breakthroughs can be expected. Work on all categories of drug can be carried out. Studies to know exact mechanism of bioenhancer could be a next step. Like conventional dosage forms, modern dosage forms can be prepared using Yogvahi. In case of products using bioenhancer yet no any standards are set by regulatory authorities, so such initiative should be expected to take to set the standards for such products.^[51]

Novel drug delivery system

Novel drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination product. Drug delivery is a concept heavily integrated with dosage form and route of administration. NDDS is advanced drug delivery system which improves drug potency, control drug release to give a sustained therapeutic effect, provide greater safety; finally it is to target a drug specifically to a desired tissue.

Various drug delivery systems have been developed and some of them under development with an aim to minimize drug degradation or loss, to prevent harmful side effects and to improve drug bioavailability and also to favour and facilitate the accumulation of the drug in the required bio- zone (site). There are no. Of novel carriers which have been established and documented to be useful for controlled and targeted drug delivery. It is important to critically evaluate different terms used under the different broad categories of novel drug delivery system.^[52]

- Rate- pre-programmed drug delivery systems provide drug action by manipulating the release of drug molecules by system design which controls the molecular diffusion of drug molecules.

Targeted drug delivery provides drug action by using carriers either for passive or active targeting or one base or self-programmed approach, usually anchored with suitable sensory devices, which recognize their receptor at the target.

Table 4: Bioavailability enhancement by Novel Drug Delivery System from bioenhancers (NDDS).

S No.	Novel System	Drug	Method	Application	References
1	Liposome	Silymarin	Ethanol injection method	Increased the bioavailability of silymarin by adopting buccal liposomal drug delivery system	[53]
2	Polymeric Nanoparticles	Daunomycin	Non-covalent (biotin-streptavidin) coupling procedure	To increase bio-availability of daunomycin	[54]
3	Niosomes	Celecoxib	Thin film hydration technique	Provide prolonged drug release and improved site specificity of drug	[55]
4	Transfersomes	Curcumin	Hand shaking method	To improve the oral bioavailability of curcumin	[56]
5	Nanoemulsion	Ramipril	Spontaneous emulsification method	Enhanced solubilisation of Ramipril (antihypertensive drug)	[57]
6	Dendrimers	Naproxen	Solvent deposition technique	Enhancement of both drug dissolution and in-vitro release rates.	[58]

Novel Drug delivery System (NDDS) NDDS is a combination of advance technique and new dosage forms which are far better than conventional dosage forms. Advantages of Novel Drug Delivery System are: Optimum dose at the right time and right location, efficient use of expensive drugs, excipients and reduction in production cost, Beneficial to patients, better therapy, improved comfort and standard of living.

Basic modes of novel drug delivery systems are: Targeted Drug Delivery System, Controlled Drug Delivery System etc. Novel Drug delivery & drug targeting is new techniques which is used in pharmaceutical science. Like targeting drug delivery, vaccine delivery, Gene therapy, commercial development of novel carries (liposomes).^[59]

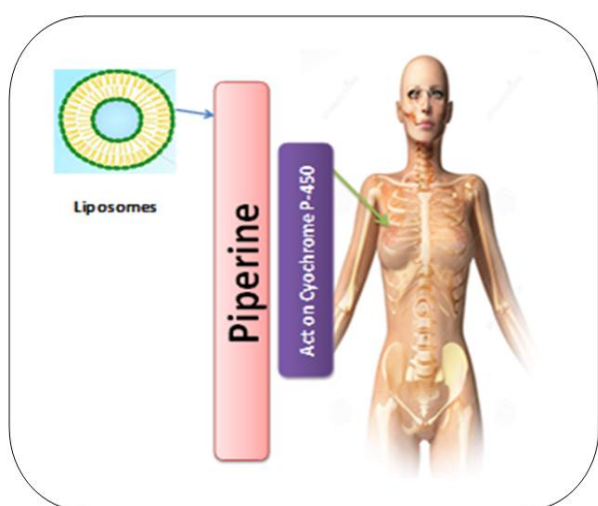


Figure 3: Piperine liposome act on the lung cancer.

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.^[60] 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.^[61]

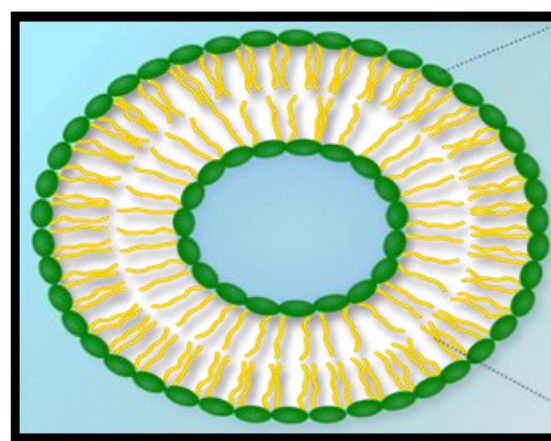


Figure 4: Structure of liposome.

Some advantages of liposome

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

Table 5: Herbal Liposomal Formulations.

S No.	Formulation	Herbal drug	Biological activity	Reference
1	Piperine Liposome	Piperine	Anti-oxidant Anti-tumor	[62]
2	Quercetin Liposome	Quercetine	Anti-oxidant Anti-cancer	[63]
3	Curcumin Liposome	Curcumine	Anti-cancer	[64]
4	Ampelopsin Liposome	Ampe-lopsin	Anti-cancer	[65]

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.^[66] 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).

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.^[67] 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 been capsulated to organic solvents and to brief periods of sonication.^[68]

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.^[69]

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.^[70]

Piperine

Piperine, along with its isomer chavicine, is the alkaloid responsible for the pungency of black pepper and long pepper. It has been used in some forms of traditional medicine. Piperine, as the most abundant alkaloid in pepper, was 1st isolated from the extract of pepper by Hans Christian orsted in 1819.^[71] Piperine is responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine).^[72] 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.^[73] Pharmacological

studies have shown that piperine possesses various activities including anti-inflammatory and analgesic, anticonvulsant, antiulcer, anti-depressant, cytoprotection, antioxidant and cognitive enhancing effect.^[74] Black pepper (*Piper nigrum* L) and long pepper (*Piper longum* L) have been in use as spices from ancient times though out the world. A major component of the *Piper* species is the alkaloid piperine (1-piperoylpipridine), which had been reported to enhance the bioavailability of drugs by inhibition of glucuronidation in the liver and small intestine.^[75] An extract from the fruits of black pepper consisting of a minimum of 98% pure piperine was evaluated in a clinical study using a double-blind design.^[76] Piperine is a naturally occurring compound present as the major pungent ingredient (1–9%) in various parts of plants from the family Piperaceae.^[77] Piperine, an alkaloid (1-peperoyl piperidine), has been previously evaluated for its potential to enhance the serum levels of drugs and nutrients in animals and humans.



Figure 5: Black pepper.

Biological source *Piper nigrum*, also known as black pepper is the member of piperaceae family. It is cultivated for getting its fruit which works as a spice and seasoning agent in many food item.

Chemical Structure

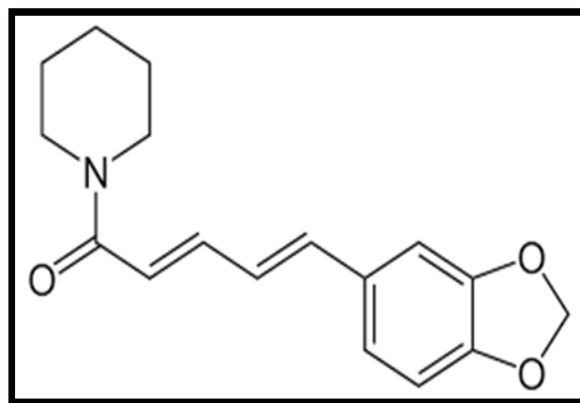


Figure 5: Chemical Structure of piperine.

Isolation -The dried unripe fruits are extracted with ethanol in a Soxhlet apparatus till extraction is complete.

The solvent is evaporated under vacuo in a Rotary Thin Film Evaporator. The residue of the alcoholic extract is digested with dilute alkali to affect saponification, when piperine remains unaffected. The residue, thus obtained is decanted and washed with distilled water several times. The resulting product is dissolved in hot ethanol and on cooling the crystalline piperine separates out.

Piperine as bioenhancer

1. Piperine is extracted from black pepper and long pepper *Piper longum* and *Piper nigrum*.
2. Piperine enhances the metabolism, raises the serotonin and dopamine level, and also enhances the memory functions.
3. It shows anti-oxidant, anti-inflammatory, anti-allergic properties.

Piperine act to inhibit the P-glycoprotein activity

Development of multidrug resistance (MDR) in cancer is a severe problem that limits the use of chemotherapeutics in successful treatment of cancer.^[78] Highly invasive

phenotype associated with malignant cancers is often due to over expression of p-glycoprotein (P-gp) (also known as MDR1 or ABCB1). P-gp, a 170 kDa membrane linked protein, belongs to the ABC (ATP-binding cassette) super family and imparts resistance to cancer cells by acting as an ATP- dependent efflux pump for an incredible series of chemotherapeutic agents.^[79] Piperine is potent inhibitor of P-gp and MRP-1^[80]. Piperine binds between the consensus sequence of Walker A/P loop and Walker C loop (linker peptide) at the nucleotide binding domain which is crucial for ATP coupled efflux through P-gp.^[81] Piperine competes with ATP binding site in P-gp and with this mind recently two low molecular weight piperine analogs Pip1 and Pip2 were synthesized which show better interaction with P-gp than piperine *in silico*.^[82] Both of these analogs when co-administered with certain drugs (such as vincristine, colchicines or paclitaxel) could reverse drug resistance in P-gp over expressing KB (cervical) and SW480 (colon) cancer cells.

Table 6: Reported work of piperine as a bioenhancer.

S. No.	Drug	Formulation	Application	References
1	Piperine, curcumin	Nanoparticles	As a bioenhancer, cancer.	[83]
2	Piperine, curcumin	Nanoparticles	As a bioenhancer	[84]
3	Piperine	Solid lipid nanoparticles	As a bioenhancer,	[85]
4	Piperine	Solid lipid nanoparticles	Brain targeted	[86]
5	Piperine	PEG-PLGA nanoparticles	Breast cancer, as a bioenhancer	[87]
6	Piperine	Piperine cream	Vitiligo	[88]
7	Piperine curcumin	Nanoparticulate	Enhance the bioavailability, anti-cancer	[89]

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, and 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 and LNCaP prostate cancer cells.^[90] Treatment with piperine also found to disrupt the androgen receptor expression in LNCaP prostate cancer cells and cause significant diminution in the level of Prostate Specific Antigen in LNCaP cells. The expression of phosphorylated STAT-3 and Nuclear factor- κ B transcription factors were reduced in LNCaP, PC-3 and DU-145 prostate cancer cells after treatment of with piperine.^[91-95] 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.^[96]

In vitro studies on various cancer cells showed that piperine possesses cytotoxic action (selective toward tumor cells) against several types of cancer, including breast, lung, prostate, cervical, and other cancers.^[97,98]

❖ Breast Cancer

The study on HER2 overexpressing breast cancer cells demonstrated inhibited proliferation and induced apoptosis by activating caspase-3 and cleavage of PARP.^[99] Moreover, it was determined that piperine inhibits HER2 gene expression at the transcriptional level and enhances sensitization of HER2 overexpressing cells to paclitaxel killing. The same study found that it inhibits AP-1 and NF- κ B activation, blocks extracellular signal-regulated kinase (ERK1/2), p38 mitogen-activated protein kinase (p38 MAPK), and Akt signaling pathways, and suppresses epidermal growth factor (EGF)-induced MMP-9 expression.^[100] Without affecting normal mammary epithelial cell growth, piperine inhibits the in vitro growth of triple-negative breast cancer cells (TNBC), and hormone-dependent breast cancer cells. Also, it increases the expression of p21 (Waf1/Cip1) and

inhibits survival-promoting Akt activation^[101], inhibits mammosphere formation, breast stem cell marker aldehyde dehydrogenase (ALDH), and Wnt signaling pathway without causing toxicity to differentiated cells.^[102] In another study, on TNBC cells, the efficacy of factor-related apoptosis-inducing ligand (TRAIL)-based therapy has been enhanced when piperine was added as an adjuvant.^[103] In a model of 4T1 murine breast cancer cells, injection of piperine into tumors (35–280 μ mol/L) inhibited the growth of 4T1 cells in a time- and dose-dependent manner, and decreased the expression of MMP-9 and MMP-13.^[104] It has been reported that piperine analogs, formed by replacing the piperidine nucleus with different amino acids and substituted aniline, exhibit significantly enhanced activity against human breast cancer cells. The best cytotoxic activity (IC₅₀—0.74 μ mol) was obtained by a histidine analog of piperine containing imidazole ring structure.^[105]

❖ Lung Cancer

A set of studies investigated the effect of piperine on lung cancer and found very promising results. Lin *et al.*^[106-108] found that piperine showed selective cytotoxicity toward lung cancer cell line (A549) by inducing apoptosis through arresting G2/Mphase of the cell cycle and activating caspase-3 and caspase-9 cascades in cancer cells. It also decreased Bcl-2 protein expression and increased Bax protein, leading to higher Bax/Bcl-2 ratio. Benzo(a)pyrene induces lung carcinogenesis, by decreasing glutathione transferase (GST), quinone reductase (QR) and UDP-GT and increasing the hydrogen peroxide level. In the study on Swiss albino mice, piperine (50 mg/kg b.wt.) was orally given to mice together with benzo(a)pyrene (BaP) for 16 weeks. In animals treated with piperine, reduced levels of lipid peroxidation, protein carbonyls, nucleic acid content, and polyamine synthesis were recorded in comparison to the control groups, which demonstrated BaP-induced lung carcinogenesis-protective effect of this compound.^[109] Piperine exerts BaP-induced cytotoxicity in V-79 lung fibroblast cells, due to a decrease in GST and UDP-GT.^[110] Administration of piperine reduces DNA damage and DNA-protein cross-links in the lung cancer-bearing animals. In this study, mitochondrial enzymes (isocitrate dehydrogenase (ICDH), ketoglutarate dehydrogenase (KDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH)), glutathione-metabolizing enzymes GPx, GR and glucose-6-phospho dehydrogenase (G6PDH) were significantly reduced, while NADPH-cytochrome reductase (NADPH-C reductase), cytochrome P450 (cyt-p450) and cytochrome b5 (cyt-b5) showed increased levels in mice administered with piperine.^[111-113] Also, in these animals, ATPase enzymes in erythrocyte membrane and tissues were shown to be increased, while sodium/potassium/magnesium ATPase enzyme activities decreased, showing the chemopreventive effect of piperine.^[114] Lung metastasis in C57BL/6 mice induced by B16F-10 melanoma cells has been significantly inhibited when piperine was co-administered together

with tumor induction. The results showed reduced lung collagen hydroxyproline, uronic acid, and hexosamine content, a significant decrease in tumor nodule formation and lung size and also a reduced serum sialic acid and serum α -glutamyl transpeptidase activity, pointing to very promising antimetastatic activity of piperine.^[115]

❖ Cervical and Ovarian Cancer

Piperine and mitomycin-C (MMC) co-treatment resulted in inactivating STAT3/NF- κ B, leading to suppression of the Bcl-2 signaling pathway in human cervical cancer. Also, this compound, together with its analogs demonstrated significant potential against Hela cervix cell line.^[116] A recent study showed that piperine (8, 16, and 20 μ M) inhibited cell viability and caused apoptosis in human ovarian A2780 cells via JNK/p38 MAPK-mediated intrinsic apoptotic pathway.^[117] Further analysis on the mechanism of its action demonstrated increased levels of cyt-c from mitochondria and consequently increased caspase (caspase-3 and -9) activities and also decreased phosphorylation of JNK and p38 MAPK following piperine treatment.

❖ Cancers of the Gastrointestinal Tract

Piperine significantly increased the levels of lipid peroxidation in 7,12-dimethyl benz [a] anthracene (DMBA)-induced hamster buccal pouch carcinogenesis. This chemopreventive efficacy of piperine was recorded by FT-IR spectroscopic technique, where decreased levels of proteins and nucleic acid content were found in comparison to untreated cancer cells. In AGS human gastric cancer cells, piperine decreases Bcl-2, XIAP (anti-apoptotic), and Akt, while p53, Bax (pro-apoptotic), cleaved caspase-9, and cleaved-PARP increased.^[118] Piperine inhibits IL-1 α -induced p38 MAPK and STAT3 activation and, in turn, blocks the IL-1 α -induced IL-6 expression in TMK-1 gastric cancer cells. It also decreases the protein levels of Bcl-2, Mcl-1, survivin, and increases the Fas levels, resulting in inhibition of the growth of HT-29, human colon cancer cells. In HT-29 colon carcinoma cells, piperine reduces the levels of cyclins (D1 and D3), cyclin-dependent kinases (CDK-4 and 6), and upregulates p21/WAF1 and p27/KIP1 expression.^[119] The study of Yaffe *et al.* found that this natural compound inhibited the growth of HRT-18 human rectal adenocarcinoma cells by causing apoptosis. The same study found that this effect has been at least partially caused by creating increased production of reactive oxygen species (ROS) in the cancer cells treated with piperine. The activation of the mechanistic target of the rapamycin complex 1 (mTORC1) was found to be associated with sustained inflammation and, thus, the progression of colorectal cancer. Piperine alone and in combination with curcumin plays a preventive role in the development of colorectal cancer by inhibiting TNF- α and mTORC1 in human intestinal epithelial cells.^[120]

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 1 β 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 metalloproteinase 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 compartment at the concentrations of 10-100 μ g/mL. It significantly inhibited the synthesis of prostaglandin E2 even at 10 μ g/mL. The expression of interleukin 6 and matrix metalloproteinase 13 were also inhibited. The migration of activator protein1 into the nucleus in interleukin 1 β treated synoviocytes was inhibited by piperine while migration of nuclear factor κ B 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.^[121]

Antidepressant Activity of Piperine

The antidepressant-like effect of piperine and its possible mechanism was evaluated in corticosterone-include 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.^[122]

Method of extraction

Piperine can be isolated from the oleoresin of *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 usage.^[123] Piperine is obtained directly from the crude residue in lesser amounts by extraction in alcohol, filtration and successive crystallization. Alkaline hydrolysis of piperine gives two compounds, one an acid, viz., piperic acid and the other an alkaloid, viz., piperidine. This confirms that piperine is the amide formed between piperidine and piperic acid.

Physical and chemical Properties of piperine

This black pepper extract is a yellow crystalline compound the melting point of which is 128 to 130 °C. The chemical structure of piperine is defined as piperoylpiperidine with chemical formula C₁₇H₁₉NO₃. It is a very weak base and in the process of acid or alkali hydrolysis breaks down into a volatile basic known as piperidine (C₅H₁₁N), and piperic acid (C₁₂H₁₀O₄).^[124] The substance is slightly soluble in water, same as other members of the lipid family. Its solubility is 40 mg/l. That fact along with certain degree of toxicity for the central nervous and reproductive systems limits its pharmaceutical activity. At the same time, this chemical is highly soluble in alcohol, ether and chloroform.^[125]

Table 7: Physical and Chemical Properties of Piperine.

IUPAC Name	1-[5-(1,3-Benzodioxol-5yl)-1-oxo-2,4-pentadienyl]piperidine
Chemical name	1-piperoyl piperidine
Molecular formula	C ₁₇ H ₁₉ NO ₃
Molecular mass	285.34 gm mol ⁻¹
Taste	Tasteless at first, but burning aftertaste
Melting point	130°C
Solubility	Insoluble in water, soluble in benzene and acetic acid and alcohol

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 40,000 times less than the LD₅₀ dose of piperine, as established in various experiments on rodents.^[126]

Advantages of piperine as bioenhancer

- 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.

- Combination of bioenhancer with drug reduces the dosage and dangers of drug resistance can be minimized.
- They can reduce inter-individual variability as well as intra-individual variability as they increase the bioavailability of drug.^[127-130]

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 glucuronic 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 passes through the liver after absorption from GIT.^[131-134] 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.^[135-137] Piperine inhibit human pglycoprotein and cytochrome P350 3A4 (CYP3A4). Both the proteins contribute to a major extent to first- pass elimination of many drugs. Some of the metabolizing enzymes 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 molecules, increasing GIT vasculature by vasodilation to increase absorption of drugs, modulation of the cell membrane dynamics to increase transport of drugs across cell membranes.^[138]

Future Prospective

There are a large number of alkaloids that can prevent the development of cancer. Many natural alkaloids have been screened, identified, and developed successfully into FDA-approved anticancer drugs. Chemoprevention, using phytochemicals from fruits, vegetables, and spices, is an important prophylactic strategy against cancer development. Piperine has recently garnered much attention for its chemopreventive properties. Piperine possesses potential chemopreventive properties which may be due to induction cell cycle arrest, increased cell apoptosis, disruption of redox homeostasis, attenuation of CSC self-renewal, inhibition of angiogenesis, modulation of ER stress, and autophagy, influence on the Wnt/ β -catenin and inhibition of PI-3K/Akt signaling pathways. Notably, the hydrophobic nature and poor aqueous solubility of piperine limits the clinical use of this natural molecule. The information collected by us in this review has revealed that piperine can target different types of cancer cells specifically and manifest specific mechanisms of action in accordance with the type of cancer it acts on. However, the exact mechanism involved in the chemopreventive effects of piperine against the cancer development is not fully understood. Therefore, the precise mechanism of action of piperine must be validated before final recommendations on the clinical use of this natural molecule can be made. The hope is that piperine could be administered with minimum risk to human subjects and that it would produce a significant chemopreventive effect.

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. Piperine, the major pungent principle of pepper, is an alkaloid with a remarkably broad spectrum of therapeutic activities. It has also been shown to enhance the bioavailability of nutritional and botanical compounds. In spite of the amazing therapeutic properties of piperine, its pharmaceutical activities have been limited due to its low aqueous solubility. This review collectively presents source, extraction, significance along with applications of piperine in different food and pharmaceutical industries. Piperine is an alkaloid present in the fruits and roots of *P. nigrum* and *P. longum* species of Piperaceae family, which contributes pungent quality to them. The two species are valued for the presence of this important alkaloid and are used medicinally to cure digestive and respiratory disorders. It has various applications in food and pharmaceutical industries. It is used as a bioavailability enhancer to increase the availability of selenium, vitamin B, β -carotene and other nutritional compounds. In addition, it possesses anti-inflammatory, thermogenic, growth stimulatory, anti-thyroid activities and also acts as a chemo preventive agent. This also displays antipyretic, analgesic, insecticidal, immunomodulatory, antitumor, anti-depressant, anti-apoptotic, anticonvulsant, anti-arthritis, anti-ulcer, antioxidant and cytoprotective effects. Recently it has been shown that, this also affects mood and cognitive disorder and acts as a bioavailability enhancer in the formulations of several drugs. 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.

ACKNOWLEDGEMENT

Authors want to acknowledge the facilities provided by the Shri Shankracharya Technial Campus, Shri Shankracharya Group of Institutes, Faculty of Pharmaceutical Science, Junwani, Bhilai, Chhattisgarh.

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