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Review on Piperine as A Natural Bioenhancer in Field of Nanotechnology

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ABSTRACT: -
Bioavailability of drugsis the most important issue when the drug is poorly bioavailable as it affects the oral absorption of the drug, given for a longer period of time. Poorly soluble drug never reaches the plasma and doesn't show pharmacological effect as it remains sub therapeutic. In recent years several approaches have been introduced to increase the oral bioavailability as it will decrease the dose of drug and increase absorption, but with discovery of natural bio enhancer piperine in the field of nanotechnology as it will increase permeability of the drug by forming nanoparticles, nanocomposites, nanofibers, Nano capsules. Bioenhancers are plant-based molecules which enhance the bioavailability of the drug and show its therapeutic effect. This review article concludes the bioavailability enhancing property of piperine in field of nanotechnology.

Keywords - Piperine, Natural bioenhancer, Solubility, Nanotechnology, Techniques to improve bioavailability

I. INTRODUCTION: -

Piperine is a major bioactive component of Black pepper and belonging to family Piperaceace it has various activity like anti-inflammatory, analgesic, antiarthritic, anticonvulsant, CNS depressant, anticancer activity, etc (Leila Gorganietal). It is a natural alkaloid which has various health effects and therapeutic properties in biological application and its major property is it enhances the bioavailability of low soluble drugs. A bioenhancer is an agent which increases bioavailability and efficacy of drug with which it is combined (Atal, N etal). (DB, M., Sreedharan etal). Piperine has been reported that it enhances the bioavailability of several drugs which have low solubility of drug whether it is by oral or intravenous route. The absorption of piperine across the intestinal barrier is very fast. Studies have indicated that piperine has a passive diffusion mechanism, a high apparent permeability coefficient and short clearance time. (PN Shingateetal and Hussain, Z., Chaudhri, etal)

Where another important factor is solubility of a drug according to the Biopharmaceutical Classification system (BCS) it is a guide provided by the U.S. Food and Drug Administration used for predicting the oral drug absorption and intestinal drug absorption of drug. It is further classified into four classes: **Class I**: High solubility and High permeability, **Class II**: Low solubility and High permeability, **Class III**: Low solubility and High permeability, **Class IV**: Low solubility and Low permeability (Chavda, V.P., and Desai. S.). Oral route is the most convenient route of drug delivery due to ease of administration as the major task is to design the drug depending on its bioavailability, solubility and route of administration. The oral solubility of a drug depends on following parameters like solubility, permeability, dissolution rate, first pass metabolism. The aqueous solubility of a drug is an important factor to evaluate oral bioavailability of orally administered drug if it is poorly soluble. (Dhillon, B., Goyal, etal) (Sajavni, K.T., Gajjar, A.K.

BIOENHANCER: -

The term "bioenhancer" is derived from the traditional system of Ayurveda. Where the bioavailability enhancers are the drug carrier which does not show activity by themselves but when used in combination, they enhance the bioavailability or the drug absorption at site of action. The term bioenhancer was first coined by Indian scientists C.K Atal, the Director of the Regional Research laboratory, Jammu. (Sahoo, C.K., Reddy, G.S)

Generally, there are various mechanisms of action of bio enhancers like acting on GI tract and increasing the absorption of drug or by inhibiting metabolism of the drug in intestine and

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liver, Inhibition of efflux mechanism. (Javed, S., Ahsan, W.) There is some characteristic of bioenhancer are as follow:

✔ It should be non-allergic, non-toxic and non-irritating
✔ Should not produce or show pharmacological activity
✔ Should be non-compatible with pharmaceutical ingredients

Classification of Bioenhancer:
The bioenhancer are classified based on origin, mechanism of action they are: (Jain G, Patil UK and Deepthi V. Tatiraju, Varsha B. Bagade, etal)

A] Based on origin:
✔ Plant origin (Natural Bioenhancer)
✔ Animal origin

B] Based on mode of action:
✔ Inhibition of P-gp efflux pump
✔ Suppressants of CYP- 450 enzyme and isoenzyme
✔ To regulate GI function for better absorption

Table 1: Classification of Bioenhancers Based on Origin

PLANT ORIGIN		ANIMAL ORIGIN
Niaziridin	Capsaicin	Cow urine distillate (*Kamdhenu ark)*
Cuminum cyminum	Quercetin	
Carum carvi	Curcumin	
Stevia	Naringin	
Lysergol	Capmul	
Glycyrrhizin	Peppermint oil	
Ginger	Gallic acid	
Allicin	Ellagic acid	
Aloe vera	Ferulic acid	
Simomenine		
Genistein		
5'-methoxy hydnocarpin		
Ammannia multiflora		

Table 2: Classification of Bioenhancers Based on Mechanism of Action

• **Inhibitors of P-gp efflux pump and other efflux pumps:** Examples: *Carum carvi* (Caraway), Genistein, Sinomenine, *Cuminum cyminum* (Black cumin), Naringin, Quercetin
• **Suppressors of CYP-450 enzyme and its isozymes:** Examples: Naringin, Gallic acid and its esters, Quercetin
• **Regulators of GIT function to facilitate better absorption:** Examples: *Aloe vera* (Aloe), Niaziridin (Drumstick pods), *Zingiber officinale* (Ginger), Glycyrrhizin (Liquorice)

Natural bioenhancer: -(Kesarwani K, Gupta R and Deepthi V. Tatiraju, Varsha B. Bagade, etal) Natural Bio enhancer is from herbal origin made up of both plant and animal origin. Where it has its

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own natural activity of increasing the absorption of poorly water-soluble drugs having low bioavailability. There are various mechanisms for bioavailability enhancement. There are various types of natural bioenhancers like (Verma, C.P.S., Verma, S.,): -

1. Piperine
2. Quercetin
3. Niaziridin
4. Genistein
5. Glycyrrhizin
6. Curcumin
7. Zinger Officinale (Ginger)
8. Lysergol
9. Alovera (Aloe)
10. Naringin

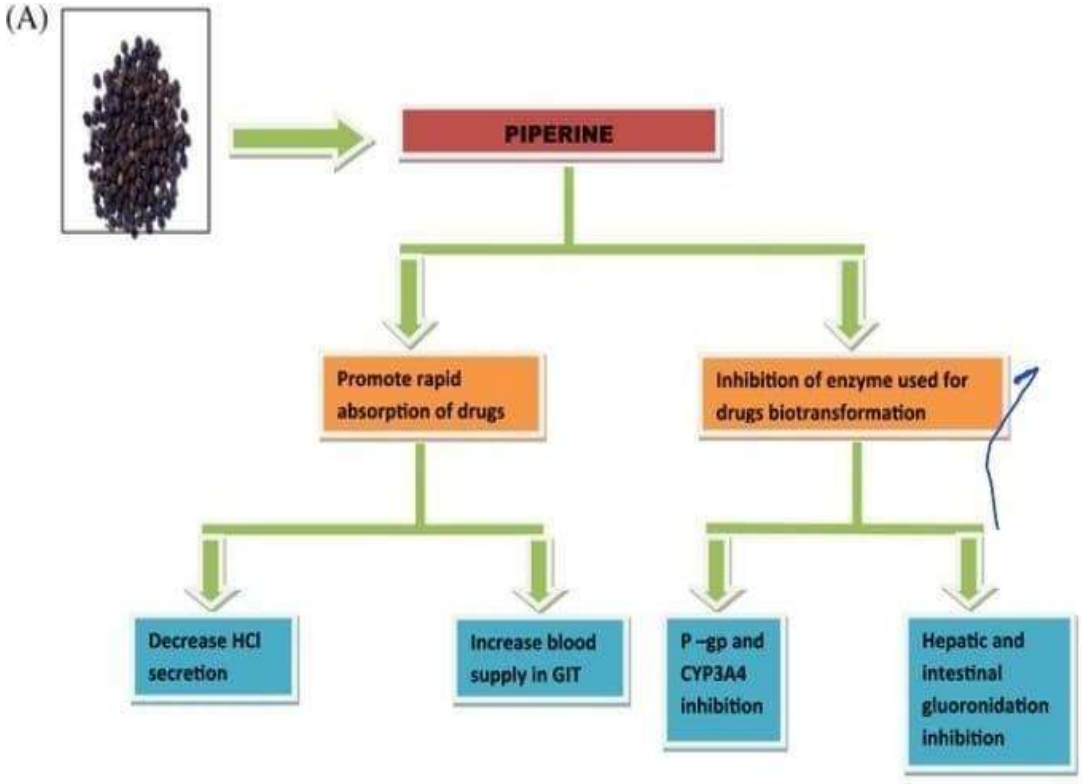
Piperine has been selected as a bioenhancer as it has various advantages in combination therapy. Piperine increases bioavailability as the potency of the drug is increased as the major activity of piperine is that it prevents first pass metabolism. By which the dose of the drug is decreased and prevents drug resistance and it also reduces the adverse drug reaction and toxicity. It has been reported to have enhanced the bioavailability of several drugs whether it is by oral or intravenous route. The absorption of piperine across the intestinal barrier is very fast. Studies have indicated that it has a passive diffusion mechanism, a high apparent permeability coefficient, and short clearance time. (Mukhopadhyay, N., Khan, S. and Mhaske DB, Sreedharan S etal)

Mechanism of Action of Bioenhancer:(Shamama Javed, Waquar Ahsan etal)

✔ The mechanisms of action of natural bioenhancers are:

✔ By enhancing blood supply to GI tract by which there is increase in absorption

✔ By extending a temporary stay in the body by decreasing elimination process



PIPERINE: -(Fatiqa Zafar, Nazish Jahan etal) (Epstein, W.W., Netz, D.F. etal)

Piperine is the major bio - active component of Black pepper (Piper nigrum L.) which imparts pungency and biting taste to it. It is a natural alkaloid which has various health effects and therapeutic properties in biological application

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and major property is it enhances the bioavailability of the low soluble drug. Piperine is a yellow crystalline compound with a melting point is 128 to 130 °c. The chemical structure of piperine was later identified as piperonyl piperidine with chemical formula $C_{17}H_{19}No_3$ and IUPAC name is 1-(5-[1,3-benzodioxol-5-yl]-1-oxo -2,4-pentadienyl) piperidine. Piperine has been reported to have enhanced the bioavailability of several drugs which have low solubility of drug whether it is by oral or intravenous route.

The absorption of piperine across the intestinal barrier is very fast. Studies have indicated that piperine has a passive diffusion mechanism, a high apparent permeability coefficient, and short clearance time.

NANOTECHNOLOGY: -(Jeevanandam, J., Barhoum, etal) (Anna Pratima Nikalje)

In recent years of drug discovery, new advanced technology in pharmaceutical and biomedical research has been introduced. One of them is nanotechnology. Nanotechnology is the advanced technology in pharmaceutical and biomedical research where new techniques have been developed in recent years. Nanoparticles (NPs) and Nanostructured (NSMs) represent active areas in research. NPs and NSMs have gained prominence in advanced technology due to its physicochemical characteristics. Nanoparticles are defined as solid particles with a size range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated and attached to a nanoparticle matrix. Nanomedicine is a new invention in nanotechnology in pharmaceutical and biomedical science to develop new drugs. Depending on the method of preparation nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are system in which the drug is confined to a cavity surrounded by a unique polymer membrane, while Nanospheres are systems in which the drug is physically and uniformly dispersed. The major goals in designing nanoparticles are to control particle size, surface properties and release of pharmaceuticals active agent and desired targeted site. The British standards Institution has approved the scientific definition terms which has been used:

- Nanoscale: The approximate size range is 1 to 1000 nm.
- Nanoscience: It deals with the science and study the size and structure of individual atoms, molecules or bulk drugs.
- Nanomaterial: Is defined as external or internal structure of materials based on nanoscale dimension.
- Nanoparticles: Are defined as solid particles with size range of 10 - 1000 nm.
- Nanofibres : Are defined as when in a nanomaterial two similar nanoscale dimensions and a third large dimension are present is called a nanofibre .
- Nanocomposites: It is a multiphase structure with one phase on nanoscale dimension
- Nanostructure: It consists of interconnected chain in the nanoscale region

HISTORY OF NANOTECHNOLOGY:-(Sudha, P.N. , Sangeetha, K, etal)

The history of nanotechnology is vast as it is traced by first known nanoparticles which were made in the 9th century in Mesopotamia by artisans.

It was used as it generated a glittering effect on the surface of the pot. The glittering effect on the pot is due to the presence of silver and copper nanoparticles which are dispersed in a glassy matrix.

One of the most interesting examples was the lycurgus cup, made by Romans in about AD400, it was made of glass that changes colour when the light is reflected on the cup.

It is composed of Au-Ag alloyed nanoparticles which make the glass look green when light is reflected but when light is passed through glass it looks red.

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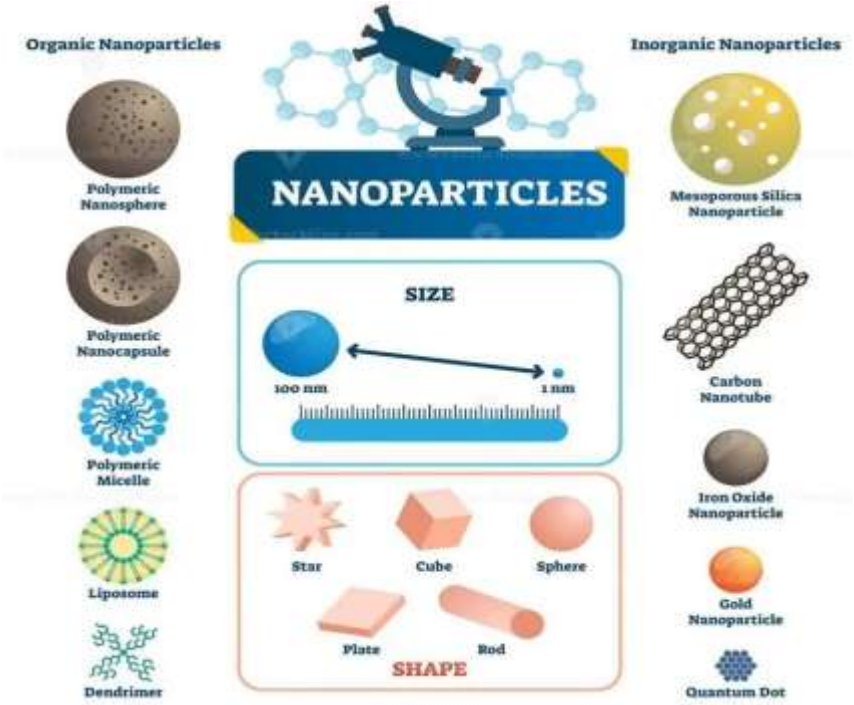
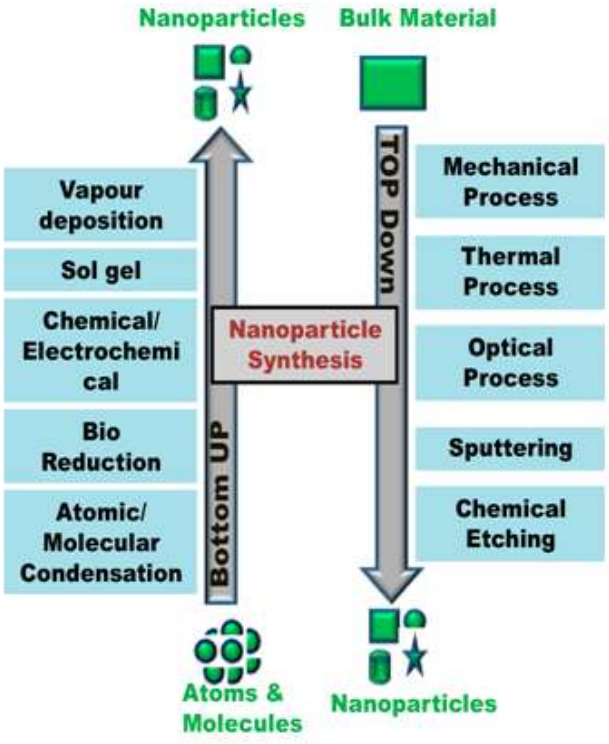
CLASSIFICATION: -(Anna Pratima Nikalje)



S**YNTHESIS OF NANOPARTICLES:** -(Samer Bayda, Muhammad Adeel, etal)



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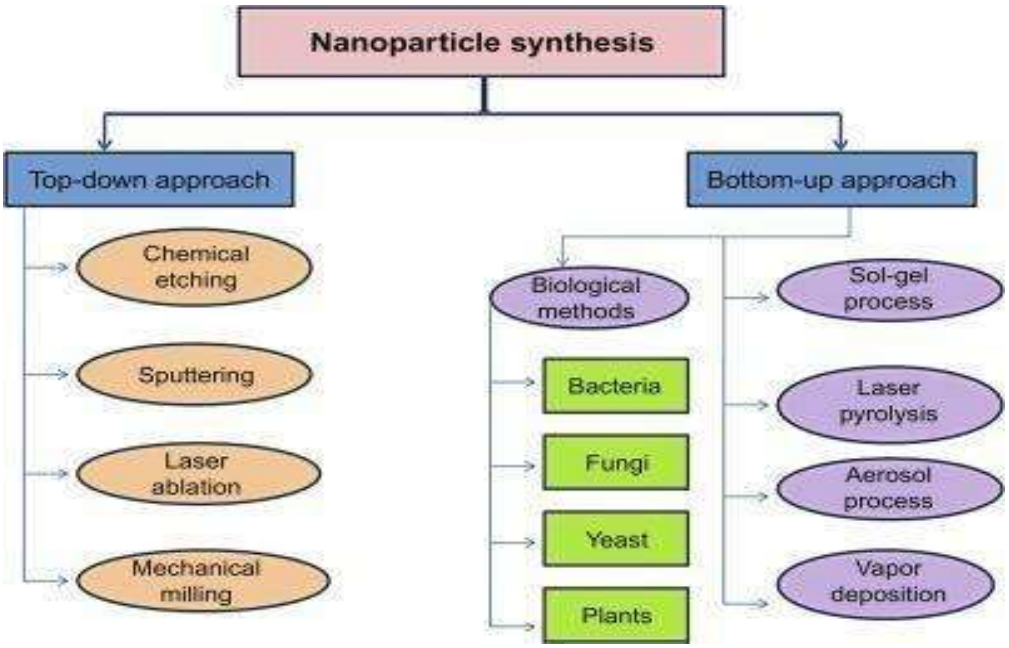

ADVANTAGES :-

1. Nano drug carriers have high stabilities
2. Have high carrier capacity
3. Feasibility of incorporation of both hydrophobic and hydrophilic substance
4. They are biodegradable, nontoxic and stable for longer period
5. Use for controlled delivery of the drug

DISADVANTAGES:-

1. Polymeric nanoparticles possess limited drug loading capacity
2. On repeated administration, toxic metabolites may be formed during ploymeric carrier biotransformation

METHODS TO IMPROVE BIOAVAILABILITY BY NANOTECHNOLOGY :-

(Patel,M.S.N., Ahmed, etal)

Where we can increase solubility by using surfactants, polymers, bioenhancers. There are different techniques for solubility enhancement they are:

Physical Modifications - Particle size reduction like nanoparticles, nanosuspension, carriers

Chemical Modifications - Change in pH, derivatization, complexation

Miscellaneous Modification - Use of adjuvants like solubilizers, surfactants, novel excipeints

A] Physical modifications –

Particle size reduction: nanonization and micronization

Crystal habit modification: Pseudoplymorphs and polymorphs Use of carriers: Solid dispersion method and eutectic mixture By complexation

B] Chemical modification –

Change in the pH of the system Salt formation

C] Formulation Based Approach –

Co-solvency

Co-crystallization Hydrotrophy

D] Modification in partition coefficient-

Formation of ester

Novel formulation approaches

E] Inhibit Hepatic First- Pass Metabolism -

Combination of drug Prodrug

Novel Drug Delivery System

F] Inhibit degradation in gastrointestinal tract -

Avoid degradation in stomach by using enteric coating Use if Floating drug delivery system

Use of mucoadhesive polymers

Colon Targeted Drug Delivery system

METHODS FOR PREPARATION OF NANOPARTICLES:-(C.Moorthi,Krishan,etal)

1. Solid Lipid Nanoparticles
2. Microemulsion Method
3. Coacervation Method

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4. Thin Film Hydration Method
5. Emulsion Polymerization Method
6. Fessi Method
7. Nanoprecipitation method

1) Thin Film Hydration Method:-

For preparation of nanoparticles first the drug and surfactant is dissolved in organic solvent under sonication (40 kHz). Further the solvent is removed under pressure by using Rotary evaporator to form thin film .Then 5mL Ultra pure water is added to thin film under sonication (40 kHz) for 5-10 cycles (5min) and nanoparticles are formed simultaneously and the solution turns turbid. To remove free drug from nanosuspension it is centrifuged at 3000 rpm for 10 min at 4°c.

2) Solid Dispersion Method:-

Drug is dissolved in organic solvent under sonication then the organic phase is added drop wise to 50mL of Ultra pure water containing surfactant with or without viscosity enhancer (e.g.: Sodium alginate) under sonication for 10 cycles per cycles 5min. And the nanoparticles are formed spontaneously and the solution turns turbid. The organic solvent us removed by continuous overnight stirring by help of magnetic stirrer and then the nanoparticles were separated by using ultracentrifuge at 19000 rpm for 45mins at -20°c and the obtained nanoparticles are washed three time with Milli-Q water and the nanoparticles are formed .

3) Emulsion Polymerization Method:-

Surfactant is added in 50mL Milli -Q water under sonication and then stored overnight at required temperature to form micelles. Then the drug is dissolved in 5mL organic solvent under sonication and further the organic phase is added in 50mL aqueous phase containing micelles by help of a magnetic stirrer at 100-500 rpm for 1 hour at room temperature. The nanoparticles are formed and the solution turns turbid and then the free drug is removed by centrifugation at 3000 rpm for 19 mins at 4°c.

WORK DONE ON PIPERINE AS NATURAL BIOENHANCER :-

Sr.no	DRUG	BIOAVAILABILITY AND BCS CLASS	WORK DONE	RESULT OBTAINED
1.	Docetaxel	8% + 6 %, BCS Class IV drug	In this PLGA was conjugated with aspartic acid and piperine was tagged with docetaxel loaded polymeric micelles .	By which the piperine compromised P -gp efflux mechanism and increased bioavailability by 3.3 folds and retained drug at targeted site .
2.	Rapamycin	14 % , BCS Class II drug	They formulated rapamycin nanoparticle by nanoprecipitation method and to prevent P- gp efflux	By using piperine as enhancer it inhibited P-gp efflux and the bioavailability was increased by 4.8 folds
3.	Nisoldipine	5 % , BCS Class II drug	Is a sunstrate for cytochrome P4503A4 enzyme, in this study nisoldipine - piperine nanoparticles were prepared by precipitation method	The results revealed that piperine being an inhibitor of cytochrome P4503A4 enzymes enhanced the bioavailability of nisoldipine by 4.9-fold

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			to increase bioavailability	in nanoparticles.
4.	Quercetin	16 %, BCS Class II drug	The present study is to increase the therapeutic potency of quercetin with piperine as a bioenhancer against chronic unpredictable stress - induced behavioral alteration	The bioavailability of the drug was increased by inhibiting P-gp efflux, these findings represent a valid rationale for co-administration of piperine with quercetin, which might act as a useful and potent adjuvant in the treatment of memory disorders.
5.	Resveratrol	<1%, BCS Class II drug	Aim of this study was to develop RES, using piperine by solvent evaporation method to enhance oral bioavailability and potency .	The oral bioavailability of RES from RES-P-MM was increased by 5.7 and 2 folds compared to pure resveratrol .
6.	Curcumin	1%, BCS Class IV drug	Curcumin has low bioavailability and high metabolism in GI tract so they prepared curcumin -piperine nanoparticles by electrospray method.	The oral bioavailability of drug was increased by 6.5 folds by inhibiting GI tract metabolism
7.	Metformin	50-60 %, BCS Class III drug	To study the bio enhancing effect of piperine with metformin in lowering blood glucose levels in alloxan-induced diabetic mice .	Piperine has bioenhancement in combination with metformin and reduce side effects
8.	Emodin	<3%, BCS Class II drug	In this study emodin and piperine combination was formulated as emodin has low bioavailability	The oral bioavailability of emodin was increased by inhibiting glucuronidation
9.	Ginsenoside	0.94 %, BCS Class IV drug	The main purpose of this study is to enhance oral bioavailability of ginsenoside by using piperine as bioenhancer.	The oral bioavailability was increased by 2.3 and 3.9 folds by inhibiting P-gp and CYP3A4 .

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10.	Etoposide	50 %, BCS Class IV drug	The aim was to enhance the bioavailability of etoposide by using piperine as bioenhancer by	The study a piperine analogue, namely, 4-ethyl 5-(3, 4-methylenedioxypheny l)-2E,4E-pentadienoic acid piperidide (PA-1),
			pharmacodynamic and pharmacokinetic study .	was shown to cause 2.32-fold enhancement of the absolute bioavailability of co-dosed etoposide in mice.
11.	Omeprazole	60 %, BCS Class II drug	To investigate the formulation of gastroretentive microspheres of omeprazole along with piperine and estimate the pharmacokinetic parameters in comparison with omeprazole alone.	There was a significant increase in 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 as gastroretentive microspheres.

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