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RECENT TRENDS ON NATURAL BIOENHANCERS: AN OVERVIEW

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ABSTRACT

Bioenhancers are the compound use to hasten the bioavailability of many herbal as well as chemical drugs which have good pharmacological efficacy but have poor bioavailability. In recent research there are many herbal bioenhancers which have good bioenhancing property and they do not have any side effects and pharmacological effects itself. They become very useful for present morden therapy because they reduce treatment cost plus they haven't any side effects, up to now research classified them in two different manners first according to their origin and second, according to their mechanism. This article gives the overview of the bioenhancers which are investigated in research till now and information about their origin, mechanism of action, number of bioenhancers their new formulations.

KEYWORDS

Bioenhancers, Classification and Prodrug.

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INTRODUCTON

Bio-enhancers are substances which stimulate and hasten the bioavailability of the drugs. Bio-enhancers are such agents, which by themselves are not therapeutic entities but when combined with an active constituent proceed to the potentiating of the pharmacological effect of the drug[1]. The phenomenon of increasing the total availability of any chemical entity (nutrient or drug molecule) in biological fluid or systemic circulation is called biopotentiation or bioenhancement and the secondary agents which are responsible for this augmentation of plasma concentration of principle ingredient are termed as biopotentiers or Bioavailability enhancers[2].

Bioenhancer, one must be capable of increasing the bioavailability and bioefficacy of the therapeutically active agents (drugs) and nutraceuticals upon co-administration, without any significant pharmacological activity of its own at the dose used[3]. Bioenhancers or biopotentiators are new to the modern science. In contrast to this, many drugs as bioavailability enhancers are being used in Ayurveda since time immemorial[7].

FACTORS RESPONSIBLE FOR POOR BIOAVILABILITY

There are many drugs which have good therapeutic value but poor bioavailability. Bioavailability is the term coined to rate and extent with which any substances reach the systemic circulation and shows the desired action[4]. There is an increasing medical demand for the improvement of bioavailability of a large number of drugs, which are given for longer period, and they are toxic and expensive. Poorly bioavailable drugs remain sub-therapeutic because of a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may lead to serious side effects or toxic effects[5].

The intake of antibiotics and drugs by human is increasing at an alarming rate. Out of the total drugs and chemicals, 20-50% of that use is unnecessary depending on the class of antibiotic. In addition, indiscriminate use of antibiotics promotes antibiotic resistance leading to multiple drug resistance and makes it difficult to control the diseases. The infected individuals have to consume more amount of antibiotics; this may be due to reduced absorption of drug in gut membrane when taken orally, restrictive uptake of drug by target microbe, and by efflux drug transporter of cell membrane, leading to indiscriminate extrusion of the antibiotics or drug molecules. So, the major amount of the applied drug is wasted and only a minor amount is being targeted to the site of infection[6]. Drug metabolism by drug metabolizing enzymes (DMEs) in the gastrointestinal membrane and the liver is also the major contributors of reduced bioavailability of drugs[4]. The size of drug molecule and lipophilicity both are the most important preventive factors for molecules to pass the biological membrane[1] and the bioavailability of an orally administered drug also depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is another limiting factor for the oral bioavailability of poorly water soluble compounds[7].

Many herbal drugs and herbal extracts also have extraordinary potential in *in-vitro* findings but, demonstrate less or no *in-vivo* actions due to their poor lipid solubility or improper molecular size or both, ultimately resulting in poor absorption and poor bioavailability[8].

To enhance bioavailability of therapeutically potent but poorly bioavailable molecules has always been a difficult aspect of drug development programmes, as it reduces the drug dosage and frequency resulting in reduced toxicity and cost for the patients[3].

To overcome this problem bioenhancers are using, bioenhancers are the substances which increase the therapeutic effectiveness of the drug by increasing availability of the drugs in blood in combination with drugs without affecting its properties away[7]. Bioenhancers can improve the bioavailability of drug molecules by alteration of the plasma membrane fluidity to increase passive transcellular drug permeation, and modulation of tight junctions in cell membrane to allow for increased paracellular diffusion; and modulation of active efflux transporter, such as P-gp-related efflux inhibition. Inhibition of metabolic enzymes such as CYP enzymes in the intestinal epithelium and liver can significantly impact upon the bioavailability of drugs that are substrates of these enzymes by means of reducing pre-systemic metabolism[9].

Piperine is identified as the world's first bioavailability enhancer and scientifically validated by Indian scientists at the Regional Research laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine) in 1979[5]. Number of natural bioenhancers of both plant and animal origins such as piperine, quercetin, genistein, naringin, sinomenine, glycyrrhizin, curcumin, lysergol, allicin, niaziridin, cow urine distillate, etc. have been investigated and documented that they

possess pharmacological and/or bioenhancer activities[3].

An ideal bioenhancer should be safe, effective, readily available and economical. In addition, it should not produce its own pharmacological effects at the dose used, should be rapid-acting with predictable and reproducible activity and should be compatible with other active pharmaceutical ingredients[11].

IDEAL PROPERTIES OF BIOENHANCERS

- It should be Nontoxic to humans or animals,
- It should be effective at a very low concentration in a combination.
- It should be easy to formulate and
- The Most important property which every bioenhancer should possess is that it should enhance uptake/absorption and activity of the drug.
- Should be unidirectional in action.
- It should be compatible with other active pharmaceutical ingredients.
- It should be stable with time and environment.
- It should be easily formulated into a various dosage form.
- It should be easily available and cost effective
- It shouldn't possess any pharmacological activity of its own at the therapeutic dose used[2,11,12].

Bioavailability enhancement can be done by the following

- By increasing the absorption of drugs from GIT.
- Inhibiting or shortening the rate of biotransformation of drugs in the liver or intestines.
- Changing the immune system in such a way that the overall need of the drug is reduced substantially.
- Increasing the penetration of the drug into the pathogens even where they persisted within the macrophages such as for *Mycobacterium tuberculosis*. This eventually ensures the killing of these organisms.
- Inhibiting the efflux mechanisms of pathogens or abnormal tissue to reject the drug, for example, frequently experienced with antimalarial, anticancer and antimicrobial drugs.
- Modifying the signaling process of host and pathogen and ensure, the accessibility of the drugs into the pathogens is increased.
- Increasing the binding period of the drug with the target sites such as receptors, proteins, DNA, RNA, which potentiate and prolong its effect which enhance, the antibiotic activity against the pathogens?
- The bioenhancers may also be useful for promoting the transport of nutrients and the drugs across the blood brain barrier, which could be immense help in the control of diseases like cerebral infections, epilepsy, and other CNS problems[6].

HISTORY AND CONCEPT OF BIOENHANCERS

The concept of bioenhancers came from Ayurveda. In ayurveda, the bioenhancer is called as yogvahi. It is used to enhance Bioavailability, tissue distribution, increase efficacy of drugs especially drugs with poor Bioavailability. Specifically yogvahis or bioenhancers are called as anupaan and sehpaan.

ANUPAAN

This means food and medicament are given together to increase the effect of medicament. For example: Amrit Dhara drops. It is used for gastrointestinal diseases. These drops are taken after they are put on sugar to increase their potency.

SEHPAAN

This means vehicle used during the manufacture of dosage forms to increase the effect of the drug. For example: Panchgavya prepared by using ghee or clarified butter to increase its effect. Examples of

yogvahis generally used in ayurvedic formulations are Piper longum, gold, cow urine distillate, etc[12].

There is another formulation called as Trikatu is a Sanskrit word witch means *Three acrids*. *Trikatu* contain three ingredients: black pepper (*Piper nigrum*), long pepper (*P. longum*) and ginger (*Zingiber officinale*)[8].

This Ayurvedic preparation "*Trikatu,*" was used especially during the period of the 7th century B.C. and the 6th century A.D. which provide more weightage to the practice of bioenhancing. In 1929 for the first time, it was found by Bose who described the antiasthmatic activity of *Vasaka* (*Adhatoda vasica* Nees.) leaves is increased by the addition of long pepper (*Piper longum* Linn.) to it. The term bioavailability enhancer was first given by Indian Scientists C.K. Atal, Director of the Regional Research Laboratory, Jammu (RRL, now known as the Indian Institute of Integrative Medicine), who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979.

Many other concepts and methods of Ayurveda such as *Yogavahi*, *Anupana, Bhaishajya Kala, Bhavana* (trituration), *Rasayana, Yoga* (formulations) and *Kalpanas* (various dosage forms), concept of *Purana Aushadhies* (old drugs), concept of action - augmenting drugs, and penetration enhancers of bio - enhancing are being used since time immemorial in Ayurveda. In addition *Samshodhana* (biopurification) can also be considered in this concept[7].

C.K. Atal, the Director of the Indian Institute of Integrative Medicine examined a list of ancient Indian Ayurvedic formulations used for the treatment of a wide range of diseases. He observed that a number of Ayurvedic formulations contained *Trikatu* otherwise one of the ingredients of *Trikatu*, namely *Piper longum* (*P. longum*) (210 formulations out of 370 reviewed) which is used in a different type of diseases. He defined the working hypothesis that *Trikatu* increased the efficacy of formulations.

In successive experiments using various drugs and extracts with Trikatu and its ingredients they observed that perticularly piperine augment the bioavailability of most of the drugs used in experiments and the role of ginger is to regulate intestinal function to ease absorption[13].

BIOLOGICAL BARRIERS FOR DRUG ABSORPTION

To produce its pharmacological activity the drug must cross the epithelial barrier of the intestinal mucosa for it to be transported from the lumen of the gut into the systemic circulation. In oral drug delivery system there are many structures in the intestinal epithelium which serve as barriers to the transfer of drugs from the gastrointestinal track to the systemic circulation. An aqueous stagnant layer because of its hydrophilic nature it is a potential barrier to the absorption of drugs. The cell membranes are lipid bilayers containing proteins such as receptors and carrier molecules. Drugs cross the lipid bilayers by passive diffusion or carrier-mediated transport which requires the energy for transportation. For the transfer of small water-soluble molecules such as ethanol there are aqueous channels within the proteins. The drug molecules larger than 0.4 nm face difficulty in passing through these aqueous channels[14].

CLASSIFICATION OF BIOENHANCERS

Bioenhancers can be classified on basis of their sourec of origin and machenasium of action.

MEOTHDS OF BIOENHANCMENT

Most of the bioenhancers may have same or different mechanism of action. Nutritional bioenhancers increase drug absorption by acting on gastrointestinal tract. Antimicrobial bioenhancers mostly act on drug metabolism process. There are some physiological alterations to enhance bioavailability such as

1. By deducting the hydrochloric acid secretion and increasing the gastrointestinal blood supply.
2. By gastrointestinal transit inhibition and decreasing the gastric emptying time and intestinal motility.

3. Modifications in GIT epithelial cell membrane permeability.
4. Cholagogous effect.
5. Bioenergetics and thermogenic properties.
6. Abolition of first pass metabolism and inhibition of drug metabolizing enzymes and acids[2].

Detailed explanation of some bioenhancment methods

Absorption enhancer

Most of the absorption enhancers are efficient in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers[11,12]. Chitosan, or trimethylated chitosan, increases the drug absorption by way of paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions cellular membrane. Bile, bile salts and fatty acids are surfactants, they act as absorption enhancers by enhancing the solubility of hydrophobic drugs in the aqueous layer or by augmenting the fluidity of the apical and basolateral membranes. Calcium chelators like EGTA and EDTA enhances absorption by reducing the extracellular calcium concentration, leading to the interruption of cell-cell contacts[14].

Solubilizers

Inadequate solubility is one of the main causes for poor bioavailability. During last decades the small part of poorly soluble compounds entry in to clinical development has been increased. So, the use of solubilizers to enhance bioavailability has become a key parameter in optimizing solubility in pharmaceutical research and development[16].eg;

Fulvic acid is used as solubilizer in many formulations fulvic acid is having a sponge-like structure punctured by voids of about 200-1000 in diameter and its molecular weight, (Mw) is about 700-2500. Earlier it was used as a carrier for poorly bioavailable drugs such as Furosemide, Carbamazapine (by humic acid), and Itraconazole to increase their bioavailability by using its great complexing ability[17].

Prodrug

Prodrug is used to enhance the bioavilability of drug by modification of chemical structure of drug this modification involves addition or removal of perticular founctional groups, it has an active and an inactive moiety in combination[1,18].

Ampicillin derivatives which are known as most common example of prodrug which enhances lipophilicity, of polar drug by pro drug phenomenon. Ampicilline has hydrophilic nature that's why only 30-40% of drug absorbed from GIT. Pivampicilline, Bacampicilln and Talampicillin are prodrugs of ampicillin which are synthesized by etherification of carboxyl group of Ampicillin. The lipophilic activity of parent compound is lesser then the prodrug which shows better bioavailability then parent compound[8].

P-glycoprotein inhibitors

P- glycoprotein inhibitors are enhance the bioavailability of drugs by inhibiting the P-gp pumps which is an efflux pump and it pumps out drugs and prevents it from reaching the target site[7].

P-gp bioenhancers can be act as an inhibitor or the substrate for P-gp pump in a competitive, or, noncompetitive manner, and as a mixed or irreversible inhibitor for P-gp drug transport. P-gp inhibitors slow down P-gp active drug transport between the luminal membrane and prevent the return of absorbed drug into the cytoplasm of enterocytes back to the lumen of the gut. By increasing net drug absorption in the gut it increases bioavailability. The P-gp bioenhancers can be given in combination with number of compounds which includes some classes such as aminoquinolines, anilides, anthracycline antibiotics, antiestrogens, benzofurans, cannabioids, cephalosporines, colchicine, cyclic peptides, epipodophyllotoxins, flavonoids, flavones, imidazole, isoquinolines, macrolides, opioids, phenylalkylamines, phenothiazines, piperazines, piperidines, polyethylene glycols, pyridines, pyridones, pyrimidines, pyrrolidines, quinazolines, quinolines, quinones, rauwolfia alkaloids, retinoids, salicylates, sorbitans, steroids, taxol, triazoles, unsaturated fatty acids, and vinca alkaloids etc[5].

Examples of P-gp inhibitors is Piperine is a pioneer alkaloid which is 1- piperoyl piperidine component of Piper nigrum Linn or Piper longum Linn. This compound can be obtained from the fruits of these herbs which contain 1-2.5% of volatile oil and 5-9% of total alkaloids. These alkaloids present in the form of piperine, piperidine, and piperetine. According to Ethnopharmacological survey piperine/pepper is usually used as antirheumatic, analgesic, diuretic, antispasmodic and antiseptic or a preservative and a perfume in some assertions, these pharmacological effects are irrelevant when it used as a bioenhancers. By research studies it have established that piperine is useful as a bioenhancers in low dose that is 10-15 mg[10].

Inhibitors of cytochrome P450 3A

Cytochrome P450 is the major class of metabolic enzymes it consist with 207 genes, there are number of isoforms, of this enzyme in that only three gene families which is CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4 are responsible for metabolism of number of drugs which are structurally different. Enterocytes of liver and intestinal lumen have many isoforms of cytochrome P450 but only a single isoenzyme family which is 3A is responsible for the most of the drugs metabolism. So by inhibiting these enzyme bioenhancers increase the time of availability of drug in the body by this drug activity is also increase.

Example: Caraway, Sinomenine, Genistein[5,15].

Caraway is also called as cumin its biological name is Carum carvi it belongs from Apiaceae family its main chemical constituent is cravone obtained from seeds of the plant the dose at which it effective as bioenhancer is 1-55 mg/kg body weight. It enhances the bioavilability of many drugs such as antibiotics, antifungal, antiviral, anticancerous and Anti-TB drugs like Rifampicin, Pyrazinamide and Isoniazid. When it used in combination with other bioenhancers like Zingiber officinale (10-150 mg/kg body weight) and piperine (3-15 mg/kg body weight) it become more effective[4,10].

Breast Cancer Resistance Protein (BCRP) inhibitors

Breast Cancer Resistance Protein (BCRP) is a protein which is present in breast carcinoma cell lines. The oral bioavailability of the pharmaceutical compounds enhanced when it co- administred with the BCRP inhibitors. BCRP inhibitors drug bioavilability enhance activity is similar to the P-gp inhibitors they also inhibits the back flux of the drug from the blood or epithelial lumen.

When drug is passing from the enterocyte BCRP inhibitors bind with the BCRprotein and inhibits its uptake. These inhibitors can be irreversible or reversible if they are reversible then they pass through the liver and removed from the body. Bioenhancers is selected in accordance to the substances that are related to known substrates for BCRP like acridine, quinoline, isoquinoline, indolizinoquinoline, camptothecin, anthraquinone, quinazoline, bisanthrene and rhodamine[5].

Permeability enhancers

The substances which increase the absorption of drug from skin temporarily, by enhancing the permeability of skin for short period are permeability enhancers. Substances which are ionizable and impermeable are delivered by using these enhancers such as Timolol maleate, Heparin. Amidon's Biopharmaceutics Classification System (BCS) by the FDA in 2000, devised as a scientific basis to grant biowaivers for in vivo bioavailability and bioequivalence studies gives the importance of solubility and permeability[19,20].

Essential oils are usefull as permeability enhancers they reduces, inter- and intra-individual variability of an orally administered hydrophobic drug when a pharmaceutical compound co-administered with an essential oil or a component of essential oil in a sufficient amount the bioavailability of drug will improve[5].

Cholagogous effect

Cholagogous effect means increase the flow of bile into the intestine. Most of the bioenhancers have this property they contract the gallbladder and increase the bile secretion into the intestine, these plant act by activation of hepatobiliary mode which is also helpful in the treatment of Cholestasis[6,14-15].

Example: Liquorice

Thermogenic properties

Thermogenesis is a metabolic process which conversion of nutrient calories into the heat energy

happens which is essential for body homeostasis, that is, thermoregulation, which maintain healthy metabolism, and control body weight[22].

Thermogenic property, means increasing the rate of metabolism by increasing the temperature. By this it can also improves the gastric mobility and interfere the absorption of cholesterol. Thermogenic and bioenergetic mechanisms are stimulated by activation of thermoreceptors and release of catecholamines and/or direct activation of beta 1, 2, 3- adrenoceptors by their agonists.

Example: Garlic, Ginger, Turmeric[14-15].

Stimulation of gamma glutamyl transpeptidase (GGT) activity

This is a membrane-bound glycoprotein present on the outer surface of the cell membrane and for liver, biliary system and pancreatic diseases it used as a marker. Amino acids are transported across the cell membranes by the help of this peptide. By the activation of gamma- glutamyl transpeptidase the transport of nutrients across the intestinal cells will be hasten.

Percent enhancement in bioavailability of different drugs/compounds by supplementation of bioactive fractions from *Z. officinale* and its combination with piperine[6].

BENEFITS

Bioenhancers have the following benefits to the drug development

1. It reduces dosage of drug.
2. It reduce cost of drug.
3. It prevent from drug resistance.
4. Decrease the percent level of adverse drug reaction or side effects.
5. It increase efficacy of drug
6. Increased Bioavailability
7. Raw material requirement for drug manufacture will be decreased.
8. Economically it is useful to the world economy.
9. Treatment cost of patient decreases.

HURDLES

Bioenhancers have many benefits in drug delivery system but it have some hurdles also like

1. Its circulation in blood, for good formulation it needs good functional surface area.
2. Protection from drug degradation, crossing biological barriers and site specific targeting.

- Large scale production is a problem in the Research and development of herbal Bioenhancers. Pilot scale production is easy for herbal Bioenhancers than the large scale production.
- There is a need of regulatory control for physicochemical and pharmacokinetic properties of newer bioenhancers[12].

Clinical models for bioenhancers study

There are different clinical models are used to know the bioavailability enhancing activity of natural and other bio enhancers mostly small animals are used for the experiments such as rats mice here some of the clinical models which are already done and reported[14].

MARKETED FORMULATIONS

Bioenhancers became very important for the drugs because there are many useful phytoconstituent and other compounds which have good pharmacological activity and can be used for the treatment of critical pathological condition with the proper dose or a small dose of those drugs but their poor bioavailability become a problem for their utility. There are number of formulations those have bioenhancers in their combination.

APPLICATIONS

Bioenhancers not only increase the availability of drug in the body it also reduce the dose of drug because the good bioavailability decrease the dose of drug which is going to administered, it also prevent from the drug resistance and toxicity of antibiotics, because of poor bioavailability persons have to take high dose of drug, which is the reason for drug resistance and toxicity, so as already mentioned bioenhancers prevent from these problems.

S.No	Category	Compound	Percent enhancement BE from *Z.officinale*	BE from *Z.officinale* + piperine
1	Macrolides	Azithromycin Erythromycin Roxithromycin	78 68 72	85 105 93
2	Cephalosporins	Cefalexin Cefadroxil	75 68	85 65
3	Penicillins	Amoxycillin Cloxacillin	80 76	90 90
4	Aminoglycosides	Kanamycin	65	92
5	Fluoroquinolones	Ciprofloxacin Pefloxacin	68 53	70 69

Bioenhancers from herbal sources[6]

S.No	Drug	Biological source	Mechanism	Dose of drug	Drug
1	Piperine (1-piperoyl piperidine)	*Piper longum*	Methylenedioxyphenyl ring in piperine helps in the inhibition of the drug metabolizing enzymes including CYP 450 enzymes and UDP glucuronyl transferase. It also inhibits P-GP and then efflux of absorbed drug from enterocytes	15 mg/kg.	Piperine is used in combination with various drugs and increases the efficacy of these drugs
2	Curcumin	Dried and fresh rhizomes of *Curcuma longa* Linn. Family-Zingiberaceae.	Curcumin suppresses drug metabolizing enzymes (CYP3A4) in the liver as well as inducing changes in the drug transporter P-glycoprotein, hence increase the Cmax and AUC of celiprolol and midazolam in rats	12g/day	Celiprolol and Midazolam
3	Ginger (Whole Part)	Rhizome of the perennial plant *Zingiber officinale* Roscoe, Family-Zingiberaceae.	Due to the presence of saponins, flavonoids, and alkaloids, Ginger acts powerfully on GIT mucous membrane. The role of ginger is to regulate intestinal function to facilitate absorption.	1-55mg /kg	Antibiotics, antifungal, antiviral and anticancerous drugs. Therapeutic activity of Anti-TB drugs like Rifampicin, Pyrazinamide and Isoniazid
4	Caraway (Seeds)	Dried ripe seeds of *Carum carvi* Linn., Family-Umbelliferaceae.	Due to a novel flavonoid glycoside it enhances the peak concentration (Cmax) and area under the curve (AUC) of rifampicin	1-55mg/kg	Antibiotics, antifungal, antiviral and anticancerous drugs. Therapeutic activity of Anti-TB drugs like Rifampicin,

					Pyrazinamide and Isoniazid.
5	Glycyrrhizin	Dried root and stolon of *Glycyrrhiza glabra* Linn, Family-Leguminosae.	It enhances cell division inhibitory activity of anticancerous drug. Inhibition of cell growth by taxol with glycyrrhizin was higher than the taxol alone. This combination is used against breast cancer. It also enhances (2 to 6 fold) transport of antibiotics.	1 µg/ml	Taxol and antibiotics like Rifampicin, Tetracycline, Nalidixic acid, Ampicillin and Vitamins B1 and B12 as bioenhancer
6.	Indian aloe (Leaves)	Dried juice of the leaves of *Aloe barbadensis* Mill., Family-Liliaceae	Longer in the plasma and increases bioavailability of Vitamin C and E in human. It also capable of inhibiting the release of reactive oxygen free radicals from activated human neutrophils.	-	Vitamin C and E
7	Quercetin	It is a flavonoid found in many fruits (apples, citrus fruits like red grapes, raspberries, and cranberries), green leafy vegetables and black and green tea	It inhibits the p-glycoprotein efflux pump and metabolizing enzyme, CYP 3A4 in the intestinal mucosa and restraint the metabolizing enzyme CYP3A4		Diltiazem, Digoxin, Epigallocate-chin gallate
8	Allicin	Aromatic bulb of *Allium sativum* Linn. Family-Liliaceae	Allicin enhances AmB-induced vacuole membrane damage by inhibiting ergosterol trafficking from the plasma membrane to the vacuole membrane	120µM allicin or a non-lethal concentration of AmB (0.5 µM)	Fungicidal activity of Amphotericin B
9	Naringin	It is a flavanone-7-*O*-glycoside occurs naturally in citrus fruits, especially in grapefruit	It inhibits the CYP3A1/2 enzymes and p-glycoprotein is modulated in rats	3.3 and 10 mg/kg	Paclitaxel, Verapamil, Diltiazem
10	Tea (Leaves and Buds)	Leaves and leaf buds of *Thea sinensis* Linn. Family- Theaceae	The thermogenic properties of tea extract shows a synergistic interaction between caffeine and catechin polyphenols that appears to prolong sympathetic stimulation of thermogenesis. Green tea also promotes fat oxidation and		Both teas promote the absorption of manganese and copper as nutrients in the blood circulation.

			decreased the absorption rate of zinc while black tea		
11	Niaziridin	Niaziridin a nitrile glycoside is isolated from the pods of *Moringa oleifera* Lam., Family-Moringaceae	Commonly act with antibiotics against gram-positive bacteria like Myobacterium smegmatis, Bacillus subtilis and gram-negative bacteria like *E. coli* to increase the absorption of it.		Vitamin B12, rifampicin, ampicillin, nalidixic acid, azole antifungal drugs such as clotrimazole
12	Lysergol	It is isolated from higher plants like *Rivea corymbosa* Linn., *Ipomoea violacea* Linn. and *Ipomoea muricata* Linn.	It promotes the killing activities of different antibiotics on bacteria. lysergol enhances the transport of antibiotics across the intestinal gut and cell membrane.	10 µg/ml	Broad-spectrum antibiotics
13	Genistein	It is an isoflavone found in a number of dietary plants like soybean (*Glycine max* Linn.) and kudzu (*Pueraria lobata* Willd.).	Genistein is reported to be able to inhibit P-gp, BCRP and MRP-22 efflux functions	3.3 mg/kg or 10 mg/kg	Paclitaxel, *Epigallocatechin gallate* the
14	Sinomenine	Root of the climbing plant *Sinomenium acutum*Thunb. Family-Menispermaceae.	The mechanism underlying the increase in bioavailability of paeoniflorin is explained as sinomenine could decrease the efflux transport of paeoniflorin by P-gp in the small intestine. This combination can be useful in the treatment of inflammation and arthritic	90mg/kg	Paeoniflorin
15	5’ methoxy hydnocarpin (5′-MHC)	Leaves of *Barberis fremontii* Torr., Family-Berberidaceae.	5′-MHC has no antimicrobial activity but it inhibits the MDR-dependent efflux of berberine from *S. aureus* cells and effectively disabled the bacterial resistance mechanism against the berberin antimicrobial action.	100 µg/ml	Berberin
16	Hydnocarpoic acid	Seeds of *Hydnocarpus wightiana* Family-Achariaceae.	It acts by blocking the synthesis and coenzymatic activity of biotin.	4 µg/ml	Biotin

17	Stevia	Leaves of *Stevia rebaudiana* Bertoni., Family-Asteraceae	Components of stevia called Stevioside and steviol stimulates insulin secretion via a direct action on beta cells. Due to the activity for reducing vascular tension it is used for patients with hypertension.	30 mg/kg	Antibiotics, antiobese drugs, antidiabetic , antifungal, antiviral, anticancer, cardiovascular, anti-inflammatory, antiarthritic agents, antituberculosis/ antileprosy , anthelmintic/respiratory , immune-modulators, antiulcer, and herbal products .
18	Capsaicin	Fruit of *Capsicum annum* Linn., Family- Solanaceae	The absorption of capsicum increases AUC of the drugs.		Theophylline
19	Cumin seeds	Dried seeds of *Cuminum cyminum* Linn., Family-Apiaceae	Possible mechanisms may be the Aqueous extract of cumin seeds stimulate β-adrenoceptors and/or inhibit histamine H1 receptors. It also worked in the opening of potassium channels and inhibition of calcium channels.	0.5 to 25 mg/kg	Erythromycin, Cephalexin, Amoxycillin, Fluconazole, Ketoconazole, Zidovudine and 5-Fluorouracil
20	Ammaniol	Methanolic extract of *Ammannia multiflora* Roxb., Family-Lythraceae	Ammaniol have the property to increase glucose uptake and shows potent antihyperglycemic activity.		Antimicrobial drugs like Nalidixic acid
21	Gallic acid	Gallic acid is a type of phenolic acid, found in gallnuts, tea leaves and oak bark etc.	Gallic acid increases net drug absorption and decrease drug biotransformation in the gut wall by inhibiting cytochrome P450 drug metabolism preference in other locations, such as the liver, which was the primary site of drug metabolism.		Acetanilides, Aminoquinolines,Benzodiazepines, benzofurans, cannabinoids, digitalis glycosides, ergot alkaloids, flavonoids, imidazoles, quinolines, macrolides, etc

S.No	Drug	Clinical model	Experimental assumption of action
1	Phenytoin Carbamazepine	Human subjects immuno assay	At a high dose, piperine diminishes the elimination or metabolism that result in higher amount available it helps in epilepsy rapidly at lower doses.
2	Pentobarbitone	Pentobarbitone induced hypnosis in rats	Significantly potentiate the sleeping time in compare with the control group due to inhibition of liver microsomal enzyme system.
3	Curcuminoids	rats and human subjects	Curcumin gets rapidly metabolised by liver and gut enzymes. Piperine increase the bioavaibility about 200% the effect is due to inhibition of hepatic and intestinal glucoronidation.
4	EGCG* (green tea)	In albino mice	This polyphenol showed chemopreventive activity animal models but with piperine activity of drug has increased by 1.3 times in compared to normal treated. mechanism works behind this concept is inhibition of glucuronidation and gastrointestinal transit time
5	Coenzyme	Double bind cross over	Supplementation of piperine with coenzyme for long time or at a high dose only can increase the bioavailability. It is assumed that piperine follows nonspecific thermogenic or bioenergetics propertics for augmentation
6	NimesulideDiclofenac sodium (peripheral)	In albino mice writhing induced by Acetic acid	Oral administration of Nimesulide/ Diclofenac can be done by supplementation of piperine because it inhibits the biotransformation and significantly increase the amount of drug in plasma. Co-administration can relieve the pain 1.5 times faster.
7	Pentazocine (central analgesic)	In albino mice tail flick method	Piperine combined with pentazocine showed significant increase in tail flick latency in comparison with pentazocinealone and control group follows same mechanism as with peripheral drugs
8	Fexofenadine	Human Caco2 cells line and male SD rats	Bioavailability can be increased up to 2- 3times than alone drug. This action of biopotentiation is due to inhibition of P-glycoprotein efflux pumps and delayed gastric emptying.

HERBAL LIPOSOMAL FORMULATION[1]

S.No	Formulation	Active ingredient	Application	Method of preparation	% entrapment efficiency	Route of administration
1	Quercetin liposome	Quercetin	Lower dose, improved dispersion in BBB	Reverse evaporation technique	60%	Intranasal
2	Liposome encapsulated silymarin	Silymarin	get better bioavailability	Reverse evaporation technique	69.22%	Buccal
3	Liposome Artemisia arboresens	Artemisia arboresens	Targeting of essential oils to cells	Film method and sonication	60-74%	*In-vitro*
4	Ampelopsin liposome	Ampelopsin	Increase efficiency	Film ultrasound method	62.90%	*In-vitro*
5	Paclitaxel liposome	Paclitaxel	Efficiency of high entrapment	Thin film hydration method	94%	*In vitro*
6	Curcumin liposome	Curcumin	Long circulation with high trap efficiency	Ethanol injection method	88.27%	*In-vitro*
7	Garlicin liposome	Garlicin	Increase efficiency	Reverse phase evaporation	90.77%	*In-vitro*

TRANSFEROSOMES[1]

S.No	Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration
1	Capsaicin transferosomes	Capsaicin	Increase skin penetration	Analgesic	150.6 nm	Topical
2	Colchicine transferosomes	Colchicine	Increase skin penetration	Antigout	-	*In-vitro*
3	Vincristine transferosomes	Vincristine	Increase entrapment efficiency and skin penetration	Anticancer	120 nm	*In-vitro*

MICROSPHERES[1]

S.No	Formulation	Active ingredient	Application	Biological activity	Method of preparation	Size in mm	Route of administration
1	Rutin-alginate chitosan microspheres	Rutin	Targeting into Cardiovascular and cerebrovascular system	Cardiovascular and cerebrovascular	Complex coacervation method	165-195	*In-vitro*
2	Zedoary oil microspheres	Zedoary	Sustained release and higher	Hepatoprotective	Quasi emulsion solvent	100-600	Oral

			bioavailability		diffusion method		
3	CPT loaded microspheres	Camptothecin	Prolonged release of camptothecin	Anticancer	Oil in water evaporation method	10	Intraperitoneal or intravenously
4	Quercetin microspheres	Quercetin	Significantly decreases the dose size	Anticancer	Solvent evaporation	6	*In-vitro*

NANOPARTICLES[1]

S.No	Formulation	Active ingredient	Application	Biological activity	Method of preparation	% entrapment efficiency	Route of administration
1	Triptolide nanoparticles	Triptolide	Enhance the penetration of drug	Antiinflammatory	Emulsification ultrasound	-	Topical
2	Nanoparticle of cascuta chinensis	Flavonoid and lignans	Improve water solubility	Hepatoprotective and antioxidant activity	Nano suspension method	90	Oral
3	Artemisinin nanocapsules	Arteminin	Sustained drug release	Anticancer	Selfassembly procedure	90-93	*In-vitro*
4	Radix salvia miltriorrhiza nanoparticles	Radix salivia	Better bioavailability	angina pectoris, Coronary heart diseases, myocardial infraction	Spray drying technique	96.68	*In-vitro*
5	Taxol loaded nanoparticles	Taxol	develop bioavailability and sustained drug release method	Anticancer	Emulsion solvent evaporative method	99.44	*In-vitro*
6	Berberine loaded nanoparticles	Berberine	Sustained Drug release	Anticancer	Ionic gelatin method	65.40	*In-vitro*

LIPID BASED HERBAL FORMULATION[1]

S.No	Formulation	Active ingredient	Application	Biological activity	Method of preparation	Dose	Route of administration
1	Ginkgo biloba lipid based systems	Flavonoids	Stabilizes ROS	Cardio protective and antioxidant activity	Phospholipidcomplexation	100mg	Subcutaneous

2	Silybin lipid based systems	Flavonoids	Inhibit lipid peroxidation	Hepatoprot-ective and antioxidant	Phospholipid complexation	120mg	Oral
3	Ginseng lipid Based systems	Flavonoids	Increases absorption	Nutraceutical immune modulator	Phospholipid complexation	150mg	Oral
4	Green tea lipid based systems	Ginsenoside	Increases absorption	Neutraceutical	Phospholipid complexation	50-100mg	Oral
5	Grape seed lipid based systems	Epigallocate chin	Increases absorption	Systemic antioxidant	Phospholipid complexation	50-100mg	Oral
6	Hawthorn lipid based systems	Procynidins	The blood TRAPn significantly elevated	Cardioprotective, antihypertensive	Phospholipid complexation	100mg	Oral
7	Quercetin lipid based systems	Flavonoids	Exerted better therapeutic efficacy	Antioxidant and Anticancer	Quercetin Phospholipid complexation	50-100mg	Oral

RECENT PATENTS ON HERBAL CONTROLLED RELEASE FORMULATIONS[1]

S.No	US patent number	Active ingredient	Novel system incorporate
1	US 5948414	Opioid analgesic and aloe	Nasal spray
2	US 6340478 B1	Ginsenosides	Microencapsulated and controlled release formulation
3	US 6890561 B1	Isoflavones	Microencapsulated formulation
4	US 6896898 B1	Alkaloids of aconitum species	Transdermal delivery system
5	US patent 2005/0142232	A Oleaginous oil of *Sesamum indicum* and alcoholic extract of Centella asiatica	Brain tonic
6	US patent 2007/0042062 A1	Glycine max containing 7s globulin protein extract, curcumin, Zingiber officinalis	Herbal tablet dosage form
7	US patent 2007/0077284	Opioids analgesics (phenanthrene gp)	Transdermal patch
8	US patent 7569236132	Flavonoids and terpenes	Microgranules

Classification based on their origin[4-15]

Plant Origin

Bioenhancers	**Biological source**
Piperine(black pepper)	*Piper longum (long pepper) and Piper nigrum (black pepper)*
Gingerol(Ginger)	*Zingiber officinale*
Glycyrrhizin (Liquorice)	*Glycyrrhiza glabra*
Caraway(cumin)	Carumcarvi
Black cumin	Cuminum cyminum
Quercetin	Citrus fruits
Niaziridin	Drumstick pods
Capsaicin	Capsicum annum
Stevia	Honey leaf
Allicin(garlic)	Allium sativum
Curcumin(Turmeric)	Curcuma longa

Animal Origin

Cow urine distillate=
Cow urine distillate is more effective as bioenhancer than cow urine. Its *Rasayana*' tatva is responsible for modification of the immune system and act as a bioenhancer

Capmul=
(mono-, di- and triglyceride) are prepared by the glycerolysis of select fats and oils and/or esterification of glycerin with specific fatty acids.

Classification based on mechanism of action[5]

Mechanism of Action	**Examples**
Solubilizers	Fulvic acid, Cyclodextrins, Gelucire etc
P-glycoprotein Inhibitors	Piperine, Sinomenine, Genistein
CYP3A4 Inhibitors	Naringin, Quercetin, Gallic acidesters Propyl gallate
BCRP (Breast Cancer Resistance Protein) Inhibitors	Camptothecin
Permeability enhancers	Essential oils obtained from cuminum cyminium, Carum carvi, Zingiber officinale etc
Miscellaneous	Lysergol, Cow urine distillate Nitrile glycoside Glycyrrhizin
Regulators of GIT function to facilitate better absorption	Niaziridin (drumstick pods), Glycyrrhizin (liquorice), Aloe vera (Aloe), *Zingiber officinale* (ginger).

CONCLUSION

The developing countries which are unable to bear health care cost like India, Pakistan, Nepal, Indonesia ,these bioenhancers are very useful because it reduce the amount of drug and amount is related to cost of drug. In new drug development strategies bioenhancers can play an important in respect of economy, most of the bioenhancers are from herbal sources which is easy to procure and easy to formulate. These are nontoxi, compatible with many drugs.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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