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Natural bioenhancers

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Abstract
Bioenhancers are such agents, which by themselves are not therapeutic entities but when combined with an active drug lead to the potentiation of the pharmacologic effect of the drug. Many synthetic and herbal drugs suffer from the problem of low bioavailability; low membrane permeability is the major cause, lower lipophilicity, ionic characteristics, poor water solubility or P-glycoprotein. This paper highlights the various bioenhancers and their mechanism that enhance bioavailability when use combinely with API. The herbal bioenhancers are easily available, safe, free from side effects, minimizes drug toxicity, shortens the duration of treatment, and lowers the drug resistance problems and minimizes the cost of treatment. Herbal bioenhancer are use for various categories of drug like neutraceuticals, antibiotics, antitubercular and anticancer and cardiovascular for immediate effects. Bioenhancers are recently used in many novel drug delivery formulations such as liposomes, transferosomes, ethosomes etc.
Researchers must be solve these issues of drug toxicity to deliver a safe and effective dose of drugs to attain desired pharmacological response.

Keywords: P-glycoprotein, prodrug, piperine, curcumin, ginger

Introduction
Medicinal plants are major components of all indigenous or alternative systems of medicines like Ayurveda, Homeopathy, Naturopathy, Siddha, Unani, etc.
Demand of herbal drug and natural plant based products is increase throughout the world due to nontoxic, no side effect, low cost and affordable available to poor [1, 2].
Many synthetic and herbal drugs suffer from the problem of low bioavailability. Low membrane permeability is the major cause, lower lipophilicity, ionic characteristics, poor water solubility or P-glycoprotein. Bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action [3]. Maximum bioavailability is attained by drugs administered via intravenous route, whereas drugs administered orally are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their bioavailability. Many natural compounds from medicinal plants have capacity to augment the bioavailability when co-administered with another drug [4].
"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].
Concept of biopotentiation was not so novel it has been so far used in old times by ayurvedic peoples so called as "*Yogvahi"* that meant to use herbs to increase or potentiates plasma concentration of drug. Piperine of black pepper was the first in this series as the major part of "*Yogvahi"*.
According to given in literature it is reveal that biopotentiator shows bioavailability enhancement if administered at lower dose with active ingredient and it do not introduce its own therapeutic action with the actual active principle at the therapeutic dose used. Piperine, naringin, quercetin, glycyrrhizin, genistein, sinomenine, nitrile glycoside and cow urine distillate have capability to augment and enhance the bioavailability. A augmentation of bioefficacy reduces dose, toxicity and adverse effects so in return shorten the time and cost of treatment. These concept covers drug categories like antibiotics, antitubercular and anticancer and cardiovascular which are so potent in nature and require quite immediate effects.
Bioenhancers are recently used in many novel drug delivery formulations such as liposomes, transferosomes, ethosomes etc [4].

Ideal properties of the bioenhancers
The contribution of bioenhancers have been reviewed which states that the ideal bioenhancers [5].
1. Should be nontoxic, non-allergenic and non-irritating.
2. Should not produce own pharmacological effects.
3. Should be rapid-acting with predictable and reproducible activity.
4. Should be unidirectional in action.
5. Should be compatible with other active pharmaceutical ingredients.
6. Should be stable with time and environment.

7. Should be easily formulated into a various dosage form.
8. Should be easily available and cost effective.

Concept of bioavailability enhancers

The concept of bioavailability enhancer is derived from traditional old age Ayurveda black pepper, long pepper and ginger are collectively called as *Trikatu*. In Sanskrit *Trikatu* means *Three acrids*. The action of bioavailability enhancer was first discovered by Bose in 1929 who described the action of long pepper to adhatoda vasaka leaves which increased activity of vasaka [6].

The term bioavailability enhancer was first coined by Indian scientist at Regional Research lab. Jammu, who discovered and named piperine as world's first bioavailability enhancer in 1979 [6].

It offers comfortable, convenient, and noninvasive way to administer drugs due to following advantages of it.

1. Dose reduction
2. Minimization of drug resistance.
3. Minimization of drug (especially true in case of anticancer drug like taxol).
4. Ecological benefit.
5. Safety of the environment [5].

Drug absorption barriers

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 and exert its biological actions. There are many anatomical and biological barriers for the oral drug delivery system to penetrate the epithelial membrane [7, 8]. 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 due its hydrophilic nature is potential barrier to the absorption of drugs. The membranes around cells are lipid bilayers containing proteins such as receptors and carrier molecules. Drugs cross the lipid membrane by passive diffusion or carrier-mediated transport which involves the spending of energy. For the passage of small water-soluble molecules such as ethanol there are aqueous channels within the proteins. The drug molecules larger than about 0.4 nm face difficulty in passing through these aqueous channels [8].

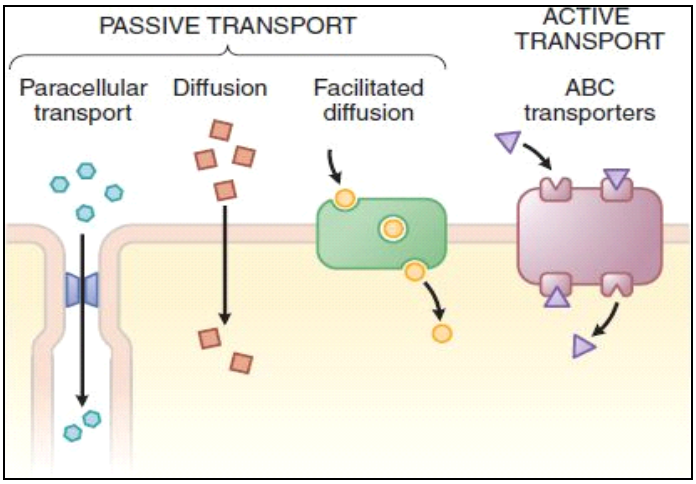

Fig 1: Drug Absorption Barrier

Recent work has shown that drug efflux pumps like Pgp possess very important role inhibiting efficient drug entry into the systemic circulation [9]. P-gp is a type of ATPase and an energy dependent trans membrane drug efflux pump it belongs to members of ABC transporters. It has a molecular weight of -170 kDa and has 1280 amino acid residues [10]. Since P-gp is gaining importance in absorption enhancement much work has still been made about its modulation due to its substrate selectivity and distribution at the site of drug absorption.

Methods used to enhance absorption of orally administered drugs

There have been many approaches in use to enhance the intestinal absorption of poorly absorbed drugs. These approaches are as follows.

1. Absorption Enhancers

Many of the absorption enhancers are effective in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers [11, 12]. Chitosan, particularly trimethylated chitosan, increases the drug absorption via paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions. Bile, bile salts and fatty acids are surfactants which act as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelators such as EGTA and EDTA enhances absorption by reducing the extracellular calcium concentration, leading to the disruption of cell-cell contacts [13].

2. Prodrugs

To enhance the drug absorption and bioavailability chemical modification of drugs to produce prodrugs and more permeable analogues has been widely studied as a useful approach. Various ampicillin derivatives are one of the well-known examples of increasing the lipophilicity of agents to enhance absorption of a polar drug by prodrug strategy [14]. Ampicillin due to its hydrophilic nature is only 30 - 40% absorbed from the gastrointestinal tract. By esterification of carboxyl group of ampicillin the prodrugs of ampicillin such as pivampicilline, bacampicilln and talampicillin were synthesized these prodrugs were more lipophilic than the parent compound following oral administration and they showed higher bioavailability in comparison with ampicillin.

3. Dosage Form and Other Pharmaceutical Approaches

Utilization of permeability-enhancing dosage forms is one of the most practical approaches to improve the intestinal absorption of poorly absorbed drugs. Various dosage formulations such as liposomes [15] and emulsions [16] enhanced the intestinal absorption of insoluble drugs. Particle size reduction such as micronization, nanoparticular carriers, complexation and liquid crystalline phases also maximize drug absorption [17, 18].

4. P-glycoprotein Inhibitors

The application of P-gp inhibitors in improving peroral drug delivery has gained special interest. Several studies to enhance

oral bioavailability have demonstrated the possible use of P-gp inhibitors that reverse P-gp-mediated efflux in an attempt to improve the efficiency of drug transport across the epithelia. P-gp inhibitors influences metabolism, absorption, distribution, and elimination of P-gp substrates in the process of modulating pharmacokinetics [19].

Mechanisms of action of herbal bioenhancers

Different herbal bioenhancers may have same or different mechanism of action. Nutritional bioenhancers enhance absorption by acting on gastrointestinal tract. Antimicrobial bioenhancers mostly act on drug metabolism process.

- Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply,
- Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility,
- Modifications in GIT epithelial cell membrane permeability,
- Cholagogous effect,
- Bioenergetics and thermogenic properties
- Suppression of first pass metabolism and inhibition of drug metabolizing enzymes and acids [20].

Classification of Bioenhancers [4].

Classification of bioenhancer according to source

Plant origin

- Niaziridin, Cuminumcyminum, Carumcarvi, Stevia, Lysergol, Glycerrhizin, Ginger, Allicin, Aloe vera, Simomenine, genistein, 5-methoxy hydnocarpin etc.

Animal origin

- Cow urine distillate.

Classification of bioenhancers based on mechanism of Action [20].

- Inhibition of p-gp efflux pump and other efflux pump: Example: Carumcarvi (Caraway), Genistein, Cuminumcyminum, Naring in etc.
- Suppressors of CYP-450 enzyme and its isoenzyme: Example: Narigin, Gallic acid and its esters etc.
- Regulators of GIT function to facillated better absorption: Examples: Aloevera (aloe), niaziridin(drumstick pods), zingiberofficinale (ginger) etc.

Bioenhancers from herbal sources

Table 1: Herbs, its source, mechanism and their dose as bioenhances [5, 21-35].

Sr. 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	It inhibits the p-glycoprotein efflux pump and metabolizing enzyme, CYP 3A4 in the intestinal mucosa and restraint the	-	Diltiazem, Digoxin, Epigallocate-chin gallate

		grapes, raspberries, and cranberries), green leafy vegetables and black and green tea	metabolizing enzyme CYP3A4		
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 decreased the absorption rate of zinc while black tea	-	Both teas promote the absorption of manganese and copper as nutrients in the blood circulation.
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 drugs, antifungal drugs, antiviral drugs, anticancer drugs, cardiovascular drugs, anti-inflammatory, antiarthritic agents, antituberculosis/ antileprosy drugs, anthelmintic/respiratory drugs, immune-modulators, antiulcer drugs, and herbal products or drugs.
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	Possible mechanisms may be the Aqueous	0.5 to 25	Erythromycin, Cephalexin, Amoxycillin,

		Cuminum cyminum Linn., Family- Apiaceae	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.	mg/kg	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, naphthalenes, opiates, oxazoles, phenylalkylamines, piperidines, polycyclic aromatic hydrocarbons, pyrrolidines, pyrrolidinones, stilbenes, sulfonylureas, sulfones, triazoles, tropanes and vinca alkaloids.

Medicinal Plants as Bioenhancers
Piperine

Fig 2: *Piper nirgum*

Fig 3: *Piper longum*

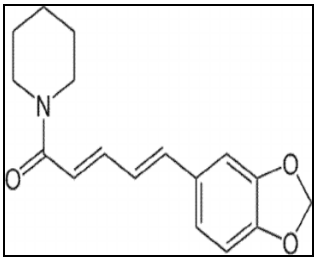

Fig 4: Structure of Piperin

Piperine is primitive alkaloid which is mile stone for the field of biopotentiation. Chemically it is 1-piperoyl piperidine. It is obtained from *Piper nigrum*or *Piper longum*whether from stem, pods or leaf part. Piperine is generally regarded as safe (GRAS) by FDA authority. Activity of piperin is due to the conjugated double bonds in side chain part. Normal dose of piperine is approximately 15-20 mg/kg for a in a day

Metabolic enzymes [36, 37]:
Piperine interacts and interferes both *in vitro* and *in vivo* with the metabolism and degradation related enzymes Studies have proved it as a nonspecific inhibitor of drug metabolism. Piperine inhibited number of enzymes in a series mainly related to P-gp and cytochrome P 450 family.

It includes othersalso like

- Aryl hydrocarbon hydroxylase (Microsomal enzyme system)
- Ethyl morphine-N demethylatse
- 7-Ethoxycoumarin-O-de-ethylase
- Uridine di phosphate glucose dehydrogenase
- Uridine di phosphate glucose dehydrogenase (UDP-GD)
- Uridine di phosphate glucuronyltransferase (UDP-GT)
- 5-Lipoxegenase (5-LOX)
- Cyclo-oxegenase-I (COX-I)

Antitubercular and Antileprotic drugs
The bioenhancing property of piperine was first utilized in the treatment of tuberculosis in human.Rifampin or Rifampicin is the drug of first line treatment in tuberculosis and leprosy. Piperin is so much useful for lowering the dose profile and shortening the treatment. Piperine was found to increase the bioavailability of rifampicin by about 60% and hence reduce the dose from 450 to 200mgRifampin acts on RNA polymerase and inhibits the transcription of the polymerase in human cells which is actually being catalyzed by *Mycobacteriumsmegmatis*. Piperine augments this activity of rifampin by several folds against RNA polymerase Piperine also stimulates the binding ability of rifampin to RNA polymerase even in resistant strains [38, 39].

Antibiotics
The consumption of antibiotics and antimicrobials are increasing at very high rate that has cause most of immune system resistance or addicted for them. Patients have to take high dose of such drugs due to reduction in GIT absorption, uptake by pathogens and cells has decreased due to resisting efflux pumps. The major portion of the target dose remains as garbage in body fluids having no therapeutic use but causing drug resistance with time. Flouroquinolones and piperine in rabbits has shown augmented bioavailability due to piperin inhibits the P-glycoprotein efflux pump [40].

Chemoprevention and Immunomodulatory
Piperine reduces the aflatoxins that are responsible for several cytotoxic effects by inhibiting CYP-P450-mediated biological activation of mycotoxins into harmful ones [41]. It inhibits the lipid peroxidation phenomena so it modifies the oxidative changes in cells that results in free radicals scavenging activity

[42]. It causes reduction in damage of DNA and DNA proteins. The antiapoptoticproperty of piperin is attributed induction of Heme-oxygenase-1. It contains pentacyclicoxindole group in it which is responsible for all these activities [43].

Nutraceuticals

It also acts as a nutritional bioenhancer which enhances bioavailability and absorption ofnutrients by acting on gastrointestinal tract [Table 2]. In a double blind cross over studies it has been revealed that herbal supplementation can increase the concentration of vitamins against placebo by 50-60%. Study suggests augmentation is due to the nonspecific mechanism &thermogenic properties of piperine [44, 45].

Piperine also showed enhanced bioavailability when combined with Nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase which is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Piperine also increases the bioavailability of curcumin, the active principle of Curcuma longa (turmeric).

Table 2

Drug	Clinical model	Experimental assumption of action
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.
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.
Curcuminoids	rats and human subjects	Curcumin gets rapidlymetabolised by liver and gut enzymes.piperine increase the bioavaibility about 200% the effect is due to inhibition of hepatic and intestinal glucoronidation.
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 noramltreated. mechanism works behind this concept is inhibition of glucuronidation and gastrointestinal transit time
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
Nimesulide Diclofenac 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. Coadministration can relieve the pain 1.5 times faster.
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
Fexofenadine	Human Caco2 cells line & 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.

Turmeric

Fig 5: Turmeric

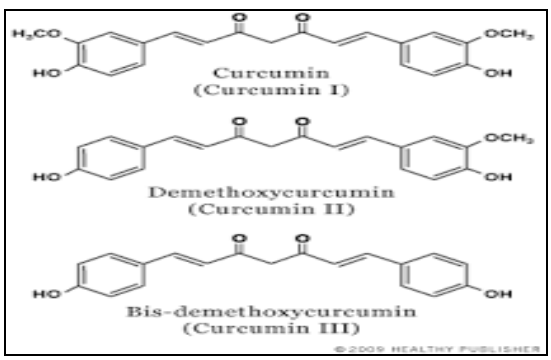

Fig 6: Curcuminoids

Biological source

It consist of dried as well as fresh rhizomes of plant known as *Curcuma Longa*, Family-Zingiberaceae.

Turmeric (*Curcuma longa*) is a common household item used as remedy for various ailments. Curcumin, a flavonoid from turmeric suppresses drug metabolizing enzymes like CYP3A4 in liver and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of celiprolol and midazolam in rats. The bioenhancer nature of curcumin is similar to piperine**.** Curcumin suppresses UDP-glucuronyltransferase level in intestine and hepatic tissues. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs.

Cow Urine

Cow urine is very effective as a biopotentiers but its distillated form is more used than normal urine. It increases the bioefficacy of antimicrobial, antifungal, and anticancer agents [46]. Cow urine has antitoxic activity itself and if used as augmenting agent with zinc against the cadmium chloride toxicity, it shows miraculous effects. In an experimental study mice treated with cadmium showed zero fertility. But on the other side when a group is treated with cadmium (Anti fertility agent), zinc (Core drug) and cow urine distillate (Biopotentier) showed high fertility index. This indicates that it can be used

as a bioenhancer of zinc incadmium fertility toxicity [47]. It also increases the activity of Rifampicin against *Escherichia coli* and gram-positive bacteria. Mechanism of action of bioenhancing is increased transport across the GIT membrane. The enhancement in transport is approximately 2–7 times. Cow urine distillate enhances both the release an activity gonadotropin releasing hormone (GRH) ultimately increase sperm motility, sperm count, and sperm morphology in male mice [48].

Recent advances of bioenhancers [49]:

Table 3: Herbal NDDS formulations

Formulation	Active ingredient	Application	Biological activity	Method of preparation	% Entrapment effeciency / size	Route of administration	Ref
Quercetin Liposome	Quercetin	Reduced dose, enhanced penetration in blood brain barrier	Anti-oxidant Anti-cancer	Reverse evaporation technique	60%	Intranasal	50
Liposome encapsulated Silymarin	Silymarin	Improve bioavailability	Hepatoprotective	Reverse evaporation technique	69.2 +-0.6%	Buccal	51
Rutin-alginate chitosan microspheres	Rutin	Targetting into cardiovascular and cerebrovascular system	Cardio-vascular and cerebro-vascular	Complex coecervation method	165-195(Size in μm)	In-vitro	52
Zedoary oil Microspheres	Zedoary	Sustained release and higher bioavailability	Hepato-protective	Quasi emulsion solvent diffusion method	100-600 (Size in μm)	Oral	53
Triptolide Nanoparticles	Triptolide	Enhance the penetration of drug through stratum corneum by increased hydration	Anti-inflammatory	Emulsification ultrasound		Topical	54
Radix salvia miltiorrhiza nanoparticles	Radix salvia	Improve the bio-availability	Coronary heart diseases, angina pectoris and myocardial infraction	Spray drying technique	96.68%	In-vitro	55
Capsaicin Transferosomes	Capsaicin	Increase skin penetration	Analgesic	-	150.6 nm (Droplet size)	Topical	56
Colchicine Transferosomes	Colchicine	Increase skin penetration	Antigout	-	-	In-vitro	57
Ginseng lipid based systems	Flavonoids	Increases absorption	Nutra-ceutcal immune modulator	Phospholipid complexation	50-100 Mg (Dose)	Oral	58
Greentea lipid based systems	Ginsenoside	Increases absorption	Nutra-ceutcal, systemic antioxidant and anticancer	Phospholipid Complexation	50-100 Mg (Dose)	Oral	58

Table 4: Recent patents on herbal controlled release formulations [59].

US patent No.	Active ingredients	Novel system incorporate
US 5948414	Opioid analgesic and aloe	Nasal spray
US 6340478 B1	Ginsenosides	Microencapsulated and controlled release formulations
Us6890561 B1	Isoflavones	Microencapsulated formulation
US6896898 B1	Alkaloids of aconitum species	Transdermal delivery system
US patent 2005/0142232 A	Oleaginous oil of Sesamum indicum and alcoholic extract of Centella asiatica	Brain tonic
US patent 2007/0042062 A1	Glycine max containing 7s globulin proteinextract,curcumin, Zingiber officinalis	Herbal tablet dosage form
US patent 2007/0077284A1	Opioid analgesic (phenanthrene gp)	Transdermal patch
US patent 7569236132	Flavonoids (such as quercetin) and terpenes	Microgranules

Conclusion

In developing countries like India cost of treatment is the major concern for modern medicines. Systematic innovative means are needed to reduce these costs. New chemical substances with new modes of action are what modern pharmaceutical research is all about. New drug development technologies are concerned about the economics of drug development. Drug discovery process has been highly aided by Ayurveda through reverse pharmacology with new means of identifying active compounds and reduction of drug development cost. The researchers are now aimed at methods of reduction of drug dosage and thus drug treatment cost making treatment available to a wider section of the society including the financially

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