Current Trends on Natural Bioenhancers: A Review

Chavhan SA*, Shinde SA and Gupta HN
Dr. Rajendra Gode College of Pharmacy, India

*Corresponding author: Chavhan SA, Dr. Rajendra Gode College of Pharmacy, Malkapur Dist- Buldana (MS) – 443101, India, Tel: 9890321493; E-mail: sarinchavhan21@gmail.com

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. When any drug molecules are being introduced in every year but many of these molecules have problems like their solubility, stability, bioavailability and its long lasting side effects. Low bioavailability is one of the serious but curable problems in case of the drug molecule. There are some other factors also which responsible for low bioavailability i.e. low lipophilicity and zwitterionic character at physiological pH, poor water solubility or efflux by P-glycoprotein (P-gp) etc. The object of this review is to explore the concept of bioavailability to achieve better therapeutic response in appropriate dose using natural drugs and natural products like ginger, caraway, aloe, quercetin, glycyrrhizin, piperine, curcumin etc. The use of natural products is the most reliable means for bioavailability enhancement because these are safe, non-toxic, economical, easily procured, non-addictive, pharmacologically inert and non-allergenic in nature etc. Herbal bioenhancer are use for various categories of drug like nutraceuticals, 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. This review explores the natural drugs from plant and animal sources with their mechanism, in-vivo study, marketed formulation and its future prospective. Researchers must 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 Biopotentiors 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, transfersomes, ethosomes etc [4].

**Ideal Properties of the Bioenhancers**

The contribution of bioenhancers have been reviewed which states that the ideal bioenhancers [5].

a) Should be nontoxic, non-allergenic and non-irritating.

b) Should not produce own pharmacological effects.

c) Should be rapid-acting with predictable and reproducible activity.

d) Should be unidirectional in action.

e) Should be compatible with other active pharmaceutical ingredients.

f) Should be stable with time and environment.

g) Should be easily formulated into a various dosage form.

h) 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.

a) Dose reduction

b) Minimization of drug resistance.

c) Minimization of drug (especially true in case of anticancer drug like taxol).

d) Ecological benefit.

e) 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].
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 transmembrane 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 use 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:

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].

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, bacampicillin 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.

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, nanoparticulate carriers, complexation and liquid crystalline phases also maximize drug absorption [17,18].

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 influence 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.

a) Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply.

b) Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility.

c) Modifications in GIT epithelial cell membrane permeability.

d) Cholagogous effect.

e) Bioenergetics and thermogenic properties.

f) 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, Glycrrhizin, Ginger, Allicin, Aloe vera, Simomenine, genistein, 5-methoxy hydnocarpin etc.

**Animal origin:** Cow urine distillate.

---

**Bioenhancers from Herbal Sources**

| 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      | Glycyrrhiza | Dried root and stolon of *Glycyrrhiza glabra* Linn, Family- Leguminosa. | 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 |
| No. | Natural Bioenhancers | Description | Effects |
|-----|---------------------|-------------|---------|
| 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. |
| 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 restrain the metabolizing enzyme CYP3A4 Diltiazem, Digoxin, Epigallocatechin 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 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 a isoflavone found in a number of dietary plants like soybean (*Glycine max* Linn.) and kudzu (*Pueraria lobata* Wild.) | 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 | Sinomenin | 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'-methoxyhydnocarpin (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 | Hydnocarpic 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 | - |
| 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 anti hyperglycemic activity. | - | - |
| 21 | Gallic acid | Gallic acid is a type of phenolic acid, found in gallnuts, tea leaves and | Gallic acid increases net drug absorption and decrease drug biotransformation in the gut wall | - | Acetanilides, Aminoquinolines, Benzodiazepines, benzofurans, cannabinoids, digitalis |
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.

**Medicinal Plants as Bioenhancers**

**Piperine**

| Herbs | Source | Mechanism | Dose |
|-------|--------|-----------|------|
| oak bark etc. | by inhibiting cytochrome P450 drug metabolism preference in other locations, such as the liver, which was the primary site of drug metabolism. | glycosides, ergot alkaloids, flavonoids, imidazoles, quinolines, macrolides, naphthalenes, opiates, oxazoles, phenylalkylamines, piperidines, polycyclic aromatic hydrocarbons, pyrroolidines, pyrroolidinones, stilbenes, sulfonylureas, sulfones, triazoles tropanes and vinca alkaloids. |

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 [36,37].

It includes others also like:

- a) Aryl hydrocarbon hydroxylase (Microsomal enzyme system)
- b) Ethyl morphine-N demethylatse
- c) 7-Ethoxycoumarin-O-de-ethylase
- d) Uridine di phosphate glucose dehydrogenase
- e) Uridine di phosphate glucose dehydrogenase (UDP-GD)
- f) Uridine di phosphate glucuronyltransferase (UDP-GT)
- g) 5-Lipoxegenase (5-LOX)
- h) 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 *Mycobacterium smegmatis*. 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. Fluoroquinolones 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 antiapoptotic property 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 of nutrients 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.

| 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 rapidly metabolised by liver and gut enzymes. Piperine increase the bioavailability about 200% the effect is due to inhibition of hepatic and intestinal glucuronidation. |
| 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 |
| 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 properties for augmentation |
| NimesulideDidofenac 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.

| Drug                        | Methodology                                      | Description                                                                                     |
|-----------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Pentazocine ( central analgesic) | In albino mice tail flick method                  | Piperine combined with pentazocine showed significant increase in tail flick latency in comparison with pentazocine alone and control group follows same mechanism as with peripheral drugs |
| Fexofenadine                | Human Caco2 cells line & male SD rats            | Bioavailability can be increased up to 2-3 times than alone drug. This action of biopotentiation is due to inhibition of P-glycoprotein efflux pumps and delayed gastric emptying. |

Table 2: Piperine also increases the bioavailability of curcumin, the active principle of Curcuma longa (tumeric).

**Turmeric:**

Figure 5: Turmeric.

Figure 6: Curcuminoids.

**Biological source**

It consists 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 a 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-glucuronyl transferase 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 distilled 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 in cadmium 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 and activity gonadotropin releasing hormone (GRH) ultimately increase sperm motility, sperm count, and sperm morphology in male mice [48].
Recent Advances of Bioenhancers [49]

| Formulation                        | Active ingredient | Application                                      | Biological activity                              | Method of preparation                  | % entrapment efficiency / 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 bioavailability                      | Coronary heart diseases, angina pectoris and myocardial infraction | Spray drying technique                | 96.68%                       | In-vitro                 | [55]      |
| Capsaicin Transfersomes           | Capsaicin         | Increase skin penetration                        | Analgesic                                      | -                                      | 150.6 nm (Droplet size)      | Topical                  | [56]      |
| Colchicine Transfersomes          | Colchicine        | Increase skin penetration                        | Antigout                                        | -                                      | -                            | In-vitro                 | [57]      |
| Ginseng lipid based systems       | Flavonoids        | Increases absorption                             | Nutra-aceutical immune modulator                | Phospholipid complexation              | 50-100 Mg (Dose)             | Oral                     | [58]      |
| Green tea lipid based systems     | Ginsenoside       | Increases absorption                             | Nutra-aceutical, systemic antioxidant and anticancer | Phospholipid Complexation             | 50-100 Mg (Dose)             | Oral                     | [58]      |

Table 3: Herbal NDDS formulations.

| 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 protein extract, 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                          |

Table 4: Recent Patents on Herbal Controlled Release Formulations [59].


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 challenged. This review will be helpful to scientists engaged in research related to bioenhancers of herbal and non-herbal origins.

References

1. Kalia A N (2006) Textbook of Industrial Pharmacognosy, 1st (Edn.), CBS publishers, pp: 1-3.
2. Jhanwar B, Gupta S (2014) Biopotentiating using Herbs: Novel Technique for Poor Bioavailable Drugs. Int J Pharm Tech Res 6(2): 443-454.
3. Brahmankar DB, Jaiswal S (1995) Biopharmaceutics and Pharmacokinetics: A Treatise. 1st (Edn.) Vallabh Prakashan pp: 24-26.
4. Gopal V, Prakash Yoganandam G, Velvizhi Thilagam T (2016) Bio-enhancer: A Pharmacognostic Perspective. European Journal of Molecular Biology and Biochemistry 3(1): 33-38.
5. Garima Jain, Umesh K Patil (2015) Strategies for enhancement of bioavailability of medicinal agents with natural products. IJPSSR 6(12): 5315-5324.
6. Gupta Rajiv, Kesarwani Kritika (2013) Bioavailability enhancers of herbal origin: An overview. Asian Pac J Trop Biomed 3(4): 253-266.
7. Hayton WL (1989) J Pharmacokinet Pharmacodyn 8: 1573-8744.
8. Kang MJ, Cho JY, Shim BH, Kim DK, Lee J (2009) Bioavailability enhancing activities of natural compounds from medicinal plants J Med Plants Res 3(13): 1204-1211.
9. Schinkel AH, Jonker JW (2003) Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. Adv Drug Deliv Rev 55(1): 3-29.
10. Juliano RL, Ling L (1976) A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. Biochim Biophys Acta 455(1): 152-162.
11. Lundin S, Artursson P (1990) Absorption of a vasopressin analog, 1-deamino-8-D-argininevasopressin (dDAVP), in a human intestinal epithelial cell line, CaCO2. Int J Pharm 64: 181-186.
12. Aungst BJ, Blake JA, Hussain MA (1991) An in vitro evaluation of metabolism and poor membrane permeation impeding intestinal absorption of leucine enkephalin, and methods to increase absorption. J Pharmocol Exp Ther 259(1): 139-145.
13. Schipper NGM, Olsson S, Hoogstraate JA, de Boer AG, Varum KM, Artursson P (1997) Chitosans as absorption enhancers for poorly absorbable drugs 2: mechanism of absorption enhancement. Pharm Res 14(7): 923-929.
14. Buur A, Bundgaard H, Falch E (1986) Prodrugs of 5-Fluourouracil. VII. Hydrolysis Kinetics and Physicochemical Properties of N-Ethoxy- and N-Phenoxy carbonyloxy methyl Derivatives of 5-Fluourouracil. Acta Pharm Suec 23(4): 205-216.
15. Patel HM, Ryman BE (1976) Oral Administration of Insulin By Encapsulation Within Liposomes. FEBS Lett 62(1): 60-63.
16. Engel RH, Riggi SJ, Fahrenbach MJ (1968) Insulin: Intestinal Absorption as Water-in-Oil-in-Water Emulsions. Nature 219: 856-857.
17. Liversidge GG, Cundy KC (1995) Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm 125: 91-97.
18. Veiga F, Fernandes C, Teixeira F (2000) Oral bioavailability and hypoglycaemic activity of tolbutamide/cyclodextrin inclusion complexes. Int J Pharm 202(1-2): 165-171.
19. Varma MV, Ashokraj Y, Dey CS, Panchagnula R (2003) P-glycoprotein inhibitors and their screening: a perspective from bioavailability enhancement. Pharmacol Res 48(4): 347-359.
20. Tatiraju DV, Bagade VB, Kambhelkar PJ, Jadhav VM, Kadam V (2013) Natural Bioenhancers: An overview. Journal of Pharmacognosy and Phytochemistry 2(3): 55-60.

21. Qazi GN, Bedi KL, Rakesh KJ, Tikoo MK, Tikoo AK, et al. (2009) Bioavailability/Bioefficacy enhancing activity of Cumin cuminum and extracts and fractions thereof. U.S. Patent US 7514105.

22. Bedi K, Gupta BD, Rakesh KJ, Khan IA, Qazi GN, et al. (2006) Use of herbal agents for potentiation of bioefficacy of anti infectives. U.S. patent US 7119075 B1.

23. SPS. Khanuja, S Kumar, JS Arya, AK Shasany, M Singh, et al. (2000) Composition comprising pharmaceutical/nutraceutical agent and a bioenhancer obtained from Glycyrrhiza glabra. United States Patent, Number 6979471 B1.

24. Imai T, Sakai AM, Ohtake H, Azuma H, Otagiri M (2005) Absorption-enhancing effect of glycyrrhizin induced in the presence of capric acid. Int J Pharm 294(1-2): 11-21.

25. Qazi GN, Tikoo L, Gupta AK, Ganju K, Gupta DK, et al. (2002) Bioavailability enhancing activity of Zingiber officinale and its extracts/fractions thereof. European patent EP 1465646.

26. A Ogita, K Fujita, M Taniguchi, T Tanaka (2006) Enhancement of the Fungicidal Activity of Amphotericin B by Allicin, an Allyl-Sulfur Compound from Garlic, against the Yeast Saccharomyces cerevisae as a Model System. Planta Med 72(13): 1247-1250.

27. Nijveldt RJ, Nood EV, van Hoorn DEC, Boelens PG, Norren K, et al. (2001) Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr 74(4): 418-425.

28. Choi JS, Li X (2005) Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. International Journal of Pharmaceutics 297(1-2): 1-8.

29. Wang P, Heber D, Henning SM, (2012) Quercetin increased bioavailability and decreased methylation of green tea polyphenols in vitro and in vivo. Food Funct 3(6): 635-642.

30. JA Vinson, H Al Kherrat, L Andreoli (2005) Effect of Aloe vera preparations on the human bioavailability of vitamins C and E. Phytoned 12(10): 760-765.

31. SPS Khanuja, JS Arya, T Ranganathan, S Kumar, D Saikia, et al. (2003) Nitrile glycoside useful as a bioenhancer of drugs and nutrients, process of its isolation from moringa oleifera. United States Patent, Number 6858588 B2.

32. Kurzer M, Xu X (2003) Dietary phytoestrogens. Annu Review on Nutr 17: 353-381.

33. Sparreboom A, van Asperen J, Mayer U, Schinkel AH, Smit JW, et al. (1997) Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. Proceedings of National Academic Sciences. 94(5): 2031-2035.

34. Cheng SS, Fu SX, Li YS, Wang NC (1964) The pharmacology of Sabianine A, the analgesic and antiphlogistic actions and acute toxicity. Acta Pharmacologica Sinica 4: 177-180.

35. Liu ZQ, Zhou H, Liu L, Jiang ZH, Wong YF, et al. (2005) Influence of co-administered sinomenine on pharmacokinetic fate of paoniflorin in unrestrained conscious rats. J Ethnopharmacol 99(1): 61-67.

36. Bhardwaj RK, Glaser H, Becquemont L, Klotz U, Gupta SK, et al. (2002) Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther 302(2): 645-650.

37. Atal CK, Dubey RK, Singh J (1985) Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. J Pharmacol Exp Ther 232(1): 258-262.

38. Balakrishnan V, Varma S, Chatterji D (2001) Piperine augments transcription inhibitory activity of rifampicin by several fold in Mycobacterium smegmatis. Current Science 80(10): 1302-1305.

39. Kapil RS, Zutshi U, Bedi KL (1995) Process of preparation of pharmaceutical composition with enhanced activity for treatment of tuberculosis and leprosy. United States Patent Number, US005439891 A.

40. Khan IA, Mirza ZM, Kumar A, Verma V, Qazi GN (2006) Piperine, a phytochemical potentiator of ciprofloxacin against Staphylococcus aureus. Antimicrob Agents Chemother 50(2): 810-812.
41. Reen RK, Wiebel FJ, Singh J (1997) Piperine inhibits aflatoxin B1-induced cytotoxicity and genotoxicity in V79 Chinese hamster cells genetically engineered to express rat cytochrome P450B1. J Ethnopharmacol 58(3): 165-173.

42. Selvendiran K, Singh JP, Krishnan KB, Sakthisekaran D (2003) Cytoprotective effect of piperine against benzo[a]pyrene induced lung cancer with reference to lipid peroxidation and antioxidant system in albino mice. Fitoterapia 74(1-2): 109-115.

43. Choi BM, Kim SM, Park TK, Li G, Hong SJ, et al. (2007) Piperine protects cisplatin-induced apoptosis via heme oxygenase-1 induction in auditory cells. J Nutr Biochem 18(9): 615-622.

44. Majeed M, Badmaev V, Rajendran R (1996) Use of piperine to increase bioavailability of nutritional compounds. United States Patent Number, US005536506 A.

45. Badmaev V, Majeed M, Norkus EP (1999) Piperine, an alkaloid derived from black pepper increases serum response of beta-carotene during 14-days of oral beta-carotene supplementation. Nutrition Research 19(3): 381-388.

46. Kekuda TRP, Nishanth BC, Kumar SVP, Kamal D, Sandeep M, et al. (2010) Cow urine concentrate: a potent agent with antimicrobial and anthelmintic activity. Journal of Pharmacy Research 3: 1025-1027.

47. Khan A, Srivastava VK (2005) Antitoxic and bioenhancing role of kamdenu ark (cow urine distillate) on fertility rate of male mice (Mus musculus) affected by cadmium chloride toxicity. International Journal of Cow Science 1(2): 43-46.

48. Ganaie JA, Shrivastava VK (2010) Effects of gonadotropin releasing hormone conjugate immunization and bioenhancing role of Kamdenu ark on estrous cycle, serum estradiol and progesterone levels in female Mus musculus. Iranian Journal of Reproductive Medicine 8(2): 70-75.

49. Kesarwani Kritika, Gupta Rajiv (2013) Bioavailability enhancers of herbal origin: An overview. Asian Pac J Trop Biomed 3(4): 253-266.

50. Ajazuddin, Saraf S (2008) Applications of novel drug delivery system for herbal formulations. Nanomed Nanotechnol Biol Med 4: 70-78.

51. Samaligy MS, Afifi NN, Mahmoud EA (2006) Evaluation of hybrid liposomes-encapsulated silymarin regarding physical stability and in vivo performance. Int J Pharm 319(1-2): 121-129.

52. Xiao L, Zhang YH, Xu JC, Jin XH (2008) Preparation of floating rutinalginate- chitosan microcapsule. Chine Trad Herb Drugs 2: 209-212.

53. You J, Cui F, Han X, Wang Y, Yang L, et al. (2006) Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil. Colloids Surf B 48(1): 35-41.

54. Mei Z, Chen H, Weng T, Yang Y, Yang X (2003) Solid lipid nanoparticle and microemulsion for topical triptolide. Eur J Pharm Biop Harm 56(2): 189-196.

55. Su YL, Fu ZY, Zhang JY, Wang WM, Wang H, et al. (2008) Microencapsulation of Radix salvia miltiorrhiza nanoparticles by spray-drying. Powder Technol 184: 114-121.

56. Xia YL, Luo JB, Yan ZH, Rong HS, Huang WM (2006) Preparation and invitro and invivo evaluations of topically applied capsaicin transferosomes. Yao Xue Xue Bao 41(5): 461-466.

57. Singh HP, Utreja P, Tiwary AK, Jain S (2009) Elastic liposomal formulation for sustained delivery of colchicine: in vitro characterization and in vivo evaluation of anti-gout activity. AAPSJ 11(1): 54-64.

58. Bhattacharya S, Ghosh A (2009) Phytosomes: the emerging technology for enhancement of bioavailability of botanicals and nutraceuticals. Inter. J Aes Anti Med 2(1): 225-229.

59. Goyal A, Kumar S, Nagpal M, Singh I, Arora S (2011) Potential of novel drug delivery systems for herbal drugs. Ind J Pharma Edu Res 45(3): 225-235.