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STRATEGIES FOR ENHANCEMENT OF BIOAVAILABILITY OF MEDICINAL AGENTS WITH NATURAL PRODUCTS

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ABSTRACT: In Advances drug design technologies, a large no of 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. Low bioavailability happens because a lot of molecules unable to permeation the gastrointestinal epithelia. 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. This review explores the natural drugs from plant and animal sources with their mechanism, *in-vivo* study, marketed formulation and its future prospective.

INTRODUCTION: India is a country where a lot of variety of the herbs with various medicinal values is available. From past to current scenario, researchers are trying to evaluate biological activities in different plant's parts like leaf, flower, stem, root etc for the treatment of various diseases. In ancient time, lot of herbal drugs were used for the treatment of the diseases in individually or in the combination with many other drugs in different dosage forms *e.g.* black pepper was used in case of coughing, while ginger was used for coughing, flavouring etc.

Combination of long pepper (*Piper longum* Linn.), black pepper (*Piper nigrum* Linn.) and ginger (*Zingiber officinale* Roscoe) collectively called "Trikatu" means "three acids", was used for the treatment of the diseases. Combination of these drugs enhances the therapeutic efficacy by means to increase the bioavailability^{1,2}.

The term bioavailability is one of the principal pharmacokinetic properties of drugs. It shows the rate and extent of the active pharmaceutical ingredients in the blood. This helps in calculating that how much amount is absorbed from blood and how much is unabsorbed and first pass metabolized.

When a drug is administered intravenously; its bioavailability is 100% means whole amount is reached into the blood circulation but when a drug is administered via. other routes such as oral, parenteral, muscular, subcutaneous etc.,

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due to incomplete absorption or first pass metabolism its bioavailability is decreased³. Because of the low bioavailability, insufficient amount of drugs is reached in to the circulation and unable to produce their therapeutic effects. This problem can be overcome by the uses of bioenhancers.

In 1929, Bose introduced firstly about the concept of bioenhancer. He used long pepper along with vasaka (*Adhatoda vasica* Nees.) leaves and determined that the antiasthmatic activity of vasaka leaves was enhanced when long pepper was used with it⁴.

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^{5,6}. The use of bioenhancers has expanded the therapeutic effectiveness of the number of drugs that can be administered non-intravenously with improving bioavailability. This approach has been worked by alter the enzymatic system, improve GIT absorption, stimulating gamma glutamyl transpeptidase (GGT) and by drug targeting etc. Extensive research during the past decades has revealed that bioenhancing approach has attracted considerable attention as regards of its many potential advantages. 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 environment⁷.

The present review highlights the current status of natural products with significant bioenhancing activities.

Ideal properties of the bioenhancers: The contribution of bioenhancers have been reviewed which states that the ideal bioenhancers^{8,9,10}.

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.

TABLE 1: BIOEHANCING PROPERTIES OF PIPERINE IN DIFFERENT CLASSES OF DRUGS WITH THEIR EXPERIMENTAL MODEL

S. no.	Drug	Class	Experimental model	Reference
1.	Rifampicin	Antituberculous	Human (<i>in vitro</i>)	11, 12, 13
2.	Phenytoin	Anticonvulsant	Human, Rats	14
3.	Pentobarbitone Barbiturate	Antihypertensive	Human	15, 16
4.	Propranolol	NSAID	Mice, Human	17, 18
5.	Nimesulide, Diclofenac sodium	Antibiotics	Rats	19
6.	Beta lactams	Anticancerous	In albino mice	20
7.	Epigallocatechin Gallate (Green tea)	Antibiotics	<i>In vitro</i> , WLH hens	21, 22,
8.	Ciprofloxacin, Oxytetracycline	Antiretroviral agents	Human Caco-2 cells line & male Sprague -Dawley rats	23,24
9.	Saquinavir mesylate, Nevirapine	Antiasthmatic	Rabbit	25

TABLE 2 BIOEHANCING ACTIVITY OF PIPERINE

S. no.	Class	Examples	Reference
1.	Herbal compounds	Boswellic acid (<i>Boswellia serrata</i> Triana & Planch.), Ginsenosides (<i>Gingko biloba</i> Linn.), Withanoloids (<i>Withania somnifera</i> Linn.), Curcuminoides (<i>Curcuma longa</i> Linn.) and Pycnogenol (<i>Pinus pinaster</i> Aiton.)	7, 26
2.	Minerals	Iodine, Calcium, Iron, Zinc, Copper, Selenium, Magnesium, Potassium and manganese	27
3.	Amino acids	Lysine, Isoleucine, Leucine, Threonine, Valine, Tryptophan, Phenylalanine and Methionine	28

4.	Vitamins	Water soluble: Vitamin B1, Vitamin B2, niacinamide, Vitamin B6, Vitamin B12, folic acid and Vitamin C Fat soluble: Vitamin A, β -carotene (provitamin), Vitamin D, Vitamin E and Vitamin K	29
5.	Gallic acid	A type of phenolic acid, found in gallnuts, tea leaves and oak bark	30, 31

Classification: Bioenhancers are classified into two classes on the basis of their origin;

Bioenhancers from herbal sources:

1. These bioenhancers are derived from various parts of botanicals. Secondary metabolites of various medicinal and aromatic plants are

I. Bioenhancers from herbal sources:

considered as rich source of bioenhancers (Table 3).

Bioenhancers from non herbal sources:

1. These bioenhancers are obtained and synthesized with non herbal and synthetic chemical substances.

TABLE 3: HERBS, ITS SOURCE, MECHANISM AND THEIR DOSE AS BIOENHANCERS

S.no.	Drug	Biological source	Mechanism	Dose of drug	Drug	Ref.
1.	Piperine (1-piperoyl piperidine)	Seeds of <i>Piper longum</i> Linn. and <i>Piper nigrum</i> Linn. Family- Piperaceae	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 (Table 1, 2)	10
2.	Curcumin	Dried and fresh rhizomes of <i>Curcuma longa</i> 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 C_{max} and AUC of celiprolol and midazolam in rats	12g/day	Celiprolol and Midazolam	32, 33, 34, 35
3.	Ginger (Whole Part)	Rhizome of the perennial plant <i>Zingiber officinale</i> 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.	10-30 mg/kg	Antibiotics like Azithromycin, Erythromycin, Cephalexin, Cefadroxil, Amoxicillin and Cloxacillin	36
4.	Caraway (Seeds)	Dried ripe seeds of <i>Carum carvi</i> Linn., Family- Apiaceae.	Due to a novel flavonoid glycoside it enhances the peak concentration (C_{max}) 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	37, 38
5.	Glycyrrhizin	Dried root and stolon of <i>Glycyrrhiza glabra</i> Linn., Family- Leguminosae.	It enhances cell division inhibitory activity of anticancerous drug. It also enhances (2 to 6 fold) transport of antibiotics	1 μ g/ml	Taxol and antibiotics like Rifampicin, Tetracycline, Nalidixic acid, Ampicillin and Vitamins B1 and B12 as bioenhancer	39
6.	Indian aloe (Leaves)	Dried juice of the leaves of <i>Aloe barbadensis</i> Mill.,	Aloe in combination with vitamins, perform the absorption slower and last		Vitamin C and E	40, 41

		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 restraint the metabolizing enzyme CYP3A4	-	Diltiazem, Digoxin, Epigallocatechin gallate	42
8.	Allicin	Aeromatic bulb of <i>Allium sativum</i> Linn. Family-Liliaceae	Allicin enhances AmB-induced vacuole membrane damage by inhibiting ergosterol trafficking from the plasma membrane to the vacuole membrane	120 µM allicin or a non-lethal concentration of AmB (0.5 µM)	Fungicidal activity of Amphotericin B	43, 44, 45, 46
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	5, 47
10.	Tea (Leaves and Buds)	Leaves and leaf buds of <i>Thea sinensis</i> 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 increased the rate	-	Both teas promote the absorption of manganese and copper as nutrients in the blood circulation.	48
11.	Niaziridin	Niaziridin a nitrile glycoside is isolated from the pods of <i>Moringa oleifera</i> Lam., Family-Moringaceae	Commonly act with antibiotics against gram-positive bacteria like <i>Myobacterium smegmatis</i> , <i>Bacillus subtilis</i> and gram-negative bacteria like <i>E. coli</i> to increase the absorption of it.	-	Vitamin B12, rifampicin, ampicillin, nalidixic acid, azole antifungal drugs such as clotrimazole	49, 50
12.	Lysergol	It is isolated from higher plants like <i>Rivea corymbosa</i> Linn., <i>Ipomoea violacea</i> Linn. and <i>Ipomoea muricata</i> 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	51
13.	Genistein	It is an isoflavone found in a number of dietary plants like soybean (<i>Glycine max</i> Linn.) and kudzu (<i>Pueraria lobata</i> 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, <i>Epigallocatechin gallate</i> the	33, 52, 53, 54

14.	Sinomenine	Root of the climbing plant <i>Sinomenium acutum</i> 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.	90mg/kg	Paeoniflorin	55, 56, 57
15.	5' methoxy hydnocarpin (5'-MHC)	Leaves of <i>Barberis fremontii</i> Torr., Family- Berberidaceae.	5'-MHC has no antimicrobial activity but it inhibits the MDR-dependent efflux of berberine from <i>S. aureus</i> cells and effectively disabled the bacterial resistance mechanism against the berberine antimicrobial action.	100 µg/ml	Berberine	58, 59, 60
16.	Hydnocarpoic acid	Seeds of <i>Hydnocarpus wightiana</i> Family- Achariaceae.	It acts by blocking the synthesis and coenzymatic activity of biotin.	4 µg/ml	Biotin	61
17.	Stevia	Leaves of <i>Stevia rebaudiana</i> 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.	62
18.	Capsaicin	Fruit of <i>Capsicum annum</i> Linn., Family- Solanaceae	The absorption of capsicum increases AUC of the drugs.	-	Theophylline	63, 64
19.	Cumin seeds	Dried seeds of <i>Cuminum cyminum</i> Linn., Family- Apiaceae	Possible mechanisms may be the Aquous 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	49, 65
20.	Ammaniol	Methanolic extract of <i>Ammannia multiflora</i> Roxb., Family-Lythraceae	Ammaniol have the property to increase glucose uptake and shows potent antihyperglycemic activity.	-	Antimicrobial drugs like Nalidixic acid	66, 67
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 P ₄₅₀ 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,	68, 69

pyrrolidines, pyrrolidinones,
stilbenes, sulfonylureas,
sulfones, triazoles, tropanes
and vinca alkaloids.

II. Bioenhancer from non herbal sources:

1. Capmul:

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

Mechanism: Due to Lipophilic nature of capmul, it acts as very effective carriers and solubilizers of active compounds. Because of its mono-diglyceride medium chain esters which are recommended for the dissolution of difficult compounds such as sterols, it also exhibited bacteriostatic activity.

Drugs: Lipophilic nature of capmul is helped to increase the solubility of Ceftriaxone⁷⁰.

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

Drugs:

- It increases the effectiveness of antimicrobial, antifungal, and anticancer drugs.
- Cow urine can be used as a bioenhancer of zinc because it has antitoxic activity against the cadmium chloride toxicity⁷¹.
- Cow urine distillate increased the activity of rifampicin against *Escherichia coli* and against gram-positive bacteria. It probably acts by enhancing the transport of antibiotics across the membrane of gastrointestinal tract⁷².
- Due to immunomodulatory properties of cow urine distillate, it is significantly enhanced the effect of gonadotropin releasing hormone on the gonadosomatic indices, sperm motility, sperm count, and sperm morphology, especially in 90- and 120-day-treated groups in male mice⁷³.
- It also enhances the potency of taxol against MCF-7 cell lines.
- It enhances the bioavailability of ampicillin in 0.05 μ g/ml concentrations and clotrimazole in 88 μ g/ml concentration by facilitating the

0 absorption of drugs across the cell membrane⁷⁴.

Common mechanism of action of Bioenhancers:

1. Alteration in the activity of the enzymatic system:

(a) Suppressors of CYP -450 enzyme and its isoenzymes: Bioenhancers inhibit CYP -450 enzyme and its isoenzymes *i.e.* CYP3A4 enzymes which are presented in enterocytes and hepatocytes and contribute to major extent to first-pass elimination of many drugs. This indicates that dietary bioenhancer could affect plasma concentrations of CYP3A4 substrates in humans, in particular if these drugs are administered orally. Some of the metabolizing enzymes *i.e.* CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4 etc are inhibited or induced by bioenhancer. Most of the drugs metabolized by these enzymes are influenced by bioenhancer.

Example: Piperine⁷⁵, Naringin⁷⁶, Gallic acid⁷⁷, Quercetin⁷⁸

(b) Inhibitors of P-gp efflux pumps: Efflux transporters such as P-glycoprotein play an important role in drug transporting in many organs. In the gastrointestinal track, P-glycoprotein pumps decrease the rate of absorption of the drug by taking back drug into the lumen. P-glycoprotein inducer, such as rifampicin, can reduce the bioavailability of some other drugs and inhibitors of P-glycoprotein increase the bioavailability of susceptible drugs by influencing absorption, distribution, metabolism and elimination of P-gp substrates in the process of modulating pharmacokinetics.

Example: Caraway²⁵, Sinomenine²⁵, Genistein⁷⁹

2. Regulation of GIT to facilitate better absorption

Herbal drugs increase the drug absorption via paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions.

They also increase the solubility of hydrophobic drugs in the aqueous layer and increase the fluidity of the apical and basolateral membranes. Bioavailability enhancing activity of drugs is also found to be partly due to the increase in the blood supply to the intrinsic vessels as a result of local vasodilation. Increased blood supply to the gastrointestinal tract is one of mechanism of bioenhancer.

Example: Aloes, Niaziridin, Ginger, Liquorice⁸⁰

3. Cholagogous effect: Bioenhancers promote the flow of bile into the intestine by the contraction of the gallbladder.

Example: Liquorice^{81, 82, 83}

4. Thermogenic properties: Bioenhancers, having thermogenic property, increase the rate of metabolism by increasing the temperature. In this way it also improves the gastric mobility and hinders the absorption of cholesterol.

Example: Garlic, Ginger, Turmeric⁸⁴

5. Stimulation of gamma glutamyl transpeptidase (GGT) activity: Gamma glutamyl transpeptidase is a membrane-bound glycoprotein located on the outer surface of the cell membrane and used as marker for the liver, biliary system and pancreatic diseases. It is responsible for the transport of amino acids across cell membranes. Bioenhancer stimulates the activation of gamma-glutamyl transpeptidase and transport of nutrients across the intestinal cells is augmented⁵⁷.

6. Alteration of gastrointestinal transit and intestinal motility: Saponins containing bioenhancers increase the permeability of intestinal mucosal cells *in vitro* and inhibit active mucosal transport. This facilitates uptake of those substances that are normally not absorbed. Saponins also lower transmural potential difference (TPD, the electrochemical gradient that acts as a driving force for active nutrient transport across the brush border membrane of the intestine) across the small intestine of rat.

Example: Alliums¹, Tea⁹, Liquorice³¹

7. Drug targeting: Bioenhancers helps to enhance the binding of the drug with the target sites such as receptors, proteins, DNA, RNA and in the pathogen also, increases GIT vasculature by vasodilation to increase absorption of drugs, modulation of the cell membrane dynamics to increase transport of drugs across cell membranes thus potentiate and prolong the effect lead to enhance activity of drugs^{85, 86}.

8. Bioenhancers may also be useful in the control of diseases like cerebral infections, epilepsy and other CNS problems by promoting the transport of nutrients and the drugs across the blood brain barrier^{87, 88}.

Marketed formulation:

Risorine: Risorine is a rifampicin containing fixed dose combination product, approved in India for the use as an antitubercular drug in place of rifampicin 450 mg and isoniazid 300 mg.

Composition: Each capsule of resorine contains: Rifampicin 200 mg IP, Isoniazid 300 mg IP, Piperine 10 mg

Dosage: For adult, one resorine capsule to be taken once daily, one hour before or two hours after meals with a full glass of water.

Indication: It is used for treatment of all forms of tuberculosis in which organisms are susceptible to rifampicin ad isoniazid^{11, 29, 31}.

Problems with bioenhancers: The concept of the bioenhancer is much demanded approach now a day in the society but there are lot of problems in research and development. In large scale production, there is a need to scale up laboratory or pilot technologies for commercialization. The challenges are related to toxicity, allergy and irritation. Its compatibility and stability with other active pharmaceutical ingredients for appropriate time and duration is also a matter.⁸⁹

Its agglomeration and the chemistry process are also creating hurdles in commercialization of bioenhancers. Some national and international agencies *i.e.* The United States Food and Drug Administration and the European Medicines Evaluation Agency are taking the initiative steps to identify possible scientific and regulatory challenges along with their solution.

By overcoming all hurdles this concept can be used for a lot of patients with highly valuable and versatile results.

CONCLUSION: The bioenhancement technology is based on traditional system of medicine but a rapidly developing field now days. New drug development technologies are also rapidly developing field but there is concerned about the economics of drug development. Bioenhancement technique would significantly increase the number of drugs suitable for diseases in which amount of drug and doses are more and more. The researchers are now aimed at methods of reduction of drug dosage and thus drug treatment cost and making treatment available to a wider section of the society including the financially sport to the country. Bioenhancing phenomenon is helpful in various challenge and relief the society due to its side effect e.g. cancer. This review will be helpful to scientists engaged in research related to bioenhancers of herbal and non- herbal origins.

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