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Bioavailability enhancers: An overview

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ABSTRACT

Oral absorption of the drug is a very important issue especially when the drug is poorly bioavailable, given for long periods and expensive. Poorly bioavailable drugs remain sub-therapeutic because a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may also lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug. Bioenhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit a synergistic effect with the drug. The various bio enhancers available are piperine, garlic, Carum carvi, Cuminum cyminum, lysergol, naringin, quercetin, aziridine, glycyrrhizin, stevia, cow urine distillate ginger.

Keywords— *Oral absorption, Bio enhancers, Improve bioavailability*

1. INTRODUCTION

Bio enhancer is defined as substances that increase the bioavailability and bio efficacy of the active substance with which they are combined without having any activity of their own at the dose used. Besides several classes of modern drugs like antibiotics, anticancer drugs, cardiovascular drugs, anti-inflammatory, central nervous drugs, etc., they also increase the bioavailability of vitamins and nutrients. Increased bioavailability means increased levels of drugs in the blood stream available for drug action. Increased bio-efficacy means the increased effectiveness of the drug due to increased bioavailability and also due to another mechanism. Plant-based medicines are used by the majority of the world's population. Our Ayurvedic texts have a thousand of herbal drugs for various drug including the rare ones.

Almost 25% of modern pharmacopoeias too contain drugs of plant origin. Some natural compounds have demonstrated to increase the absorption and bioavailability of coadministered drugs. Bioavailability of drugs with naturally occurring compounds from plants are considered to be very simple and relatively safe. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there are a need for molecules which themselves have no therapeutic activity but when combined with other drugs and molecules enhance their bioavailability. Many natural compounds from medicinal plants have the capacity to augment with bioavailability we co-administered with other drugs. Thus bio enhancer is chemical entities which promote and argument the bioavailability of drugs which are mixed with them and do not exhibit synergetic effect with the drug.

2. IDEAL PROPERTIES OF NATURAL BIOENHANCER

- Should be effective at a very low concentration in a combination.
- Nontoxic, nonallergenic, non-irritating to humans or animals.
- Most importantly, enhance uptake/absorption and activity of drugs.
- Should be easy to formulate into a various dosage form.
- Should easily available and cost-effective.
- Should not produce own pharmacological effect?
- Should be rapid acting with predictable and reproducible activity.

3. MECHANISM OF ACTION OF BIOENHANCER

The following are the chief mechanism via which the various bioenhancer exert their bioavailability enhancing properties on the drug substance:

- By enhancing the absorption of orally administered drugs from GIT tract by increases in blood supply.
- By modulating the active transporters located in various locations eg.glycoprotein (p-GP) is an efflux pump which pumps out drugs and prevents it from reaching the target site. Bioenhancer in such cases acts by inhibiting the p-up.

- Decreasing the elimination process thereby extending the sojourn of the drug in the body.
- Inhibiting the drug metabolisms enzymes like CYP3A4, CYP1A1, CYP1B2, CYP2E1, in the liver, gut, lungs and various other location. This will in addition help to overcome first pass effect administered drugs.
- Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibiting p-up and facilitating passive tubular reabsorption. Sometimes biliary clearance is also affected by inhibiting the UDP glucuronosyl transferase enzyme which conjugates and inactivates the drug.

In addition to above-mentioned mechanism, few other postulated theories foe herbal bioenhancer are

- Reduction in hydraulic acid secretion and increases in GIT blood supply
- Inhibition of GIT transit, gastric emptying time and intestinal motility.
- Modification in GIT epithelial cell membranes permeability.
- Cholagogues
- Bioenergetics and thermogenic properties.
- Suppression of first-pass metabolism and inhibition of drug metabolizing enzymes and stimulation of gamma-glutamy transpeptidase (GGT)activity which enhances uptake of amino acid

4. NEEDS OF BIOAVAILABILITY ENHANCER

- Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane and to be absorbed systemically following the oral or topical administration.
- Several plant extract and phytoconstituents, despite having excellent bioactivity in vitro demonstrate less or no in vivo action due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and poor bioavailability.
- It is often found that when individual constituents are isolated from the plant extract there is a loss of specific bioactivity.
- Sometimes some constituents of the multi-constituents plant extract are demonstrated in the gastric environment when taken orally.
- They reduce the dose, shorten the treatment period and thus reduce drug resistance problems. Due to the economy, they make treatment cost-effective, minimize drug toxicity.

5. CLASSIFICATION OF BIOENHANCER

Bio enhancers can be classified based on the origin and mechanism of action (Table 1 and 2).

Table 1: Classification of bioenhancer based on origin

Plant origin	Animal origin
Cuminum cyminum Carum carvi Stevia Lysergol Glycyrrhizin Ginger Allicin Aloe vera Simomenie Genistein 5'-methoxy hydnocarpin Ammannia multiflora Capsaicin Quercetin Curcumin Naringin Peppermint oil Gallic acid Ellagic acid Ferulic acid	Capmul, cow urine distillate (Kamdhenu ark)

Table 2: classification of bioenhancer based on mechanism of action

Inhibitors of P-gp efflux pump & other efflux pumps	Example:carum carvi(caraway) Genistein, Black cumin, Naringin, quercetin
Suppressors of CYP-450 enzyme and it's isozymes	Examples: Nargingin, Gallic acid & its ester, Quercetin
Regulators of GIT function to facilitate better absorption	Example: Aloe vera(Aloe), Niaziridin(drumstick pods), zingiber officinale(ginger), Glycyrrhizin(liquorice)

6. CLASSIFICATION OF BIOENCHANCER BASED ON ORIGIN

6.1 Bioenchancer from herbal sources

These enhancers are derived from various part of botanicals. Secondary metabolites of various medicinal and aromatic plants are considered a rich source of bioenhancer.

6.1.1 Piperine: Piperine (1-piperoyl1 piperidine) is an amide alkaloid found in a seed of piper longum Linn and Pipernigrium Linn, Family- Piperaceae. The bioenhanching dose of piperine is approximately 15 mg/person/day and no more than 20 mg/day in divided doses, which corresponds to from several thousand to up to 40,000 times less than LD50 dose of piperine, as established in various experiments on rodents. The effective bioenhanching dose of piperine for the drug compound varies, but a dose of approximately 10%(w/w) of the active drug could be regarded as an appropriate bioenhanching dose for most drugs. Piperine or mixture containing piperine has been shown to increase bioavailability, blood levels and efficacy of many drugs. A 20 mg dose of piperine can increases the bioavailability of curcumin by 20 fold in humans. 16 several animals studies on piperine have shown promising results in bioenhancing capacity of piperine for various drugs.

Fig. 1: Piper longum

Fig. 2: Piper nigrum

6.1.2 Curcumin: Curcumin is a curcuminoids Dried & fresh rhizomes of curcuma longa Family- Zingiberacea. It suppresses drug metabolizing enzymes (CYP3A4)in the liver, includes changes in drug transporter p- glycoprotein increases Cmax & AUC of celiprolol & midazolm in the rat. Its dose is 12g/day and drugs used are celiprolol, midazolm.

6.1.3 Naringin: Narigin is a flavonoid glycoside found in grape fruit, tea, apple, onion. It is a flavone-7-O-glycoside occurs naturally in citrus fruits, especially in grapefruit and dose of naringin is 3.3 & 10mg/kg. It mainly inhibits CYP3A1/2 enzymes and p-glycoprotein is modulated in rats. Drugs used as naringin are Paclitaxel, Verapamil, Diltiazem.

6.1.4. Quercetin: Quercetin is flavnoid found in many fruits (apples, citrus fruit like red grapes, raspberries and cranberries), green leaf vegetables and black and green tea. It works by inhibiting CYP3A4 and p-gp efflux pump. It increases bioavailability, blood levels. Drugs used as quercetin are Diltiazem, Digoxin, Epigallocatechin gallaate.

6.1.5 Caraway/cumin: Caraway/cumin is a novel flavonoid found in adried ripe seeds of carum carvi Linn, Family-Apiaceae. Its mechanism is due to novel flavonoid glycosides it enhances the peak concentraion(Cmax) and area under the curve of rifampicin. Its dose ranging from 1-55 mg/kg. Drugs used are Antibiotics, antifungal, antiviral and anticancer drugs.

6.1.6 Ginger: Ginger is a saponin, flvanoids, alkaloids and it is found in the rhizome of the perenninal plant Zingiber Officinale Roscoe, Fimaly- Zingiberaceae. Its mechanism is due to the presence of saponins, flavonoids, alkaloids. It acts powerfully on GIT mucous membrane. The role of ginger is to regulate inyestinal function to faciliate absorption. The dose used is 10-30 mg/kg and drugs used are mainly Antibiotics like Azithromycin,, Erythromycin, Amoxycillin and Cloxacillin.

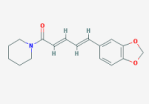
6.1.7 Glycyrrhizin: Glycyrrhin is a saponin found in dried root & stolen of glycyrrhiza glabra Family- leguminosae. The mechanism of glycyrrhizin that it enhances cell divison which inhibits the activity of the anticancer drug.Dose containg 1ug/ml and drugs used are Taxol,antibiotics like rifampicin,tetracycline,nalidixic acid ampicillin,vitB2,vitB12as bioenhancer.

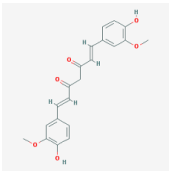
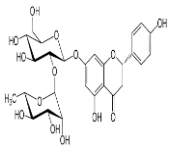
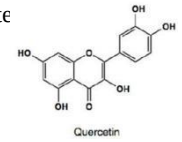
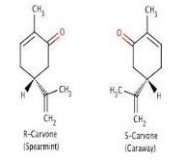
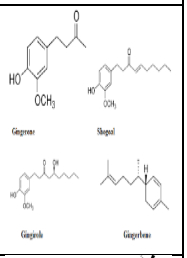
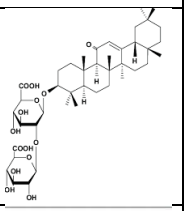
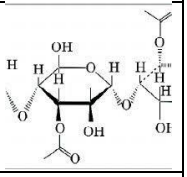
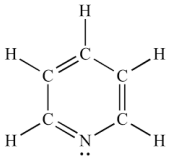
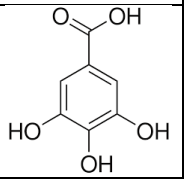
6.1.8 Indian aloe: Indian aloe (leaves) consist of lilopsida found in dried juice of leaves of aloe barbadensis mill Family-lileaceae. Its mechanism is that it inhibits release of reactive oxygen free radical from activated human neutrophils, increases bioavaliblity of vit b & c in human and mainly drugs used are vitamin B & vitamin C.

6.1.9 Niaziridin: Niaziridin is nitrile glycoside and it is isolated from pods of moringa oleifera. Mechanismof action of niaziridin is that it commonly acts with antibiotic against gampositive bacteria like myobacterium smegmatis &gramnegative bacteria like E.coli. Drugs mainly used are Vitamin B12, rifampicin , ampicillin, nalidixic acid.

6.1.10 Gallic acid: Gallic acid is a phenolic acid which is mainly found in gallnuts, tealeaves & oak bark etc. The main mechanism of action of gallic acid is that it increases drug absorption & decreases drud biotransformation in gut wall inhibiting cytochrome P450. Drugs used are Acetanilides, benzodiazepines,diditalis glycosides, ergot, alkaloids, flavonoids,napthalenes.

Table 1: List of various bio enhancers in brief

S no	Bioenhancer	Dose	Biological source	Class	Meachanism Of Action	Drug	Structure
1	Piperine	15mg/kg	Seeds of *Piper longum* Linn.and *Piper nigrum* Linn. Family-Piperacea	Amid alkaloid	Inhibits metabolising enzymes(UDP-glucuronyl transferase)	It is used in combination with various drugs and increases efficacy of these drugs	

2	Curcumin	12g/day	Dried & fresh rhizomes of curcuma longa Family-zingiberaceae	curcuminoids	It suppresses drug metabolizing enzymes(CYP3A4)in the liver, includes a change in drug transporter P-glycoprotein, increases Cmax & AUC of celiprolol & midazolzm in rat	Celiprolol, midazolzm	
3	Naringin	3.3 & 10 Mg/kg	It is a flavanone-7-O-glycoside occurs naturally in citrus fruits, especially in grapefruit	Flavonoid glycosides Found in grape fruit,tea,apple,onion	It inhibits CYP3A1/2 enzymes and p-glycoprotein is modulated in rats	Paclitaxel, Verapamil, Diltiazem	
4	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	flavonoid	It works by inhibiting CYP3A4 and P-gp efflux pump. Quercetin increase bioavailability, blood levels	Diltiazem, Digoxin, Epigallocatechin gallaate	
5	Caraway /cumin	1-55 mg/kg	Dried ripe seeds of Carum carvi Linn., Family- Apiaceae	Novel flavonoid	Due to a novel flavonoid glycoside, it enhances the peak concentration (Cmax) and area under the curve (AUC) of rifampicin	Antibiotics, antifungal, antiviral and anticancer drugs.	
6	Ginger	10-30 mg/kg	The rhizome of the perennial plant Zingiber officinale Roscoe., Family- Zingiberaceae	Saponins, flavonoid, alkaloids	Due to the presence of saponins, flavonoids, &alkaloids, Ginger acts powerfully on GIT mucous membrane. The role of ginger is to regulate intestinal function to facilitate absorption.	Antibiotics like Azithromycin, Erythromycin, Amoxycillin and Cloxacillin	
7	Glycyrrhizin	1ug/ml	Dried root &stolen of glycyrrhiza glabra Family - leguminosae	saponin	It enhances cell divison which inhits activity of anticancer drug	Taxol,antibiotics like rifampicin,tetracycline,nalidixic acid ampicillin,vitB2,vitB 12as bioenhancer	
8	Indian aloe (leaves)	-	Dried juice of leaves of aloe barbadensis mill Family-lileaceae	lilopsida	It inhibits release of reactive oxygen free radical frpm activated human neutrophils, increases bioavaliblity of vit b & c in human	Vitamin B & C	
9	Niaziridin	-	It is isolated from pods of moringa oleifera	Nitrile glycoside	It commonly acts with antibiotic against grampositive bacteria like myobacterium smegmatis & gramnegative bacteria like E.coli	Vitamin B12,rifampicin,ampicillin,nalidixic acid	
10	Gallic acid	-	Found in gallnuts, tea leaves & oak bark etc	Phenolic acid	It increases drug absorption & decreases drug biotransformation in gut wall inhibiting cytochromr P450	Acetanilides, benzodiazepines, diditalis glycosides, ergot, alkaloids, flavonoids, napthalenes	

6.2 Bioenchancer from non herbal sources

6.2.1. Capmul

- Source campul (mono-di- and triglyceride) are prepared by the glycerolysis of select fats and oils and/or esterfication of glycerin with specific fatty acids.
- Mechanism Due to the lipophilic nature of campul, it acts as very effective carries and solubilzers of active compounds. Because of its monodi-glyceride medium chain ester which is recommended for the dissolution of difficult compounds such as sterols, it also exhibited bacteriostatic activity.
- Drugs lipophilic nature of campul is helped to increas the solubility of ceftriaxone 70.

6.2.2 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.

6.2.3 Drugs

- It increases the effectiveness of antimicrobial, antifungal and anticancer drugs.
- Cow urine can be used as abioenhancer of zinc because it has antitoxic activity against the cadmium chloride toxicity.
- Cow urine distillate increased the activity of rifampicin against Eschericha coli and against grampositive bacteria. It probably acts by enhanching the trasnport of antibiotic across the membrane of the GIT tract.

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 or 120 day treated groups in male mice.

7. CONCLUSION

The bioenhancement technology is based on the traditional system of medicine but rapidly developing feild nowadays. New drugs development technologies are also rapidly increasing but it is concerned about the economics of drugs development. The researchers are now aimed at a method of reduction of drug dosage and thus drug treatment cost and making treatment available to a wider section of society including the financial support to the country. Bioenhanching phenomenon is helpfull in the various challenge and relief the society due to its side effect eg. Cancer.

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