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PROMISING NATURAL ORAL BIOAVAILABILITY ENHANCERS

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ABSTRACT

In advance drug design technology, a large number of new drug molecules are introduced every year. Due to problems like solubility, stability, Bioavailability, more side effects, many drug molecules shows less biological effects. Low Bioavailability is the serious major problem. But it is curable. Low lipophilicity and Zwitter ion are the factors affecting for low Bioavailability. The object of this review is to enhance the concept of natural compounds as oral bioavailability enhancer. Several compounds include Piperine, Naringin, Curcumin, Glycyrrhizin, Ginger, Quercetin etc. The use of natural drugs is more because these are nontoxic, safe, non-addictive, pharmacologically inert, better therapeutic response. This review also explores the natural drugs from plant and animal sources with biological source, mechanism, uses and dose of drug.[1]

KEYWORDS: Bioavailability, Natural drugs, Bioenhancer, Classification of Bioenhancer.

INTRODUCTION

Bioavailability is the rate and increase to which a substance enters systematic streams and become available at the specified site of movement. It depends on the residences of drug and path of administration.[2] The three methods used in overcoming bioavailability troubles are- 1. The pharmaceutical method (involves changes of formulation, manufacturing manner, physicochemical homes of drug without changing chemical structure) 2. The pharmacokinetics method (altered by changing chemical structure). 3. The biological method (course of management change from oral to parenteral management). The drug with bad bioavailability is associated with terrible aqueous solubility and sluggish dissolution rate in biological fluid. The course of administration determines the quantity of dose absorbed into

the circulation. Enhancers are used to enhance the fine of something. Usually it is used in a combining form. Excipients used to improve the aqueous solubility of active pharmaceutical ingredient. Their surfactive and dispersive properties can improve absorption and oral bioavailability. Also lipid excipients used for poorly water soluble APIs to improve oral bioavailability.[2]

The biopharmaceutical Classification System (BCS):[3]

Class 1: High solubility, High permeability

Class 2: Low solubility, High permeability

Class 3: High solubility, Low permeability

Class 4: Low solubility, Low permeability

Based on this BCS, the drugs will be divided.

History

The action of Bioenhancer was first discovered by Bose in 1929. The time period Bioavailability enhancer turns out to be coined via Indian scientists on the regional research laboratory, Jammu located and scientifically tested Piperine as the world's first bioavailability enhancer in 1979. Bioenhancer is the idea of natural origin track lower back from Ayurveda system. Use of Ayurvedic preparation "Trikatu" that is Sanskrit phrase meaning three acrids. Three acrids consult with a combination of black pepper, long pepper and ginger which includes active issue Piperine which beautify Bioavailability of drugs.[4]

Need for Bioavailability Enhancers[1]

1. Reduce dose of oral drug to obtain the desired blood level.
2. This reduced dose needed beneficial impact on raw material intake to develop tablet. For any country to excuisite savings.
3. This also advantage in case of rare and expensive plant based totally tablets. Eg. Costly anticancer drug Taxol derived from very slow growing Yet trees.
4. This also reduce cost of drugs.

Ideal Properties of Bioenhancers[5]

1. It should be nontoxic.
2. It should reduce side effects.
3. It should reduce drug resistance.
4. It should improve tolerability.

5. Effective at very low concentration.
6. Easy to formulate.
7. Ease of compliance.
8. Ease of acceptance because of the low cost.
9. Easily available.
10. It should be non-irritating, non-allergic.
11. It should be stable at environment and rapid acting.

Mechanism of Action of Bioenhancers[6]

1. By enhancing the supply of blood, the absorption of orally administered drugs from GIT takes place.
2. By modulating the active transporters located in various locations. Eg. P-gp is efflux pump and avoid it from reaching target site. Bioenhancers act by means of inhibiting P-gp.
3. Decreasing the elimination process, thereby extending the sojourn of drug in the body.
4. The drug metabolizing enzyme like CYP3A4, CYP1A1, CYP1B2, CYP2E1 inhibit in the liver, lungs and various locations to overcome the first pass effect administered drug.
5. Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibition of P-gp and facilitating passive tubular reabsorption.

Mechanism of Action of Herbal Bioenhancers[7]

1. Increase GIT blood supply and reduction in HCl secretion.
2. Inhibition of gastrointestinal transit, gastric emptying time.
3. Cholagogue effect.
4. Bioenergetics and thermogenic properties.
5. Inhibition of drug metabolizing enzyme and suppression of first pass metabolism.

Classification of Bioenhancers[8]

I. Classification of Bioenhancers Based on Origin

A. Plant origin: eg. Piperine, Cuminum cyminum, Allicin, Niaziridin, Carum carvi, Ginger, Stevia, Lysergol, Quercetin, Curcumin, Gallic acid, Glycyrrhizin.
B. Animal origin: eg. Cow urine distillate (Kamdhenu ark).

II. Classification of Bioenhancers primarily based on mechanism of action

A. Inhibitors of P-gp efflux pump and other efflux pumps:

Eg. Genistein, Sinomenine, Cuminum cyminum, Naringin, Quercetin.

B. Suppressors of CYP-450 enzyme and its isoenzymes: Eg. Naringin, Gallic acid, Quercetin.

C. Regulations of GIT function to facilitate better absorption: Eg. Aloe Vera, Zingiber officinale, Glycyrrhizin, Niaziridin.

Table 1: A. Bioenhancers based on plant origin.

Sr. No.	Drugs	Biological Source	Mechanism	Uses	Dose of drug	Ref. No.
1	Piperine	Seeds of Piper longum Linn. And Piper nigrum Linn. Family- Piperaceae	Inhibition of DMEs, EDTs, stimulation of gut amino acid transporters, increased. intestinal glucoronic acid secretion, inhibit P-gp and CYP3A4 etc.	It produces antioxidant, anti-inflammatory, antihypertensive, antithyroid, antitumor, antiasthmatic activity etc.	15 mg/kg	[1], [11], [14]
2	Cuminum cyminum	Dried seeds of Cuminum cyminum Linn. Family- Apiaceae	The aqueous extract of cumin seeds stimulates beta adrenoreceptors and inhibit histamine H1 receptor. It also opens the K+ channels and inhibit calcium channels.	It is used in respiratory problems, inflammatory disease, different type of human cancer, etc.	0.5 to 25 mg/kg	[1], [21]
3	Allicin	Aeromatic bulb of Allium sativum Linn. Family- Liliaceae	Inhibit ergosterol trafficking to enhance AmB – induced vacuole membrane damage from plasma membrane to the vacuole membrane.	Used in health problems like diabetes, atherosclerosis, High blood pressure, high cholesterol etc.	120 microme tre allicin.	[1], [11]
4	Niaziridin	Niaziridin is a nitrile glycoside which is isolated from the pods of Moringa oleifera Lam Family- Moringaceae	It is acting with antibiotics against gram positive bacteria like myobacteriun etc.	It is utilized in aggregate therapy. It reduces drug associated toxicity and reduce cost and duration of chemotherapy.	-	[1], [12], [19]
5	Carum carvi (Caraway)	Dried ripe seeds of Carum carvi Linn. Family- Apiaceae	It has antihyperglyacemic activity. This effect appears to be independent of insulin secretion. It inhibits production of glucose by the liver and increase uptake of glucose by peripheral tissue.	It is used in digestive problems. Caraway oil used in cough, phlegm, control urination, constipation, etc. Caraway used in mouthwashes and skin rubs to improve blood flow.	1-55 mg/ kg	[1], [24]
6	Ginger	Rhizomes of the perennial plant Zingiber	Ginger has a powerful effect on the GIT mucous membrane. It regulates	Used in nausea, vomiting, menstrual cramp, osteoarthritis,	10-30 mg/kg	[1], [8], [16]

		officinale Roscoe Family- Zingiberaceae	the intestinal function to facilitate absorption.	diabetes, migraine and used as a flavoring agent etc.		
7	Stevia	Leaves of Stevia rebaudiana Bertoni Family- Asteraceae	Stevia's component called as stevioside and steviol stimulate insulin secretion by direct action on beta cells. It also reduces vascular tension.	It is used as a sweetener, weight loss, controlling blood sugar level, food additives, antioxidant, reduce blood pressure etc.	30 mg/kg	[1], [25]
8	Lysergol	It is isolated from higher plant such as Rivea corymbosa Linn. (Pomoea vistacea Linn and pomoea muriceta Linn)	It shows the killing activities of different antibiotics.	It is used as antioxidant, purgative, febrifuge, cardiac depressant, spasmolytic, hypotensive, antibacterial, and antifungal agent.	10 microgra m per ml	[1], [10], [17]
9	Quercetin	It is flavonoid found in many fruits like citrus fruit, raspberry fruit, grapes etc., green leafy vegetables and black and green tea	It inhibit the production of enzyme responsible for manufacturer's potent leukotrienes like P-gp efflux pump and CYP3A4.	It is used as antioxidant, anti-inflammatory, antitumoral, antiviral, antihyperglyacemic, antiobesity agent.	400-600 mg of coated tab 1to 3 times daily.	[1], [8], [13], [18],
10	Curcumin	Dried and fresh rhizomes of Curcuma longa Linn. Family- Zingiberaceae	Curcumin suppresses drug metabolizing enzyme CYP3A4 in the liver, also inducing modification in drug transporter P-gp hence increase Cmax and AUC of celiprolol and midazolam in rats.	It acts as anti- cancer, anti-inflammatory, antirheumatic. Also, it is used to reduce blood sugar and glycosylated hemoglobin level in alloxan induced rats of type 2 diabetes. It is used in cosmetic also. And also act as a flavoring agent in food.	12 g/day	[1], [8], [15]
11	Gallic acid	Gallic acid is a type of phenolic acid found in gallnuts, tea leaves, etc.	It increases net drug absorption and decrease drug biotransformation in the gut wall by inhibiting cytochrome P450 drug metabolism in another location such as the liver which is site of metabolism.	It is used as anti-inflammatory, antioxidant. Also used in tanning, ink dyes and the manufacturing of paper etc.	-	[1], [22], [23]
12	Glycyrrhizin	Dried root and stolon of	It shows more potent absorption enhancing	It is used as a flavoring agent and aroma in	1 microgra	[1], [10]

		Glycyrrhiza glabra Linn. Family- Legiminoseae	activity. The absorption enhancing interest of glycyrrhizin changed into increased with the aid of the presence of other absorption enhancers.	manufacturing foods, beverages, dietary supplements etc.	m per ml	
13	Genistein	It is an isoflavone found in a number of dietary plants like soyabeans and kudza.	It is able to inhibit P-gp, BcRP and MRP – 22 efflux function.	It is used to reduce symptoms of menopause, control blood glucose and help to lower the chances of prostate and breast cancer.	3.3 mg/kg or 10mg/kg	[1], [10]
14	Sinomenine	Root of the climbing plant Sinomeniun and acutum thunb. Family- Menispermaceae	It increases the Bioavailability of paeoniflorin and explained as Sinomenine could decrease the efflux transport of paeoniflorin by P-gp in the small intestine.	It is used as anti-inflammatory additionally beneficial in analgesic therapy. It helps to maintain cardiovascular function.	90 mg/kg	[1], [10], [20]
15	Naringin	It is flavonone-7-o- glycoside occurs naturally in citrus fruits. Eg. Apple, Grapefruit	It inhibits CYP3A1/2 enzymes and P-glycoprotein is modulated in rats.	It shows antioxidant property. It acts as Bioenhancer. It shows anticarcinogenic activity.	-	[1], [8], [10]
16	Aloe Vera	Dried juice of the leaves of the Aloe barbadensis mill. Family- Liliaceae	It improves absorption of both vitamins C and E. Also increase Bioavailability of vitamin C and E in humans.	It is used to manufacture commercial products. Aloe gel used to make topical medication for skin conditions such as burns, wounds, rashes, dry skin etc.	-	[1], [28]
17	Tea	Leaves and leaf buds of Thea sinesis Linn. Family- Theaceae	The thermogenic properties of tea extract show a synergistic interaction between caffeine and catechin polyphenols that appears to extend sympathetic stimulation of thermogenesis.	It lowers BP. Green tea is a rich source of flavonoids, bioactive compound that can reduce oxidative stress, reduce the risk of heart attack, help in weight loss etc.	-	[1], [27]
18	Capsaicin	Fruit of Capsicum annum Linn. Family- solanceae	It increases AUC of drugs by absorption of Capsicum.	It is used to control chemotherapy and radiotherapy induced mucositis, control peripheral nerve pain. Also act as analgesic.	-	[1], [26]

B. Bioenhacer based on Animal origin[9]

Eg. Cow urine distillate

-It will increase the effectiveness of antimicrobial, antifungal and anticancer drugs.

-The cow urine distillate is more effective than cow urine, because of the modulation of the immune system and it act as Bioenhancer.

-It enhances the potency of Taxol against the MCF-7 cell line.

-It enhances transport of antibiotics across the membrane of GIT.

ll) Classification of Bioenhancers primarily based on mechanism of action[1]

A. Inhibitors of P-gp efflux pump and other efflux pumps.

At GIT, by taking drugs into the lumen, P-gp pump decrease rate of absorption of the drug. P-glycoprotein inducer reduce the Bioavailability of some other drugs and P-glycoprotein inhibitors increase bioavailability of drugs by influencing absorption, distribution, metabolism, elimination of P-gp substrate.

Eg. Sinomenine, Genistein, Naringin, etc.

B. Suppressors of CYP-450 enzyme and its isoenzymes

Bioenhancers inhibit CYP-450 enzyme and its coenzyme CYP3A4, which are responsible for first bypass elimination of many drugs. Bioenhancer inhibit the metabolizing enzyme like CYP1A1, CYP1B2, CYP1B1, CYP2E1, CYP3A4, etc.

Eg. Gallic acid, Piperine, Naringin, Quercetin, etc.

C. Regulations of GIT function to facilitate better absorption

Herbal drug increase solubility of hydrophobic drugs in aqueous layer and increase fluidity of the apical and basolateral membrane. Increased blood supply of intrinsic vessels results vasodilation by enhancing activity of the drug. Also increase the blood supply to GIT is one of the mechanism of Bioenhancers.

Eg. Aloe Vera, Zingiber officinale, Glycyrrhizin, Niaziridin

CONCLUSION

The bioavailability enhancer technology is based on the traditional system of medicine, Ayurveda. The natural drugs are used because of its less side effects and several properties. This review will be helpful to Bioenhancers of plant and animal origin. Bioenhancers are easily available because of the low cost and shows rapid action. They are effective at low concentration or dose and should reduce drug resistance.

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