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An Extensive Analysis of Natural Bioenhancers: A Review

Salman DS*

Department of Pharmacy, Dr. Babasaheb Ambedkar Technological University, India

***Corresponding author:** Salman D Shaikh, Department of Pharmacy, Matoshri Institute of Pharmacy, lonere, Dr. Babasaheb Ambedkar Technological University, Post Talegaon dighe, Sangamner, Maharashtra, India, Tel: 8208049386; Email: salmanshaikh164619@gmail.com

Review Article

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Abstract

The concept of bioavailability enhancer is new to the modern system of medicine. Basically, this concept originated in Ayurveda and being used in this system of medicine since centuries. Chemical substances known as "bioenhancers" work to increase the bioavailability of medications when they are combined with them and do not have a synergistic impact on the drug. The bio-enhancement leads to reduction in therapeutic dose of principal drug, thus reducing the possibilities of toxicity and side effects of drug, potentiating the efficacy, reducing the resistance, decreasing the requirement of raw material for drug manufacture, and ultimately benefitting to the world economy by reducing the manufacturing cost. A bioenhancers do not introduce its own therapeutic action with the actual active effect at the therapeutic dose used. Herbal bioenhancers are derived from both plant and animal origins. The compounds from plant origin majorly used as a bioenhancer are piperin, naringenin, niaziridin, quercitine, aloe, etc.

Keywords: Bioenhancer; Bioavailability; Biopharmaceutical Classification System; Piperine; Quinidine

Abbreviations: SFE: Supercritical Fluid Extraction; CD: Cyclodextrins.

Introduction

Today there is a great interest and medical need for the improvement of bioavailability of a large number of drugs which are poorly bioavailable, given for long periods, and are toxic and expensive. Poor 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 lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug [1].

Need of Study

Improving the bioavailability of expensive, hazardous, and poorly bioavailable drugs that are taken for extended periods of time is now needed and desired in medicine. Because a large percentage of the dosage never reaches a plasma drug concentration or exerts its pharmacological activity until and unless exceptionally high dosages are administered, which can have serious side effects, poorly bioavailable medications remain sub-therapeutic [2].

Bioavailability

Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic

circulation, thereby accessing the site of action [3].

Bioenhancer

Bioenhancers are defined as substances that increase the bioavailability leading to increased bio-efficacy of active substances with which they are combined without having any pharmacological activity of their own at the dose used [4].

Origin of Bioenchancer

Bioenhancers is an ancient word of Ayurveda, which means the growing effect of the drug, as "Yogvahi" in Sanskrit, which in combination indicates an increase in effect. In 1929, bioenhancer action was documented by Bose where he used long pepper to increase *vasaka's* antihistaminic ability [5].

Ideal Properties of Bioenhancers

1. Should not produce own pharmacological effects
2. Should be rapid-acting with predictable and reproducible activity.
3. Should be unidirectional in action.
4. Should be compatible with other active pharmaceutical ingredients.
5. Should be stable with time and environment.
6. Should be easily formulated into a various dosage form.
7. Should be easily available and cost effective.
8. Should be nontoxic, non-allergenic and nonirritating [6].

Advantages of Using Bioenhancers

1. As it increases bioavailability drug dose can be reduced.
2. Due to reduced dose cost will also reduce.
3. It reduces drug resistance.
4. Also reduces side effects and adverse drug reactions.
5. It increases efficacy of drug.
6. In short decreases total treatment cost [7].

Methods of Bioavailability Enhancement

1. Micronization
2. Nanonization
3. Sonocrystalisation
4. Supercritical fluid process
5. Use of surfactants
6. Molecular encapsulation with cyclodextrins
7. Complexation
8. Ion pair [8]

Micronization: Micronization is the process of reducing the average diameter of a solid material's particles. Traditional techniques for micronization focus on mechanical means, such as milling and grinding. Modern techniques make use of the properties of supercritical fluids and manipulate the principles of solubility [9].

Nanonization: Nanonization of drugs is the reduction of particles to nanoscale, increasing the surface area and consequently the saturation solubility and dissolution rate and resulting in higher bioavailability [10].

Sonocrystalisation: Sonocrystallization involves the application of ultrasound energy to control the nucleation and crystal growth of a crystallization process.

Supercritical Fluid Process: Supercritical fluid extraction (SFE) is the process of separating one component (the extractant) from another (the matrix) using supercritical fluids as the extracting solvent. Extraction is usually from a solid matrix, but can also be from liquids.

Use of Surfactants: Surfactants can reduce surface tension and improve the dissolution of lipophilic drugs in the aqueous medium [11].

Molecular Encapsulation with Cyclodextrins: cyclodextrins (CDs) have emerged as suitable carriers of VOCs, giving rise to so-called VOC/CD inclusion complexes. CDs constitute an inexpensive viable solution for encapsulating VOCs to improve their properties, namely their apparent solubility and stability toward pH, light, and temperature [12].

Complexation: The solubility of a precipitate can be improved by adding a ligand capable of forming a soluble complex with one of the precipitate's ions.

Ion Pairing: The use of hydrophobic counter ion to form a hydrophobic ion-pair is a unique approach for enhancing organic or oil solubility of a compound that otherwise does not effectively partition into non-polar media such as oils and lipids [13].

Biopharmaceutical Classification System (BCS)

Class	Solubility	Permeability	Example
Class I	High	High	Propanolol
Class II	Low	High	Naproxen
Class III	High	Low	Ranitidine
Class IV	Low	Low	Hydrochlorthiazide

Table 1: Biopharmaceutical Classification System [14].

Classification of Bioenhancers [15]

1. Solubilizers e.g: Cyclodextren
2. P-gp Inhibitors e.g: Piperine
3. CYP3A4 Inhibitors e.g: Galic acid
4. BCRP Inhibitors e.g: Campothecin
5. Permeability Enhancers e.g: *Zingiber Officinale*

Bioenhancer	Biological Source	Mechanism of Action	Reference
Aloe	It is obtain from bark of *Aloe Barbadensis*	Intercellular modulation	16
Ammaniol	Methanolic extract of *Ammannia multiflora Roxb*.	Increase glucose uptake and shows potent anti-hyperglycemic activity.	16
Allicin	Aeromatic bulb of *Allium sativum Linn*.	Allicin enhances AmB induced vacuole membrane damage by inhibiting ergosterol trafficking from the plasma membrane to the vacuole membrane.	16
Caraway	Dried ripe seeds of *Carum carvi Linn*.	Due to a novel flavonoid glycoside it enhances the peak concentration (Cmax) and area under the curve (AUC) of rifampicin.	17
Capsaicin	Fruit of *Capsicum annum Linn*.	The absorption of capsicum increases AUC of the drugs.	17
Curcumin	Dried and fresh rhizomes of *Curcuma longa Linn*	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	18
Cumin seeds	Dried seeds of *Cuminum cyminum Linn*.	Stimulate β adrenoceptors and/or inhibit histamine H1 receptors.	18
Diosmin	Citrus fruit	Efflux transporter (P-gp) inhibition.	19
Emodin (Anthraquinone derivative)	*Cassia angustifolia*.	Efflux transporter (P-gp) inhibition.	20
Fulvic acid	Plant decomposed material	Metabolism enhancement (enhanced drug water solubility).	20
Gallic acid ester	It is obtain from Plant (gallnuts, sumac, witch hazel, tea leaves, oak bark)	Metabolism (CYP3A) inhibition.	21
Genistein	It is an isoflavone found in a number of dietary plants like soybean (*Glycine max Linn*.) and *kudzu* (*Pueraria lobata Willd*.).	Genistein is reported to be able to inhibit P-gp, BCRP and MRP- 22 efflux functions.	21
Ginger	It is obtain from rhizomes of ginger officinalis.	facilitates better absorption by regulating GI tract function.	21
Gokhru extract	It is obtain from Plant *Tribulus Terrestris*	Local mucosal tissue modulation	22
Grapefruit juice	It is obtain from Plant *Citrus paradise*.	Efflux transporter (P-gp, MRP2); metabolism (CYP3A4) inhibition; renal uptake transporter (OATP) inhibition.	22,21
Hydnocarpoic acid	Seeds of *Hydnocarpus wightiana* Family Achariaceae.	It acts by blocking the synthesis and co-enzymatic activity of biotin.	22
Lycopene (Carotenoid)	It is obtain from red fruits and plant.	Dual carotenoid/LDL receptor mechanism for targeted hepatic delivery.	22
Lysergol	It is obtain from Plant of *morning glory Ipomoea spp*.	Efflux transporter (BCRP) inhibition; metabolism inhibition.	22

Liquorice	It consists of dried, peeled or unpeeled, root and stolon of *Glycyrrhiza glabra*.	It improves the absorption and p- gp efflux pump inhibition.	23
*Moringa oleifer*a pods	It is obtain from Plant *Moringa oleifera*.	Metabolism (CYP450) inhibition.	23
Naringin (Flavonoid glycoside)	It is obtain from Plant likes grapefruit, apple, onion, tea.	Efflux transporter (P-gp) inhibition; metabolism inhibition.	23
Niaziridin	Niaziridin a nitrile glycoside is isolated from the pods of *Moringa oleifera Lam*.	Promotes fat oxidation and decreased the absorption rate of zinc.	23
Peppermint oil	It is obtain from Plant *Mentha pipertita*.	Metabolism (CYP3A) inhibition.	23
Piperine (Alkaloid)	It is obtain from Plant *Piper longum* and *Piper nigrum*.	Local mucosal tissue modulation; thermogenic activity.	23
Quercetin	It is obtain from Plant, citrus fruits, vegetables, leaves, grains	Efflux transporter (P-gp) inhibition.	23
Quinidine	It is obtain from Plant *cinchona* tree.	Efflux transporter (P-gp) inhibition.	23
Resveratrol	It is obtain from blackberries.	Efflux transporter (P-gp, MRP- 2) inhibition; reduced elimination; renal uptake transporter (OAT1, OAT3) inhibition.	23
Sinomenine	It is obtain from Plant *Sinomenium acutum*.	Efflux transporter (P-gp) inhibition.	23
Stevia	Leaves of *Stevia rebaudiana Bertoni.*	Stimulates insulin secretion via a direct action on beta cells.	23
Tamarixetin	It is obtain from plant of *Heracleum Stenopterum*	Metabolism (CYP2C isozyme) inhibition.	23

Table 2: An Overview of Some Natural Bioenhancers.

Formulation	Bioenhancer	Therapeutic Activity	Mode of Administration	References
Nanocapsules of artemisinin	Artemisinin	Anti-cancer	In vitro	24
Nisoldipine- piperine nanoparticles	Piperine	Calcium channel blocker	Oral	25
Amphotericin B- piperine nanoparticles	Piperine	Anti-leishmanial	Oral	26
Paclitaxel- piperine, quercetin nanoparticles	Piperine, Quercetin	Anti-cancer	Oral	27
Colchicine- Cyclodextrin Transferosome	Colchicine	Acute gout	In vitro	28
Capsaicin- mitoxantrone hydrochloride Transferosome	Capsaicin	Anti-arthritic	Topical	29
Isoniazid- piperine microspheres	Piperine	Tuberculosis	In vitro	30

Table 3: Formulation Containing Natural Bioenhancers.

Ayurvedic Formulation and Methods to Enhance Bioavailability

Anupana: Anupana refers to the administration of a medication or substance along with or following the main medication. According to Acharya Charaka, when consumed properly, Anupana aids in the appropriate digestion and absorption of food and medicine, thus increasing bioavailability. Additionally, the classics describe how to use Anupana based on Dosha [31].

Bhaishajyakala: The appropriate time for administering medicine in relation to eating is described in Ayurveda. Classical texts specify ten Kala (times) for administering medication in connection to eating; these may also aid in boosting drug absorption rates [31].

Abhakta: Administration of medicine after proper digestion of food, i.e., on empty stomach. Especially indicated in Kapha Vriddhi and for the individual with good strength [16].

Bhavana (Trituration): It is a special method for enhancing the bioavailability of drugs. In this, the drug/drugs are triturated with the Svarasa, Kvatha, etc., of another drug during the manufacturing of dosage forms to increase the effect of the drug. One important example of Bhavana Dravya includes Gomutra (cow urine). Gomutra is a well-established bio-enhancer of animal origin [30]

Samshodhana (Bio-Purification): Samshodhana is a unique sort of management that is outlined in the Ayurvedic medical system. It is a form of bio-purification that is used to remove the body's vitiated Dosha (morbid humors) in order to manage various ailments or as a preventative strategy. Samshodhana strengthens Agni, enhancing its capacity for digestion and enhancing the absorption of medications and nutrients [31]. Ultimately increases the bioavailability of nutrients and drugs. The process of bio-purification also cleanses the body channels, thereby improving their patency, microcirculation, and flow of biomolecules [31].

Purana Aushadhies: After one year of collecting, it is advised to take some of the medications prescribed by Ayurveda, such as Vidanga, Pippali, Jaggery, Dhanyaka, Ghrita, and Honey. Most likely, this increases their efficacy, and if they are provided alongside other medications, they may improve the bioavailability of those medications.

Result and Discussion

Although it is based on the current medical system, enhancement technology is a quickly developing field. The economics of drug research are a worry, notwithstanding the rapid advancement of new drug discovery techniques. Scientists are now investigating ways to lower medication dosages, and consequently treatment costs, and increase therapeutic accessibility for a wider range of people, including providing financial support for the nation.

Conclusion

The current review recognizes various plants that improve bioavailability. The bioenhancer technology is based on traditional system of medicine. It is a fast evolving technology for increasing the bioavailability of medicines with limited bioavailability. There are synthetic substances that also enhance the bioavailability of drugs but synthetic drugs have a number of side effects. As compared to synthetic substances Bioenhancers have fewer side effects. Bioenhancers being cheaper in cost are easily available to a larger section of the world. Bioenhancing phenomenon is helpful to overcome from various challenges.

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