A COMPREHENSIVE REVIEW ON BIOENHANCERS

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ABSTRACT: Bioenhancers, originating from Ayurveda and now widely recognized in modern medicine, enhance the effectiveness and availability of active ingredients without exerting their own activity at the given dose. Herbal bioenhancers, derived from plant and animal sources, show promise in reducing drug dosages, treatment durations, and combating drug resistance across diverse therapeutic areas. Examples include piperine, naringenin, niaziridin, quercetin, aloe vera, Cuminum cyminum, ghee, and cow urine. Their integration into treatments offers advantages such as improved bioavailability, safety, reduced toxicity, and lowered costs. This novel approach enhances therapeutic outcomes while addressing limitations of traditional treatments, making it a valuable addition to modern medical practice. Our review explores various herbal bioenhancers and their mechanisms, shedding light on their potential to enhance treatment effectiveness and patient well-being.

KEYWORDS: Bioenhancer, Modern medicines, Bioavailability improvement, Bioavailability enhancers.

1. INTRODUCTION

1.1 Bioenhancers: Bioenhancers refer to chemical entities that enhance the bioavailability of drugs when combined with them, without exerting any synergistic effects at the administered dose. Essentially, these substances facilitate the absorption, distribution, metabolism, or excretion of a drug, leading

to increased concentrations of the drug in the body. It's important to note that the bioenhancer itself does not necessarily have a therapeutic effect on its own but rather improves the efficacy of the co-administered drug by influencing its pharmacokinetics[1].

A bioenhancer is a chemical entity that, when co-administered with a medication, enhances the drug's bioavailability without altering its pharmacological action at the given dose. In other words, a bioenhancer primarily focuses on enhancing the process of Metabolism, Excretion, Distribution, or Absorption of the drug without directly influencing its therapeutic effects[2].

Researchers are currently exploring herbal bioenhancers due to their non-toxic nature and effectiveness at low concentrations. This quality makes them convenient for formulation, offering a potential means to enhance the pharmacological functions of medications or nutrients[3].

Multiple methods are employed to enhance bioavailability via the use of bioenhancers. These techniques involve micronization, prodrugs, permeability enhancers, absorption enhancers, and the development of sustained and delayed release dosage forms that include emulsions and liposomes. Furthermore, inhibiting P-glycoprotein (P-gp) has been proposed to be a further tactic[4,5].

In the traditional Ayurvedic medicinal system, the formulation known as "Trikatu" was utilized to enhance bioavailability. Trikatu is a blend of black pepper (Piper nigrum Linn.), long pepper (Piper longum), and ginger

(Zingiber officinale). This combination was traditionally believed to have the potential to increase the bioavailability of minerals and vitamins within the body[6].

Enhancing the bioavailability of a medication becomes crucial when the drug exhibits low bioavailability, requires prolonged treatment duration, is associated with toxicity, and is financially burdensome. This is essential because bioavailability directly impacts the concentrations of drugs in the bloodstream, influencing the overall therapeutic effectiveness. Improving bioavailability is imperative, as it not only affects the efficacy of the treatment but also contributes to the overall cost of the medication and may mitigate potential drug toxicity[7].

1.2 Origin of Bioenhancers:

The term "Bioenhancers" in Ayurveda can be understood as an ancient concept denoting the augmenting effect of a drug. In Sanskrit, it is often referred to as "Yogvahi," signifying an enhanced or increased effect, especially when drugs are combined. This concept implies that the combined use of certain substances or formulations can lead to a greater overall therapeutic effect.

In 1929, Bose documented the bioenhancer action by utilizing long pepper to enhance the antihistaminic ability of vasaka.

The concept of a "bioavailability enhancer" was initially introduced in 1979 by Indian scientists at the Indian Institute of Integrative Medicine in Jammu, formerly known as Regional Research Laboratory, Jammu. They made a groundbreaking discovery by scientifically validating piperine as the world's first bioavailability enhancer. Subsequently, C.K. Atal, the director of the institute, examined various ancient Indian Ayurvedic formulations used for treating diverse diseases. He noted that "Trikatu," a combination of black pepper, long pepper, and ginger, was a common component in many Ayurvedic formulations,

further highlighting its potential as a bioavailability enhancer[8,9].

1.3 Optimal Characteristics of Bioenhancers:

The review of the contribution of bioenhancers suggests that the most desirable bioenhancers possess the following characteristics: An ideal bioenhancer should possess the following characteristics:

a. Non-Toxic, Non-Allergenic, Non-Irritating: The bioenhancer should be free from toxicity, allergenic reactions, and irritation, ensuring its safety for use in pharmaceutical formulations.

b. No Pharmacological Effects: It should not exert its own pharmacological effects to avoid unintended consequences when combined with drugs.

c. Rapid-Acting and Predictable: The bioenhancer should have a quick onset of action with predictable and reproducible activity to ensure consistent results.

d. Unidirectional Action: It should act in a specific and unidirectional manner, targeting the desired processes related to drug absorption, distribution, metabolism, or excretion without causing unwanted effects.

e. Compatibility with Other Ingredients: The bioenhancer should be compatible with various active pharmaceutical ingredients, allowing for versatility in drug formulations.

f. Stability: It should remain stable over time and under different environmental conditions, ensuring the longevity of its effectiveness.

g. Ease of Formulation: The bioenhancer should be easily formulated into various dosage forms without compromising its stability or efficacy.

h. Availability and Cost-Effectiveness: It should be readily available and cost-effective to facilitate its practical application in pharmaceutical products.[10]

1.4 Benefits of Using Bioenhancers:

a. As it increases bioavailability drug dose can be reduced.
b. Due to the reduced dose cost will also reduce.
c. It reduces drug resistance.
d. Also reduces side effects and adverse drug reactions.
e. It increases efficacy of drug vi. In short decreases total treatment cost[11].

2. Action Pathways for Herbal Bioenhancers:

Herbal bioenhancers operate through various action pathways, and specific bioenhancers derived from herbs may share similar or distinct mechanisms of action. Proposed action pathways for herbal bioenhancers encompass:

a. Enhancing Blood Flow and Reducing Hydrochloric Acid Secretion: Improving circulation and reducing the secretion of hydrochloric acid are mechanisms through which herbal bioenhancers may operate.

b. Inhibiting Gastric Emptying, Gastrointestinal Transit, and Intestinal Motility: Some bioenhancers may suppress the period of gastric emptying, slow gastrointestinal transit, and inhibit intestinal motility to enhance drug absorption.

c. Modifying Gastrointestinal Epithelial Cell Membrane Permeability: Herbal bioenhancers can bring about changes in the permeability of epithelial cell membranes in the gastrointestinal tract, influencing drug absorption.

d. Cholagogic Effect: Bioenhancers may exhibit a Cholagogic effect, facilitating the release of bile and aiding in the digestion and absorption of lipophilic compounds.

e. Thermogenic and Bioenergetic Properties: Certain bioenhancers may possess thermogenic and bioenergetic properties, potentially influencing metabolic

processes to enhance drug efficacy.

f. Inhibition of Drug Metabolizing Enzymes and Suppression of First-Pass Metabolism: Herbal bioenhancers might inhibit drug metabolizing enzymes, particularly those involved in the first-pass metabolism, leading to increased bioavailability.

g. Enhancement of Gamma Glutamyl Transpeptidase (GGT) Activity: Activating GGT can enhance amino acid absorption, contributing to improved drug absorption in the gastrointestinal tract.

h. Inhibition of P-glycoprotein (P-gp) and Other Efflux Pumps: Some bioenhancers may suppress the activity of P-gp and other efflux pumps, prevent the efflux of drugs and enhance their intracellular concentration.

i. Suppression of CYP-450 Enzymes and Isoenzymes: Herbal bioenhancers can act as suppressors of cytochrome P450 enzymes and their isoenzymes, influencing drug levels[12-20].

3. Classification of Bioenhancers:

i. Plant origin: Niaziridin, Cuminum cyminum, Carum carvi, Stevia, Lysergol, Glycyrrhizin, Ginger, Allicin, Aloe vera, Simomenine, genistein, 5-methoxy hydnocarpin etc[21].
ii. Animal origin: Cow urine distillate, honey, ghee[22].

4. Mechanism of action:

i. Caraway (Carum carvi), genistein, cumin (Cuminum cyminum), naringin, and similar compounds have been observed to inhibit P-glycoprotein (P-gp) and other efflux pumps. These substances act as bioenhancers, diminishing the expulsion of drugs from cells. As a result, they contribute to elevated drug

concentrations within cells, ultimately enhancing the overall bioavailability of the drugs. This effect is achieved by impeding drug metabolism and leading to increased systemic levels of the administered drugs.

ii. Inhibition of cytochrome P450 enzymes and their isoenzymes is observed with bioenhancers like naringin, gallic acid, and its esters. These compounds act as suppressors, influencing drug metabolism and potentially resulting in heightened systemic drug levels, thereby enhancing overall bioavailability.

iii. Substances such as Aloe vera (aloe), Niaziridin from drumstick pods, and Zingiber officinale (ginger) function as regulators of gastrointestinal (GIT) function. They contribute to improved absorption by modulating the GIT function, potentially enhancing the absorption of drugs or nutrients. This modulation of gastrointestinal function may lead to increased bioavailability of the administered substances.[20]

5. List of some Herbal Bioenhancers:

5.1 Piperine:

Piperine, found in both Piper longum (long pepper) and Piper nigrum (black pepper), is an active compound known for its bio-enhancing effects. Typically administered at a dosage of 15mg/kg body weight, piperine inhibits various enzymes, including P-glycoprotein (P-gp), CYP3A4, and other drug-metabolizing enzymes, notably UDP glucuronosyl transferase (UGT), within the gastrointestinal tract. Additionally, piperine promotes increased blood supply in the enteric vessels through its local vasodilatory effects[23]. Piperine has been observed to enhance the bioavailability of various drugs, including diclofenac sodium, pentazocine, phenobarbitone, propranolol, theophylline, metronidazole, methotrexate, etoposide, 18-β glycyrrhetic acid, nateglinide, ibuprofen, resveratrol, fexofenadine, carbamazepine, nevirapine, phenytoin, cyclosporine A, nimesulide, vasicine, sparteine, ampicillin, norfloxacin,

rifampicin, tetracycline, pyrizinamide, INH, epigallocatechin-3-gallate, sulfadiazine, fexofennadine, curcumin, saquinavir, nelfanavir, lopanavir, amprenavir, ritonavir, ofloxacin, ciprofloxacin, indomethacin, atenolol, oxytetracycline, beta-lactams, oxyphenylbutazone, midazolam, linarine, and mercaptopurine.[24].

Piper longum (long pepper)

Piper nigrum (black pepper)

5.2 Ginger:

Ginger exerts a pronounced impact on the gastrointestinal mucous membrane. Its function in aiding absorption involves the regulation of intestinal function. Ginger is employed as a bioenhancer at a dosage ranging from 10-30 mg/kg body weight[25]. In the presence of ginger, the bioavailability of different antibiotics, including Azithromycin (85%), Erythromycin (105%), Cephalexin (85%), Cefadroxil (65%), Amoxicillin (90%), and Cloxacillin (90%), experiences a notable and significant increase.[26].

Ginger

5.3 Allicin:

The combination of amphotericin B and allicin demonstrates enhanced antimicrobial activity against pathogens such as Candida albicans, Aspergillus fumigatus, and Saccharomyces cerevisiae. This synergistic effect results in increased efficacy, particularly in the case of Saccharomyces cerevisiae[27]. Allicin enhances the destruction of vacuoles induced by Amphotericin B by inhibiting the transport of ergosterol from the plasma membrane to the vacuole membrane, thus, functioning as a bioenhancer[28]. The effective dose of allicin for this purpose is 120μM, or a non-lethal concentration of Amphotericin B at 0.5 μM[25].

Allicin

5.4 Curcumin:

Curcumin, derived from Curcuma longa, is utilized at a dosage within the range of 12 grams per day[25.] It functions by inhibiting the metabolism of drug enzymes and suppressing the activity of P-glycoprotein (P-gp) efflux pumps[29,30]. Additionally, it inhibits drug-metabolizing enzymes like CYP3A4 in the liver, as well as lowers levels of UDP glucuronyl transferase in both intestinal and hepatic tissues. Furthermore, it influences the physiological function of the gastrointestinal tract, promoting heightened drug absorption.[31]. Examples of drugs include norfloxacin, midazolam, celipropol, docetaxel, midazolam, methotrexate[29,30].

Curcumin

5.5 Niaziridin:

Niaziridin, a newly identified nitrile glycoside found in Moringa oleifera pods, enhances the bioavailability of rifampicin, ampicillin, and nalidixic acid by 1.2-19 times against gram-positive bacteria. It also augments activity by 5-6 times against Candida albicans when used in combination with azole antifungal drugs like clotrimazole. Additionally, Niaziridin improves the absorption of vitamin B12.[32]

Moringa oleifera pods

5.6 Quercetin:

Derived from citrus fruits, berries, leaves, and grains, this compound exerts its bio enhancing action by inhibiting the activity of CYP3A4 enzymes and/or the transporters associated with P-glycoprotein (P-gp) efflux pumps. [34]. Quercetin has been observed to enhance the effectiveness of various drugs, including

paclitaxel, ranolazine, valsartan, clopidogrel, doxorubicin, etoposide, irinotecan, digoxin, polyphenols from green tea, pioglitazone, diltiazem, epigallocatechin, toxaphene, and pioglitazone[35].

Quercetin

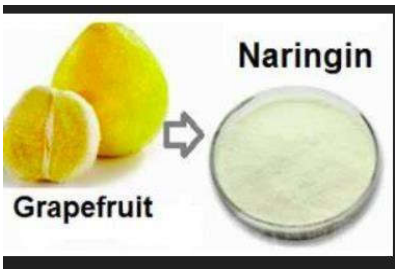
5.7 Glycyrrhizin:

It is a saponin glycoside derived from Glycyrrhiza glabra and is applied within the concentration range of 1 µg/ml. Glycyrrhizin enhances drug absorption and inhibits P-glycoprotein (P-gp) efflux pumps. Medications such as rifampicin, tetracycline, aconitin, ampicillin, clotrimazole, taxol, vitamin B1, B12, and nalidixic acid are among the drugs that can benefit from bio enhancement with glycyrrhizin.[36,37]. Additionally, glycyrrhizin enhances the inhibitory effects of anticancer drugs, including Taxol. Furthermore, it is documented to improve the transport of antibiotics such as rifampicin, tetracycline, nalidixic acid, and ampicillin across the gastrointestinal membrane[38].

Glycyrrhizin

5.8 Naringinin:

This flavonoid glycoside, sourced from grapefruit, apples, onions, and tea, is administered within the dosage range of 3.3 to 10 mg/kg[25]. Naringenin functions by inhibiting CYP3A4, CYP3A1/2, and P-glycoprotein (P-gp) efflux pumps. Medications that experience enhancement in their effectiveness due to naringenin include diltiazem, verapamil, clopidogrel, tamoxifen, quinine, nimodipine, felodipine, 17-α ethinylestrdiol, paclitaxel, saquinavir, cyclosporine A, nitrendipine, terfenadine, and others[34,39].



Naringinin

5.9 Cuminum cyminum:

Cuminum cyminum, derived from black cumin, exhibits potential mechanisms of action, including the stimulation of β-adrenoceptors and/or inhibition of histamine H1 receptors when used in aqueous extract form. Additionally, it has the ability to open potassium channels. Administered at doses ranging from 0.5 to 25 mg/kg body weight, Cuminum cyminum significantly increases the bioavailability of various drugs, such as Erythromycin (105%), Cephalexin (75%), Amoxicillin (111%), Fluconazole (126%), Ketoconazole (156%), Zidovudine (270%), and Fluorouracil (290%).[40]

Cuminum cyminum

5.10 Indian Aloe (Aloe vera):

Research has shown that both Aloe vera gel and whole leaf extract significantly enhance the transportation of the macromolecular peptide drug, insulin, across Caco-2 cell monolayers[41]. It improves the oral absorption of both vitamin C and vitamin E[42].

Indian Aloe (Aloe vera)

5.11 Genistein:

Genistein, an iso-flavonoid derived from Glycine max and Pueraria lobata, functions by inhibiting the efflux functions of P-glycoprotein (P-gp), MRP 2 (multidrug resistance-associated protein 2), and BCRP 2 (breast cancer resistance protein 2). It enhances the actions of paclitaxel and epigallocatechin-3-gallate. The recommended dose range for Genistein is 3.3 mg/kg to 10 mg/kg[25].

Genistein

5.12 Sinomenine:

Sinomenine alkaloid obtained from Sinomenium acutum. They act by decreasing efflux transport by P-gp. The dose is in the range of 90mg/kg[25]. The drugs like verapamil, quinidine, paeniflorin, digoxin is bio enhanced using sinomentine[36,37].

Sinomenine

5.13 Capsaicin:

Capsaicin, derived from capsicum, enhances the bioavailability of theophylline[43].

Capsaicin

5.14 Peppermint oil:

Peppermint oil has the potential to increase the bioavailability of cyclosporine[44].

Peppermint oil

5.15 Gallic acid:

It exhibits a synergistic effect when combined with piperine and also improves the bioavailability of nifedipine and saquinavir[45].

Gallic acid

5.16 Tulasi oil:

Tulasi, also known as Ocimum sanctum, functions as a bioenhancer for naproxen and nimesulide[4].

Tulasi oil

5.17 Clove Oil:

Clove oil enhances the bioavailability of carvedilol[47].

Clove Oil

5.18 Cinnamic acid:

It improves the bioavailability of saquinavir[45].

Cinnamic acid

Bioenhancers from animal source:

5.19 Cow urine:

According to Ayurveda, cow urine is deemed as the elixir of life and is considered highly effective in treating various infections, particularly kidney and liver infections. Pure cow urine is now preferred over filtered cow urine, cow urine distillate, distilled cow urine, and cow urine fraction. The drugs that experience bio-enhancement in the presence of cow urine include rifampicin, tetracycline, ampicillin, paclitaxel, zinc, taxol, INH (isoniazid), clotrimazole, cyanocobalamin, and mercaptopurine[48-50]

Cow urine

5.20 Ghee:

In numerous Ayurvedic formulations like Brahmi ghrita and Trikutrayadi lauha, cow urine functions as a bioenhancer[22].

Ghee

5.21 Honey:

It's also known as Madhu. It is a sweet bee food that uses flowers nectar. It is used in crystallized, pasteurized, raw, strained, filtered, ultrasonic, creamed, dried forms in modern practice, and now a days there are also honey decoctions. Used in Trikutrayadi lauha as a bioenhancer[22].

Honey

Conclusion

Bioavailability, safety and cost are important issues in the pharmaceutical industry. That's why innovation is happening today. The use of herbs and APIs is a new method developed by Ayurveda. The herb is safe, effective and also increases bioavailability and efficacy through multiple mechanisms of action.

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