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Bioenhancers in advanced herbal technology: A comprehensive review of mechanisms and applications

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Abstract
A drug's bioavailability is critical to its therapeutic efficacy. Chemicals with significant medical potential frequently exhibit poor pharmacokinetics due to low solubility and permeability. Bioenhancers are novel concepts that alter the pharmacokinetics of medications with low bioavailability. Since ancient times, the Ayurvedic medical system has been the first to use a herbal bioenhancer. Herbal bioenhancers are safer, more effective, and widely available. The Ayurvedic pharmaceutical system was the first to use a herbal bioenhancer in antiquity. Herbal bioenhancers provide increased safety, efficacy, and availability. Ginger, caraway, aloe, piperine, quercetin, and curcumin are some of the most popular herbal bioenhancers. Herbal bioenhancers are increasingly being used in drug delivery research to improve the bioavailability, safety, and efficacy of pharmaceuticals.
Herbal bioenhancers enhance the bioavailability of nutraceuticals, antibiotics, anticancer, antitubercular, and cardiovascular medications, resulting in a speedier onset of effect. Bioenhancers influence drug membrane permeability and presystemic metabolism, reducing the therapeutic efficacy of potent drugs. Herbal bioenhancers are being used in a variety of novel medication delivery techniques including nanotechnology, as well as standard dosages. Herbal bioenhancers are used in modern drug delivery methods, including as liposomes, transferosomes, ethosomes, and nanoparticles, to increase drug bioavailability via many routes of administration. This chapter presents new insights into contemporary trends in herbal bioenhancers, their biomedical applications, and the current patent landscape.

Keywords: Bioavailability, herbal, novel drug delivery system, bioenhacer

Introduction
Bioavailability is an important aspect that affects how a drug works. Better bioavailable drugs have an effective therapeutic impact at lower dosages. Because a smaller dose is required for therapeutic efficacy, increased bioavailability reduces the hepatic and nephrotic load. If bioavailability improves, many active pharmacological entities may be able to exert possible therapeutic effects. As a result, improving bioavailability is a major study area around the world. The key factors influencing bioavailability are first-pass metabolism, permeability, and solubility [1]. Herbal bioenhancers improve drug absorption without significantly altering or interfering with the body's physiology or the way the drug operates [8]. Bioenhancers provide additional benefits such as price, simplicity of availability, and less side effects. Herbal bioenhancers are being utilized to boost the absorption and, ultimately, bioavailability of several drugs used to treat disorders involving the cardiovascular system (CVS), gastrointestinal tract, and central nervous system [14]. Vitamins are among the nutraceuticals with low bioavailability; as a result, herbal bioenhancers are in high demand to improve nutraceutical bioavailability.

The idea of bioavailable boosters
The concept stems from the age-old practice of using "bioavailability enhancers". Ayurveda is the science of life. Black pepper, long pepper, and ginger are all included in Ayurveda. The three acids are commonly referred to as "trikatu" in Sanskrit. As a result of bioenhancers, Bose was the first to document the relationship between long pepper and Adhatoda vasika in 1929.

The presence of leaves improved Adhatoda vasica leaves' anti-esthetic properties. C.K. Atal, Chairman of the Regional, created the term "bioavailability enhancer." Piperine was discovered and scientifically confirmed at the Research Laboratory in Jammu. Bioenhancers will be the world's first bioavailability enhancer in 1979 [3, 1].
Substances that, when ingested alone, have no pharmacological effects, but which improve biological activity or the absorption of the active component and boost bioavailability during combination therapy [5].

Necessity of a bioavailability enhancer
It is estimated that around 250 million antibiotic doses are administered worldwide each year. Depending on the type of antibiotic, 20-50% of that usage is excessive. Furthermore, broad antibiotic use frequently results in the spread of antibiotic resistance, which can progress to multidrug resistance. The total amount of medication or antibiotics given for the treatment of any disease. There are far more cases of the disease than are actually required. The dosage of the medication is determined by the use of bioavailability boosters. Lessened, and the chance of medication resistance is reduced. Additionally, it reduces dose-dependent toxicity. Specifically for anticancer medicines [4, 2].

Classification and mechanism of action of bioenhancer
The basic purpose of using herbal bioenhancers is to improve bioavailability. They are divided into three categories based on their manner of action. Bioenhancers increase the bioavailability of numerous therapeutic compounds by decreasing P- levels. Medication efflux via glycoprotein (P-gp), suppression of cytochrome P-450 (CYP-450), and enhanced penetration
Dudhatra, Ghanshyam B.; Shailesh K. Mody; Madhavi M. Awale; Hitesh B. Patel; Chirag M. Modi; Avinash Kumar; Divyesh R. Kamani; and Bhavesh N. Chauhan. 2012a:
1. Blocking P-Glycoprotein Drug Efflux
2. Inhibition of Cytochrome P-450 (Cyp-450) enzymes.
3. Absorption enhancers [5, 6].

Blocking the efflux of drugs from p- glycoprotein
The efflux membrane transporter that governs intracellular uptake and distribution is known as P-gp. Including a variety of alien chemicals and toxins. This P-gp inhibits the efflux process, which is responsible for the permeability and absorption of various drugs, ultimately resulting in lower bioavailability. To ensure that the medicine is efficiently delivered and has the highest bioavailability [6]. It is critical to inhibit the P-gp efflux. P-gp efflux can be inhibited by altering the integrity of lipids in the cell, inhibiting the drug binding site of the P-gp Membrane, or interfering with the breakdown of adenosine triphosphate.

Inhibition of cytochrome P-450 (CYP-450) enzymes
The first-pass metabolism is predominantly carried out by enzymes from the CYP-450 family, which eliminates many drugs. This increases the substance's bioavailability. It is critical to inhibit these enzymes and avoid the first-pass metabolism of compounds. Curcumin, piperine, and other herbal bioenhancers all block several enzymes. CYPA1, CYP1B1, CYP1B2, CYP3A4, and CYP2E1 inhibit the first-pass elimination of many pharmacological compounds and improve their bioavailability [7, 2].

Absorption boosters
Membrane permeability limits the use of many drugs in the biopharmaceutical business. BCS class III and IV are classified using the Classification System (BCS). The limited penetration of these drugs reduces their absorption and therapeutic efficacy. Improved permeability can help with the absorption of these less penetrating medications. Several herbal bioenhancers, including, contribute to the mechanism of increased permeability. Aloe vera, ginger, niaziridine, and *Carum carvi* are some of the bioenhancers that help medication molecules penetrate biological membranes, resulting in higher absorption and bioavailability [9, 8].

The ideal property of bio-enhancers
The ideal bio-enhancers should be non-allergenic, non-irritating, and nontoxic.
- Unique pharmacological activities, predictable and repeatable activity, one-way operation, compatibility of active pharmaceutical components, and stability across time and environment. Easily available in many dose forms [14].
- Cost-effective.

Bacopa monnieri
Name of Plant: *Bacopa monnieri*. The *Bacopa monnieri* plant Synonyms include Brahmi, Water Hyssop, and Thyme-leaved Gratiola. *Bacopa monnieri* is a perennial plant found in wetlands throughout Asia, particularly in India and Nepal. *Bacopa monnieri* contains a wide range of chemical components. Bacosides, alkaloids, flavonoids, and saponins are among the compounds that give it its distinct characteristics. Exhibiting cognitive-enhancing and adaptogenic properties. Applications: *Bacopa monnieri* has long been utilized in Ayurvedic medicine for its adaptogenic characteristics, which help in stress management. Recent study has focused on its ability to do the following: It is a beneficial herb in the realm of mental health since it enhances cognitive function and memory wellbeing [12].

Moringa oleifera
Plant Name: *Moringa oleifera* The *Moringa oleifera* Leaf and Pods, as shown on the tree, are also known as the Drumstick tree, Miracle tree, and Ben oil. *Moringa oleifera*, sometimes known as the Miracle Tree, is a fast-growing, deciduous tree native to Africa, Asia, and the Indian subcontinent.

Chemical Composition: *Moringa oleifera* is a nutrient-dense superfood. Minerals (calcium, potassium, and iron) are examples, as are antioxidants and vitamins C, A, and B, which include a range of amino acids, chlorogenic acid, and quercetin.

Applications: *Moringa oleifera* has a variety of applications. Its leaves and pods can be consumed, giving essential nutrients. It has been recognized for its anti-inflammatory, antioxidant, and antibacterial properties. Furthermore, *Moringa oleifera* has been used in a wide range of applications. Due to its coagulant properties in water filtration, demonstrating its flexibility [13].

Ginger

Ginger (*Zingiber officinale*) has a strong effect on the GIT mucous membrane. It modulates intestine function to improve absorption. Ginger is utilized as a bioenhancer in doses ranging from 10 to 30 milligrams per kilogram of body weight. It increases the bioavailability of antibiotics such as Azithromycin (85%), Erythromycin (105%), Cephalexin (85%), Cefadroxil (65%), Amoxycillin (90%), and Cloxacillin (90%) [8, 14].

Distillate from cow urine: Cow urine works less well as a bio-enhancer. It has strong antibacterial and antifungal properties and improves the efficiency of anti-cancer drugs. US Patent Nos. 6896907 and 6410059 have been awarded. Cow urine has been granted therapeutic benefits, most notably as a bio-enhancer with antibiotics, cancer medications, and antifungal medications. Paclitaxel has shown increased potency against MCF-7, a human breast cancer cell line, in *in vitro* tests (US Patent No. 6410059). A cow Urine distillate boosted rifampicin's efficacy against Escherichia coli by five to seven times. It is probably effective against Gram-positive bacteria three to eleven times. Most likely, it operates by improving the transport of Antibiotics can pass through the digestive tract membrane. The improvement in transportation is two to seven times higher. The gonadtropin-releasing hormone combination has a detrimental impact on the reproductive system. Cow urine distillate acts as a bio-enhancer, regulating female mice's hormones and estrous cycles. When assessing immunization effectiveness, take these impacts into account [15].

***Cuminum cyminum* (black cumin)**

Cuminum cyminum increases the bioactivity of erythromycin. Some of the drugs included include cephalexin, amoxycillin, fluconazole, ketoconazole, zidovudine, and 5-fluorouracil. The dosage resulting in enhanced bioavailability ranged from 0.5 to 25 mg/kg body weight. It functions effectively as a carminative, stomach stimulant, and anthelmintic. Its therapeutic applications include diuretics, galactagogues, anti-diarrheals, and assists in the treatment of hoarseness [18].

Annual casicum

It is often known as the chili pepper, and it produces capsaicin, which amplifies the substance's strength. Theophylline and ciprofloxacin are bioavailable. In a rabbit oral dosage trial, the second maintenance dose of bioenhancer was given using capsaicin alone or in conjunction with theophylline. After 11 hours, theophylline's plasma levels increased [17].

Recent Case Studies: Nano/microcarriers can improve the bioavailability of herbal elements such flavonoids, tannins,

and glycosides that are poorly absorbed in water. Because of their enormous molecular size and low lipid solubility, their capacity to move across lipid-rich cell membranes will be severely restricted. The use of nano/microcarriers enhances the therapeutic action of poorly soluble plant extracts. Recent case studies use nano/microformulations to deliver herbal bioenhancers/products [4, 2].

Upcoming Prospectus for Herbal Bioenhancers

Bioenhancers are utilized in medicine delivery to minimize doses and prevent antibiotic resistance. The reduced dosage helps to a reduction in drug toxicity, which is especially advantageous when dealing with powerful drugs. Taxol is an example of an anticancer drug. Taxol, a popular treatment for breast and ovarian cancer, is extracted from the bark of The Pacific yew tree, one of the world's slowest growing trees, is well-known. Traditionally, The removal of taxol to cure a single patient required the felling of six trees, each of which was between 100 and 200 years old. However, the use of bioenhancers avoids the need for such long periods. The devastation is reduced. This enhances the treatment's ecological sustainability while also exhibiting a more conscientious attitude toward the environment. The reduction in the number of trees needed Because the method of medication extraction aligns with a more sustainable and environmentally responsible manner of doing things. The manufacture of medications. Not only does this approach to bioenhancer integration benefit the patient. Health, but also provides a positive contribution to larger environmental challenges [14].

Conclusion

Bioenhancers enhance therapeutic compounds' bioavailability, efficacy, and safety, making them a significant advancement in herbal technology. Their inclusion in herbal formulations lowers dosage requirements, eliminates side effects, and improves patient compliance. Piperine, quercetin, glycyrrhizin, and gingerol are examples of naturally derived bioenhancers that have showed promise in optimizing medication distribution while maintaining the medicine's inherent effectiveness. With continued study, bioenhancers have the potential to generate cost-effective, synergistic, and sustainable herbal-based therapies, ultimately integrating ancient wisdom with current pharmaceutical advances.

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