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BIOENHANCERS IN DRUG DEVELOPMENT: CURRENT TRENDS AND FUTURE DIRECTIONS

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ABSTRACT

Bio-enhancers, or bioavailability enhancers, are agents that increase the absorption and efficacy of co-administered drugs without possessing therapeutic activity of their own. Originating from traditional medicine systems such as Ayurveda where they are known as *Yogavahi* bioenhancers have gained significant attention in modern pharmaceutical research due to their ability to overcome barriers like poor solubility, rapid metabolism, and drug resistance. This review highlights the classification of bioenhancers based on their source, mechanism of action, and therapeutic application, with key examples including piperine, quercetin, and curcumin. Their mechanisms—ranging from inhibition of P-glycoprotein and CYP450 enzymes to modulation of membrane permeability—are explored in detail. The review also discusses pharmaceutical applications such as fixed-dose combinations, nanotechnology-based formulations, and their role in reducing drug doses and costs. Current research trends include their use in biologics, targeted delivery systems, and personalized medicine. Despite promising benefits, challenges such as regulatory ambiguity, safety concerns, and limited clinical validation persist. The future of bioenhancers lies in the rational design of synthetic analogs, advanced delivery systems, and

their integration into global health strategies. Overall, bioenhancers represent a versatile and evolving tool in enhancing therapeutic outcomes and optimizing drug development.

KEYWORDS: Drug bioavailability, Pharmacokinetic modulation, Synergistic effect, Drug absorption enhancers, Gene therapy bioenhancement.

INTRODUCTION

Definition of Bioenhancers

Bioenhancers, also known as bioavailability enhancers, are agents that enhance the bioavailability and efficacy of drugs without possessing significant pharmacological activity of their own at the dose used. They work by increasing the absorption, distribution, metabolism, and excretion (ADME) profiles of co-administered drugs.

They are particularly useful in improving the oral bioavailability of poorly absorbed drugs, reducing the dose required, minimizing side effects, and enhancing patient compliance. Bioenhancers can act through multiple mechanisms, such as:

- Inhibition of drug-metabolizing enzymes (e.g., CYP450s)
- Inhibition of efflux transporters (e.g., P-glycoprotein)
- Modulation of gastrointestinal (GI) permeability
- Enhancing solubility or dissolution rate.

Bioenhancers are natural or chemical moieties that enhance or promote the rate of drug's bioavailability when used with them but do not have a synergistic action with the drug. They work through a number of processes that can affect the metabolism, absorption, and target action of the drug.[1]

The current focus of researchers in the pharmaceutical field is on several elements of discovering new chemical compounds with novel mechanisms of action. The current global focus is on ways for shortening drug treatment durations and lowering drug treatment costs. The lower therapy expenses will make treatment more feasible for those who are financially challenged. Because India is a developing country, the cost of therapy for new allopathic drugs is a major concern. Innovative approaches for lowering drug costs are urgently required as internationally, billions of dollars are being spent annually because of the drugs which are poorly bio-available. For example, The invention of piperine as a bioenhancer in 1979 introduced a new notion into research, with the administration of piperine dramatically

increasing the blood levels of propranolol, Rifampicin, phenytoin, spartein, sulfadiazine, theophylline and tetracycline in the human. Taxol is used to treat breast cancer. This drug is extracted from the new, a slowest growing tree in the world, and to obtain taxol for one patient, six trees of 25–100 years are needed to be chopped. But instead combining a bioenhancer with Taxol means that lesser trees need will be chopped lead which will come out as a benefit for the ecology.[2]

Comprehensive research on these Bioenhancers is critically needed so that they could be utilized in formulations of drug in the future.

The motion of Bioenhancers has led to a dramatic change in the manner of therapeutic treatment because of the progress in drugs improving bioavailability of drugs. Lately, it has been observed that there is an upsurge in the tendency of acquiring the drugs from herbal plants by the humans due to their lower risk benefit if compared to the contemporary allopathic medications.[3]

Historical Background

The nation of natural herbal bioenhancer has a history that could be dated back to the Ayurvedic medicine system's ancient knowledge. The term for this concept in Ayurveda is "yogvahi," and it is utilized to promote the therapeutic effect of drugs by increasing their tissue distribution, enhancing their bioavailability through oral route, lowering their dose and harmful effects, and avoiding parenteral drug administration.

Since the 7th century. through the 6th century, people used the Ayurvedic treatment "Trikatu," a Sanskrit term which means "three acids." It contains the combination of black pepper (Piper nigrum), long pepper (Piper longum), and ginger (Zingiber officinale) that contains the active principle piperine, which enhances bioavailability of drugs, nutrient, and vitamin absorption. Base introduced the notion of bioavailability enhancers in the year of 1929, when he detailed how adding long pepper to leaves of Vasaka increased its anti-asthmatic benefits.

At the Indian Institute of Integrative Medicine in Jammu, Indian scientists were the first to coin the phrase, "bioavailability enhancer". In the year of 1979, they developed piperine, the world's very first bioenhancer and scientifically confirmed it.[1]

IMPORTANCE OF BIOENHANCERS

Bioenhancers are gaining significant importance in modern pharmaceutical sciences for the following reasons:

1. Improved Bioavailability: Drugs with poor water solubility or permeability often face limitations in reaching systemic circulation. Bioenhancers help boost absorption, reducing variability in pharmacokinetics

2. Reduced Drug Dosage: Enhancing bioavailability enables dose reduction without compromising therapeutic efficacy, leading to cost-effective therapy and reduced risk of dose-dependent toxicity.

3. Combatting Drug Resistance: In antimicrobials and anti-tuberculosis treatments, bioenhancers like piperine or quercetin can inhibit drug resistance mechanisms, enhancing efficacy.

4. Pediatric and Geriatric Benefits: Lower dosing and improved bioavailability make drug therapy safer for vulnerable populations such as children and the elderly.

5. Enhanced Therapeutic Outcomes: Bioenhancers contribute to better patient compliance and treatment success due to improved pharmacokinetics and pharmacodynamics.[1]

CHARACTERISTICS OF BIOENHANCERS

- It should not have any of its own pharmacological effects.
- Should exhibit reproducible and predictable activity.
- They must be non-irritating, non-toxic, and non-allergenic.
- They must be rapid acting.
- The action of bioenhancers must be one-directional.
- They must be cost-effective.
- Compatibility of Bioenhancers with the pharmacologically active ingredient (API's) is essential.
- They must be capable of being easily formulated into different dosage forms.
- They must be readily available and should be stable throughout.[12]

CLASSIFICATION OF BIOENHANCERS

Bioenhancers can be classified into different categories based on their **source**, **mechanism of action**, and **target drug class**. These classification help in understanding their function, scope, and application in pharmaceutical formulations.

1. Based on Source

a. Natural Bioenhancers: These are derived from natural sources such as plants, herbs, spices, and marine organisms. They are widely used due to their safety profile and traditional use.

Table 1: Natural bioenhancer and their mechanism.

Bioenhancer	Source Plant	Mechanism Highlights
Piperine	*Piper nigrum*, *Piper longum*	Inhibits CYP450 enzymes, P-gp efflux, enhances GI absorption
Quercetin	Found in apples, onions, berries	Inhibits P-gp and BCRP efflux transporters, antioxidant
Curcumin	*Curcuma longa* (Turmeric)	Inhibits P-gp, modulates metabolic enzymes, anti-inflammatory
Glycyrrhizin	*Glycyrrhiza glabra* (Licorice)	Enhances membrane permeability, antiviral properties
Aloe Vera extract	*Aloe barbadensis*	Enhances paracellular transport
Capsaicin	*Capsicum* species	Alters membrane fluidity and tight junctions

These agents are generally non-toxic, cost-effective, and have multiple synergistic therapeutic roles.[22]

b. **Synthetic Bioenhancers:** These are chemically synthesized compounds designed to enhance the pharmacokinetic properties of co-administered drugs.

Labrasol – A synthetic surfactant used in lipid-based formulations.

D-alpha-tocopheryl polyethylene glycol succinate (TPGS) – A water-soluble derivative of Vitamin E used to inhibit P-gp efflux and increase solubility.

Sodium caprate (C10) – Enhances paracellular absorption by opening tight junctions.

Bile salts (e.g., sodium taurocholate) – Increase solubility and membrane transport.

Synthetic bioenhancers are useful in controlled delivery systems and poorly soluble drug formulations, but may require extensive safety evaluations.[22]

2. Based on Mechanism of Action

Bioenhancers work through diverse mechanisms, depending on the nature of the drug and site of action.

Table 2: Mechanism and their description with example.

Mechanism	Description	Example Bioenhancers
Enzyme inhibition	Inhibition of drug-metabolizing enzymes (e.g., CYP3A4, CYP2D6), thereby reducing first-pass metabolism	Piperine, Quercetin
Efflux pump inhibition	Inhibiting P-glycoprotein (P-gp) and other transporters, allowing increased intracellular drug accumulation	TPGS, Curcumin, Capsaicin
Permeation enhancement	Enhancing GI tract or skin permeability by modulating membrane fluidity or tight junctions	Sodium caprate, Labrasol, Aloe vera extract
Solubility aenhancement	Increasing solubility/dissolution of poorly soluble drugs	Surfactants, Lipid carriers, Bile salts
Synergistic pharmacodynamic activity	Directly enhancing the pharmacological activity of the drug	Gingerols, Glycyrrhizin
Protection from degradation	Preventing degradation by enzymes or acidic pH	Cyclodextrins, Bioadhesive polymers

Many bioenhancers exhibit multiple mechanisms simultaneously, which adds to their versatility in formulations.[4]

3. Based on Target Drug Class

Bioenhancers are often used selectively with certain **classes of drugs** that have known limitations in bioavailability or metabolic instability.[11]

Table 3: Targeted drug class with their example.

Drug Class	Issue Addressed	Example Bioenhancer Use
Antibiotics (e.g., Rifampicin, Amoxicillin)	Poor oral bioavailability, rapid metabolism	Piperine, Quercetin
Antitubercular drugs	Resistance, metabolism, side effects	Piperine (R-cinex formulation)
Antiretrovirals (e.g., Zidovudine, Lopinavir)	CYP3A4-mediated metabolism	Quercetin, Curcumin, TPGS
Anticancer drugs (e.g., Paclitaxel, Doxorubicin)	P-gp-mediated efflux, poor solubility	TPGS, Curcumin, Capsaicin
NSAIDs (e.g., Diclofenac, Ibuprofen)	Gastric side effects, low solubility	Glycyrrhizin, Ginger extract

Antiepileptics (e.g., Phenytoin)	Poor absorption, variable metabolism	Piperine
Nutraceuticals (e.g., Curcumin, Resveratrol)	Extremely low bioavailability	Piperine, Lecithin

Drug classes requiring chronic administration, low dosing, or high variability benefit the most from bioenhancers.[9]

MECHANISMS OF ACTION OF BIOENHANCERS

Bioenhancers function by altering the pharmacokinetics (absorption, distribution, metabolism, and excretion) of co-administered drugs without exerting therapeutic effects of their own at effective concentrations. Their mechanisms involve interacting with drug-metabolizing enzymes, transporters, and cellular membranes, leading to increased drug bioavailability, efficacy, and safety.[4]

1. Enhanced Gastrointestinal (GI) Absorption

Many drugs face poor absorption in the gastrointestinal tract due to low solubility, poor permeability, or degradation in the gut.

Bioenhancers improve GI absorption by:

- Stimulating intestinal enzyme secretion (e.g., bile salts)
- Modulating mucosal permeability by altering tight junctions (e.g., sodium caprate)
- Reducing mucosal degradation of drugs
- Improving dissolution and wetting of poorly soluble drugs.

Example: Piperine increases the absorption of curcumin and rifampicin by increasing the residence time of drugs in the GI tract and enhancing their permeability.

Impact: Results in higher plasma drug concentration from oral administration, with improved therapeutic outcomes.[8]

2. Inhibition of P-glycoprotein (P-gp) Efflux

P-glycoprotein is an ATP-dependent efflux pump located in the apical membranes of intestinal, hepatic, and brain capillary endothelial cells. It pumps drugs out of cells, reducing their absorption and intracellular concentrations.

Bioenhancers act as P-gp inhibitors, thereby:

- Preventing drug efflux from intestinal mucosa
- Increasing drug accumulation in systemic circulation
- Enhancing penetration into the brain or target tissues.

Examples: Quercetin, Curcumin, and TPGS inhibit P-gp, enhancing the oral bioavailability of drugs like paclitaxel, doxorubicin, and lopinavir.

Impact: Critical in improving the bioavailability of anticancer, antiretroviral, and CNS drugs.[9]

3. Inhibition of CYP450 Enzymes (e.g., CYP3A4)

Cytochrome P450 (CYP) enzymes, especially CYP3A4, are responsible for the metabolism of nearly 50% of marketed drugs. These enzymes metabolize drugs in the liver and intestine, leading to first-pass metabolism.

Bioenhancers inhibit CYP enzymes, thus

- Reducing pre-systemic metabolism
- Extending half-life of the drug.

Examples: Piperine inhibits CYP3A4 and CYP2D6 enzymes, improving the bioavailability of drugs like phenytoin, theophylline, and rifampicin.

Impact: Enables lower dosages, prolonged action, and improved safety profiles.[4]

4. Modulation of Membrane Permeability

Bioenhancers improve drug transport across biological membranes by altering the fluidity and integrity of the lipid bilayer or by modifying tight junctions in epithelial layers.

Mechanisms include

- Disruption of membrane lipid packing
- Opening of tight junctions in intestinal epithelium
- Increased paracellular transport.

Examples: Sodium caprate opens tight junctions in intestinal epithelia, facilitating paracellular drug transport.

Impact: Crucial for drugs with low permeability, like peptides, macromolecules, and BCS Class III drugs.[4,6]

5. Improved Bioavailability and Pharmacokinetics

All the above mechanisms converge to result in:

- Increased Cmax (peak plasma concentration) and AUC (area under the curve)
- Improved therapeutic index
- Reduced Tmax (time to reach peak concentration) and inter-patient variability.[4]

Examples: TPGS improved oral bioavailability of paclitaxel by inhibiting P-gp and enhancing solubility.[4,6]

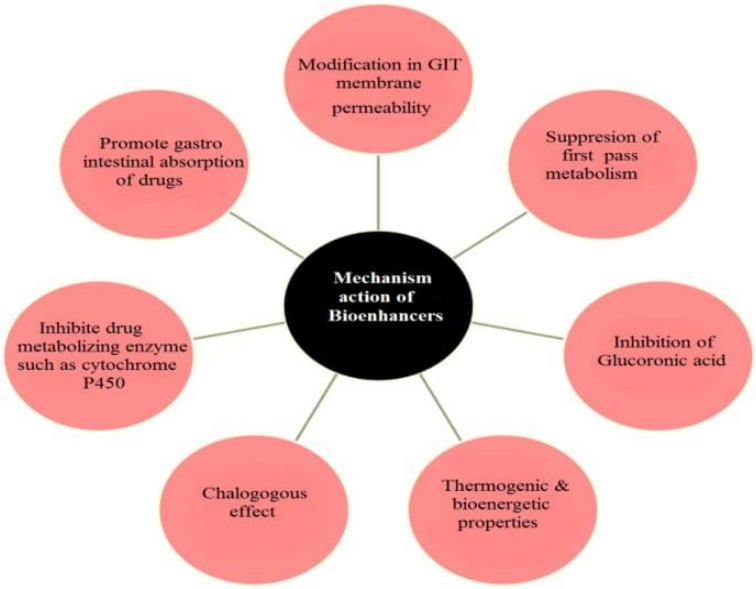

Fig. 1: Mechanism action of bioenhancers.[21]

MODES OF ACTION OF BIOENHANCERS

Several mechanisms of action are used by Bioenhancers. Nutritional Bioenhancers act on the GI tract to promote absorption. Few Bioenhancers work by inhibiting antimicrobial drugs from being metabolized.

The following are some of the proposed modes of action for Bioenhancers

- Increases the drug's bioavailability throughout the GI tract's membrane.
- The enzymes involved in drug metabolism are inhibited, lengthening the final period of action.
- By improving the effect of the drug through conformational interaction.

- They may act as self-receptor for molecules of drug.
- Active drugs are engineered so that they become responsive to their target cells of action.
- P-glycoprotein activity on the luminal membrane is inhibited.
- Increased mobility of gut brush border membrane, resulting in weakening of the physical barrier.
- Reducing the gastric acid secretion.
- Modulation of the permeability of the gastrointestinal mucosal cell membrane.
- Thermogenic and bioenergetic characteristics change.
- Renal clearance is inhibited by avoiding the presence of drug in glomerular filtration, lowering tubular secretion by P-glycoprotein inhibition, and increasing the passive tubular re-absorption.
- By Inhibiting First-pass Metabolism.
- Gamma glutamyl transpeptidase (GGT) activity is elevated, which aids in amino acid absorption.
- Therapeutic drugs bind better and longer to target areas including DNA, RNA, receptors, and proteins, potentiating and extending their therapeutic impact against microbes.[5]

EXAMPLES OF BIOENHANCERS

Bioenhancers, both from natural and synthetic origins, play a crucial role in improving the absorption, metabolism, and therapeutic efficacy of a wide range of drugs. This section highlights prominent natural bioenhancers, their sources, mechanisms of action, and real-world examples of drug–bioenhancer combinations.

1. Piperine

A key example of a bioenhancer is piperine, an alkaloid obtained from black pepper (Piper nigrum) and long pepper (Piper longum). Piperine enhances the bioavailability of various drugs and nutrients by inhibiting drug-metabolizing enzymes such as CYP3A4 and UDP-glucuronyltransferase, and by modulating intestinal membrane permeability to improve absorption. It is known to significantly increase the oral bioavailability of compounds like curcumin, rifampicin, phenytoin, and propranolol. By enhancing absorption and reducing metabolism, piperine allows for lower drug doses, improved therapeutic efficacy, reduced side effects, and potentially lower treatment costs, making it a widely recognized and valuable bioenhancer in pharmaceutical formulations.[20,19]

2. Quercetin

Quercetin, a naturally occurring dietary flavonoid found abundantly in fruits, vegetables, and leaves, functions as a bioenhancer by inhibiting metabolic enzymes like CYP3A4 and efflux transporters such as P-glycoprotein. Co-administration of quercetin with tamoxifen in animal studies significantly increased tamoxifen's plasma exposure (AUC and C□ ax) by approximately 20–60% in rats, indicating enhanced absorption and reduced first-pass metabolism. Similarly, in human volunteers, a short 7-day regimen of quercetin (500 mg three times daily) raised the AUC and C□ ax of fexofenadine by roughly 55% and 68%, respectively, by suppressing P-glycoprotein efflux in the gut. These findings highlight quercetin's potential as a natural bioenhancer that improves drug bioavailability through modulation of metabolic and transport pathways. Improves systemic availability of flavonoids, antivirals, and anti-inflammatory agents.[7]

3. Curcumin

Curcumin is the principal polyphenolic compound found in turmeric (*Curcuma longa*). Curcumin exhibits antioxidant, anti-inflammatory, and antimicrobial properties and can enhance the bioavailability of certain drugs and nutrients. It acts by inhibiting drug-metabolizing enzymes such as CYP3A4 and P-glycoprotein[13] efflux pumps, as well as by modulating cell signaling pathways and improving intestinal absorption. Curcumin has been shown to increase the effectiveness of antibiotics, anticancer agents, and other therapeutic compounds, making it a valuable natural bioenhancer in both traditional and modern medicine.[14,16]

4. Gingerols (from Ginger)

Gingerols is the pungent phenolic compounds found in fresh ginger (Zingiber officinale). Gingerols enhance the bioavailability of drugs and nutrients by stimulating gastrointestinal motility, increasing gastric and pancreatic secretions, and improving intestinal blood flow, which together promote better absorption. They also inhibit certain drug-metabolizing enzymes and P-glycoprotein efflux pumps, reducing drug elimination. Gingerols have been reported to enhance the therapeutic effects of antibiotics, anticancer agents, and anti-inflammatory drugs, making them an important natural bioenhancer in both herbal and pharmaceutical applications.[18]

5. Naringenin

Naringenin is a flavonoid commonly found in citrus fruits such as grapefruit and oranges. Naringenin enhances the bioavailability of various drugs by inhibiting drug-metabolizing enzymes like CYP3A4 and drug transporters such as P-glycoprotein, thereby reducing drug breakdown and efflux. It also improves intestinal absorption by modulating membrane permeability. Naringenin has been shown to boost the therapeutic effectiveness of antibiotics, anticancer agents, and cardiovascular drugs, making it a valuable natural bioenhancer in pharmaceutical formulations.[18]

6. Other Noteworthy Bioenhancers

Table 4: Bioenhancers with their application.

Bioenhancer	Source	Application
Glycyrrhizin	*Glycyrrhiza glabra* (Licorice)	Enhances uptake of hydrophilic drugs, inhibits liver enzymes
Capsaicin	*Capsicum* species	Inhibits P-gp and enhances brain uptake
Sodium caprate	Synthetic fatty acid salt	Opens tight junctions in intestinal epithelium
TPGS (Vitamin E derivative)	Synthetic	Surfactant, inhibits P-gp, used in cancer formulations[7,18]

Case Studies of Drug–Bioenhancer Combinations[15]

Table 5: Drug bioenhancer combination and their outcome.

Drug	Bioenhancer	Outcome
Curcumin	Piperine	↑ Bioavailability by ~2000%, enhanced anticancer activity[10,16]
Rifampicin	Piperine	↑ Absorption in TB treatment, reduced resistance
Paclitaxel	TPGS / Quercetin	↑ Bioavailability and tumor targeting, ↓ resistance
Zidovudine	Quercetin	↓ Metabolism, ↑ systemic exposure
Ibuprofen	Gingerols	↓ GI side effects, ↑ absorption
Atorvastatin	Naringenin	↑ Plasma concentration and cholesterol-lowering effect

PHARMACEUTICAL APPLICATION OF BIOENHANCERS

Bioenhancers have shown transformative potential in modern pharmaceutical development by improving drug efficacy, optimizing formulations, and enhancing therapeutic outcomes. Their application spans from innovative dosage forms to cost-effective therapies, and even integrates traditional medicinal systems into mainstream practice.

1. Formulation Development

Bioenhancers are now widely incorporated into advanced pharmaceutical formulations to improve drug absorption and therapeutic efficiency. In formulation development, bioenhancers are incorporated to improve the absorption and bioavailability of poorly available drugs without modifying their chemical structure. They are used in tablets, capsules, suspensions, and novel drug delivery systems to overcome barriers such as poor solubility, rapid metabolism, and efflux by transport proteins. Examples include adding piperine to curcumin formulations or antibiotics to boost their therapeutic effect. This approach allows for lower drug doses, reduced side effects, enhanced patient compliance, and cost-effective treatment.

Impact: Enhances drug delivery performance, especially for Biopharmaceutical Classification System (BCS) Class II and IV drugs.[2]

2. Fixed-Dose Combinations (FDCs)

In fixed-dose combinations (FDCs), bioenhancers are included alongside the active drug to increase its bioavailability and therapeutic effect. By inhibiting drug-metabolizing enzymes or efflux transporters, bioenhancers like piperine or gingerols help the main drug reach higher and sustained plasma levels. This allows for lower doses, reduced dosing frequency, and fewer side effects. FDCs with bioenhancers are especially useful in tuberculosis therapy (e.g., rifampicin with piperine) and nutraceutical formulations (e.g., curcumin with piperine), improving treatment efficacy and patient compliance.

Impact: Supports treatment compliance, dose simplification, and improved clinical outcomes in chronic and infectious diseases.[2,22]

3. Dose Reduction

In dose reduction applications, bioenhancers are used to increase a drug's bioavailability so that the same therapeutic effect can be achieved with a lower dose. By improving absorption, reducing metabolism, or preventing drug efflux, bioenhancers like piperine, naringenin, and gingerols allow for significant dose minimization. This not only lowers the risk of side effects and toxicity but also reduces treatment costs and improves patient compliance, making therapies safer and more economical.

Impact: Especially valuable in resource-limited settings and for long-term therapies.[10]

4. Bioenhancers in Herbal/Traditional Medicine Systems

In traditional medicine systems, bioenhancers are used to potentiate the effects of herbal and natural remedies. Ayurveda first documented this concept in 1979 with the discovery of piperine from Piper longum as a "yogavahi" (synergistic agent) that enhances the absorption and action of other herbs and drugs. In traditional formulations, bioenhancers like piperine, gingerols, and naringenin are combined with medicinal plants to improve their therapeutic efficacy, reduce required doses, and minimize side effects. This practice is common in Ayurvedic, Unani, and Traditional Chinese Medicine to maximize the benefits of herbal preparations.

Impact: Bridges traditional knowledge with modern drug delivery systems, promoting holistic and evidence-based phytotherapy.[1,22]

5. Use in Poor Bioavailability Drugs

In the poor bioavailability drug application, bioenhancers are used to improve the absorption and effectiveness of drugs that are poorly soluble, rapidly metabolized, or actively effluxed from the body. By inhibiting metabolizing enzymes (e.g., CYP3A4) or transport proteins (e.g., P-glycoprotein), and by increasing intestinal permeability, bioenhancers like pipe1rine with curcumin or naringenin with certain antibiotics can significantly raise plasma drug levels. This results in better therapeutic outcomes, reduced doses, and improved patient compliance for drugs that otherwise show limited bioavailability.

Impact: Improves the success rate of formulations with poor pharmacokinetics, and supports repurposing of challenging APIs.[22]

CURRENT TRENDS IN BIOENHANCERS RESEARCH

As drug development advances toward more complex therapeutic challenges—including poor solubility, drug resistance, and biological targeting—the role of bioenhancers is evolving beyond traditional formulations. Current research focuses on novel delivery systems, integration with biologics, and personalized treatment strategies to enhance therapeutic outcomes.

1. Nanotechnology and Bioenhancer-Loaded Nanoparticles

Nanotechnology and bioenhancer-loaded nanoparticles represent a current trend in bioenhancer research aimed at overcoming the limitations of poorly bioavailable drugs. In

this approach, bioenhancers such as piperine, curcumin, or naringenin are incorporated into nanoparticles, liposomes, nanoemulsions, or solid lipid nanoparticles to improve their stability, solubility, and targeted delivery. These nanoformulations can provide controlled release, protect bioenhancers from degradation, and enhance their interaction with intestinal membranes, further boosting drug absorption. This strategy is increasingly explored for anticancer agents, antibiotics, and nutraceuticals, offering higher efficacy, reduced doses, and improved patient compliance in modern pharmaceutical development. Co- loading of drug and bioenhancer in Solid lipid nanoparticles (SLNs), Polymeric nanoparticles, Nanostructured lipid carriers (NLCs), Liposomes and micelles.[28]

2. Use in Biologics and Vaccines

In current bioenhancer research, use in biologics and vaccines focuses on improving the stability, absorption, and immune response of large, complex molecules. Bioenhancers such as saponins, piperine, and flavonoids are being investigated to increase the permeability of biological membranes, protect biologics from enzymatic degradation, and enhance antigen presentation in vaccines. In vaccine formulations, certain bioenhancers act as adjuvants, boosting the body's immune response and enabling lower antigen doses. This trend is particularly important for oral biologics, mRNA vaccines, and protein-based therapeutics, where delivery efficiency is a major challenge.[23]

3. Bioenhancers in Targeted Drug Delivery Systems

In current research, bioenhancers in targeted drug delivery systems are being explored to improve the site-specific delivery and bioavailability of drugs while minimizing systemic side effects. Bioenhancers such as piperine, quercetin, and gingerols are incorporated into liposomes, nanoparticles, micelles, and ligand-conjugated carriers to increase permeability, inhibit drug efflux pumps, and protect drugs from premature metabolism. When combined with targeted delivery systems, bioenhancers can ensure that a higher concentration of the active drug reaches the intended tissue or organ, which is particularly valuable in oncology, neurological disorders, and infectious diseases, leading to enhanced efficacy with reduced doses.[23]

4. Co-inhibition Use with Drug Resistance Modulators

In current research, bioenhancers in targeted drug delivery systems are being explored to improve the site-specific delivery and bioavailability of drugs while minimizing systemic side effects. Bioenhancers such as piperine, quercetin, and gingerols are incorporated into

liposomes, nanoparticles, micelles, and ligand-conjugated carriers to increase permeability, inhibit drug efflux pumps, and protect drugs from premature metabolism. When combined with targeted delivery systems, bioenhancers can ensure that a higher concentration of the active drug reaches the intended tissue or organ, which is particularly valuable in oncology, neurological disorders, and infectious diseases, leading to enhanced efficacy with reduced doses.[28]

5. Personalized Medicine and Pharmacogenomics Considerations

In current bioenhancer research, personalized medicine and pharmacogenomics are increasingly considered to optimize drug therapy. Bioenhancers like piperine, naringenin, and curcumin can modulate drug-metabolizing enzymes (e.g., CYP450) and transporters (e.g., P-glycoprotein), but their effects may vary depending on a patient's genetic profile. By integrating pharmacogenomic data, formulations can be tailored to individual metabolic capacities, maximizing drug absorption and efficacy while minimizing adverse effects. This trend supports precision medicine, allowing bioenhancer-based therapies to be customized for specific patient populations for improved safety and therapeutic outcomes.[27,28]

CHALLENGES AND LIMITATIONS OF BIOENHANCERS

While bioenhancers offer significant advantages in pharmaceutical development, their integration into mainstream therapy is limited by several scientific, regulatory, and practical challenges. Understanding these limitations is crucial to guide future research and ensure safe, effective application in clinical settings.

1. Regulatory Concerns and Lack of Standardized Guidelines

There is no globally unified regulatory framework specific to bioenhancers. Regulatory bodies like FDA, EMA, and CDSCO often lack dedicated classification or approval pathways for bioenhancers unless they are part of a combination product or excipient. Often classified inconsistently as excipients, herbal additives, or actives, creating ambiguity during formulation approval. Difficulty in proving bioenhancer-specific contribution in combination products adds complexity during regulatory submissions. Since bioenhancers are often natural compounds or herbal extracts, their composition, purity, and potency can vary, making it difficult to ensure consistent quality. There is limited regulatory guidance on their evaluation, safety, dosage, and interaction with other drugs, which complicates their approval in pharmaceutical formulations.[30]

2. Toxicity and Safety Evaluation

Despite their natural origin, not all bioenhancers are inherently safe—especially at higher doses or with long-term use. Piperine, curcumin, and capsaicin have shown dose-dependent hepatic, gastrointestinal, and neurological toxicities in some animal models. Lack of comprehensive toxicological profiling, especially when bioenhancers are combined with synthetic drugs. Although many bioenhancers, such as piperine or curcumin, are derived from natural sources, they can interact with drug-metabolizing enzymes and transporters, potentially leading to unintended drug accumulation, toxicity, or adverse effects. Comprehensive preclinical and clinical safety studies are often limited, and there is a lack of standardized protocols for evaluating long-term effects, dose limits, and interactions with multiple drugs. These uncertainties make it difficult to fully predict their safety profile, posing a significant limitation for their incorporation into pharmaceutical formulations and therapeutic regimens.[30]

3. Variable Response Among Individuals

:Genetic polymorphisms in CYP450 enzymes and efflux transporters (e.g., P-gp) significantly affect individual response to bioenhancers. Age, sex, diet, microbiota, disease state, and co-medications further contribute to interindividual variability. Risk of drug–bioenhancer interactions due to altered metabolism in susceptible individuals. For example, the effect of piperine or naringenin on drug-metabolizing enzymes and transporters may vary, leading to differences in drug absorption, efficacy, and potential toxicity. This inter-individual variability complicates dose standardization and makes it difficult to predict therapeutic outcomes reliably, limiting the universal application of bioenhancers in pharmaceutical formulations.[30]

4. Limited Clinical Trials

Most bioenhancer data are derived from in vitro or preclinical studies. Very few well-designed, large-scale clinical trials confirm their efficacy and safety in humans. Lack of clear clinical endpoints and surrogate biomarkers makes it difficult to attribute improved outcomes specifically to the bioenhancer. This limitation makes it difficult to determine optimal dosing, long-term safety, drug interactions, and efficacy in diverse populations. Without sufficient clinical evidence, regulatory approval and adoption in pharmaceutical formulations remain constrained, slowing the translation of promising bioenhancer research into safe and effective therapies.[30]

5. Stability and Compatibility in Formulations

Many bioenhancers (e.g., curcumin, quercetin) are chemically unstable, especially under heat, light, or pH changes. Potential for incompatibility with APIs or excipients in multi-drug formulations. May interfere with drug release kinetics or disrupt formulation integrity. Stability and compatibility in formulations are significant challenges for bioenhancers. Many bioenhancers, such as curcumin, piperine, and gingerols, are chemically unstable, sensitive to light, heat, and oxidation, which can reduce their effectiveness over time. Additionally, they may interact with other formulation components, including excipients or active drugs, leading to reduced bioavailability, precipitation, or degradation. Ensuring consistent stability, solubility, and compatibility in pharmaceutical products requires careful formulation design, specialized delivery systems, or protective carriers like nanoparticles or liposomes, which can increase development complexity and cost.[24]

USES OF BIOENHANCERS

1. Piperine is marketed as mono-preparation bio enhancer and as a constituent of nutritional additive that contain different vitamins, curcumin resveratrol or coenzymes.
2. Since bio enhancers can reduce the dosage and cost of expensive medication while making treatment safer, in humans first time its application has been done in treating TB for which the existing drugs are toxic and expensive and they are administered for longer period.
3. Techniques of bio enhancers is principally targeted the toxic drugs, expensive drugs, rare drugs, poorly bioavailable drugs and the drugs which are used for longer duration.
4. In addition, there are studies reporting clear evidence of improvement of oral absorption and bioavailability of HMPs (Herbal Medicinal Products) by concomitant use of bioenhancers.[29]

FUTURE DIRECTIONS

As the pharmaceutical landscape continues to evolve, bioenhancers are poised to play a transformative role in optimizing drug delivery, improving access to healthcare, and personalizing therapies. Several promising avenues are being explored to expand the scope, precision, and impact of bioenhancer applications.

1. Synthetic Bioenhancer Design Using Computational Tools

With the advent of in silico technologies, the rational design of synthetic bioenhancers is gaining momentum.

Emerging Strategies

- Use of computational modeling, molecular docking, and QSAR (Quantitative Structure–Activity Relationship) to design bioenhancers that can:
  - Inhibit specific metabolic enzymes (e.g., CYP3A4)
  - Interact with transporter proteins (e.g., P-gp, BCRP)
  - Enhance membrane permeability
- Development of structure-activity optimized analogs of natural bioenhancers (e.g., synthetic piperine derivatives).[25,28]

2. Clinical Validation Through Large-Scale Studies

For bioenhancers to gain regulatory and clinical acceptance, robust clinical trial data is essential.

Future Clinical Focus

- Desgning randomized controlled trials (RCTs) to validate bioenhancer efficacy and safety
- Exploring dose–response relationships
- Establishing biomarkers and pharmacokinetic endpoints
- Long-term safety studies for chronic co-administration.

3. Integration with Nanocarriers, Liposomes, and Micelles

Bioenhancers are being incorporated into advanced drug delivery systems (DDS) to overcome solubility and permeability barriers.

Focus Areas:

- Co-loading of drugs and bioenhancers in:
  - Liposomes, Micelles, Solid lipid nanoparticles (SLNs).

4. Use in Global Health to Reduce Drug Dosage and Costs

Bioenhancers hold strategic value in public health by:

- Lowering drug doses needed to achieve therapeutic effects
- Reducing treatment costs, especially for high-priced or chronic medications
- Making therapy more accessible in low- and middle-income countries (LMICs).

5. Exploration of Novel Natural Compounds as Bioenhancers

Nature remains a vast untapped resource for discovering new bioenhancers.

- High-throughput screening of herbal extracts and marine organisms

- Ethnopharmacological studies to identify traditional plant-based enhancers
- Phytochemical isolation and structure elucidation of novel compounds.[17]

CONCLUSION

We can conclude that one of the major methods or tools to increase bioavailability of poorly bioavailable drugs is the use of Bioenhancers. Bioenhancers is a fresh and original concept that is rooted on the ancient and traditional structure of Indian medicine. They result in lower treatment costs, toxicity, and side effects. Further more, they are simple to produce, acquire, are cost-efficient, safe, non-addictive, and effective, and have a variety of uses.

Bioenhancers have emerged as a powerful and versatile class of agents in pharmaceutical science, offering significant benefits in improving the bioavailability, efficacy, and safety of therapeutic drugs. Originally rooted in traditional medicine, the concept of bioenhancement has evolved into a scientifically validated and technologically advanced strategy to address long-standing challenges in drug delivery.

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