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# DRUG DELIVERY TECHNOLOGY

## HERBAL BIOENHANCERS IN PHARMACEUTICALS

*Edited by Prashant L. Pingale*

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# Chapter 11
# Future perspectives of herbal bioenhancer

Abstract: Bioenhancers or drug facilitators are excipients that when added with therapeutically active agents improve their absorption, permeation, solubility, and bioavailability. Nowadays, bio-enhancers have secured a significant position in drug delivery research and applications as they help in the reduction of dose, toxicity, and drug resistance, as also improve potential use of drugs. Bioenhancers of herbal origin have gained special attention as they are ecologically safe, inexpensive, easily solicited, non-obsessive, pharmacologically dormant, and nonallergenic nature. In the last five years, many reports have been published claiming cheaper, safe, and good bioavailability of chemotherapeutic drugs, when used in combination with natural bioenhancers. At the same time, a few reports have also shown no change in pharmacokinetic parameters, which might be due to the rapid metabolism of bioenhancer or different target sites of active pharmaceutical ingredients. However, almost 60–65% of findings showed improvement in pharmacokinetic/pharmacodynamic parameters, and some of them are in clinical trial. This chapter aims to compile literature on the future perspective of herbal bioenhancers. For this purpose, information related to their novel delivery approaches such as liposomes, transfersomes, ethosomes, and nanoparticles have been described. The ecological benefits of these bioenhancers are discussed, along with several examples. Further, their applications in a different category of diseases including viral diseases, cancer, tuberculosis, ocular diseases, and gastrointestinal problems are compiled. Advances in bioenhancers have also raised challenges in regulatory control. Therefore, a brief of regulatory aspects of using herbal bioenhancers is also discussed in this chapter.

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## 11.1 Introduction

The concept of bioenhancer was derived from Trikatu, which means three acrids, mentioned in traditional Ayurveda . These three agents were long pepper, black pepper, and ginger, which were used in a combination for treating different ailments. The role of bioavailability enhancers was first identified by Bose in 1929. He reported the role of long pepper when administered with adhatodavasaka leaves in increasing its activity [1, 2]. However, in 1979, the world's first bioenhancer was discovered by an Indian scientist in Jammu at the Indian Institute of Integrative Medicine, formerly Regional Research Lab. He discovered the role of piperine as a bioavailability enhancer, at that time. After getting the international patent and completion of phase IIIb clinical trials, the Drug Control General of India (DCGI) granted the license to the market drug "Risorine" in India, to be used for antituberculosis treatment. The formulation contains 300 mg of isoniazid (INH), 200 mg of rifampicin, and 10 mg of piperine [3]. Similarly, the herbal *Carum carvi* L. was found to be a good bioenhancer and modifies the kinetics of antitubercular treatment, favorably [4]. Piperine was also found to boost the curcumin serum levels, absorption, and bioavailability in humans and rodents with minimal toxicity [5]. Curcumin's pleiotropic properties are due to its capacity to affect a variety of signaling molecules. Curcumin's safety, tolerability, and nontoxicity at large doses have all been proven in human clinical trials. Curcumin has been shown to have therapeutic potential against a wide range of human ailments when administered alone or in combination with other medicines [6].

After this progress, the Ayurveda concept of bioenhancers has merged with synthetic medicines for many other benefits besides bioavailability enhancing. To date, there are many unexplored areas of bioenhancers. These include interaction with active molecules, possible mode of actions, possible combinations with other therapeutic agents, their clinical outcomes, and evaluation of toxicity. Hence, exploring novel bioenhancers with versatile mechanisms and fewer side effects is the need of the hour [7].

## 11.2 Application of different herbal bioenhancer

### 11.2.1 Bioavailability/bioefficacy-enhancing activity

To gain the maximum therapeutic efficacy of any drug, bioavailability should be maximized, because the extent of bioavailability immediately impacts plasma concentrations. Therefore, for years, the development of a product with maximum bioavailability has been of utmost interest, as most of them have unwanted poisonous or aspect results, are expensive, and require frequent administration as well as extensive management.

However, bioavailability enhancement by replacing the principal therapeutic agent with a secondary agent has gained extensive recognition. However, as per data from Ayurvedic literature, the usage of herbal bioenhancers as a secondary agent is a very good option for increasing the bioavailability of poorly soluble drugs [8].

By enhancing bioavailability, highly priced tablets may become less expensive and decrease in the toxic outcomes by reducing the specified dose of medicine may be possible. Poorly bioavailable capsules remain subtherapeutic because a first-rate part of a dose never reaches the plasma or exerts its pharmacological impact, except when very huge doses are given, which can also lead to severe side effects. Any big development in bioavailability will result in reducing the dose or the dose frequency of that unique drug. Intersubject variability is a special concern for a drug with a narrow safety margin. Incomplete oral bioavailability includes bad dissolution or low aqueous solubility, terrible intestinal membrane permeation, degradation of the drug in gastric or intestinal fluids, and presystemic intestinal or hepatic metabolism. Many healing treatments are also accompanied by a lack of essential nutraceuticals within the direction of therapy. Bioenhancers improve nutritional status through growing bioavailability/bioefficacy of diverse nutraceuticals, which includes metals and nutrients [9].

Bioavailability enhancement may be accomplished by many mechanisms, together with promoting the absorption of the medication, inhibiting or decreasing the charge of biotransformation of medication in the liver or intestines, modifying the signaling method among host and pathogen, making sure elevated accessibility of the medication to the pathogens, while adjusting the immune response in a manner that the general requirement of the drug is decreased considerably. Besides the above mechanisms, bioenhancers are also useful for promoting the transport of nutrients and medication across the blood-brain barrier, which is essential in many cases including different central nervous system (CNS) disorders, cerebral infections, and epilepsy.

Fundamental classes of medicine that have shown increased bioenhancement encompass respiratory, cardiovascular, gastrointestinal tract, CNS, antibiotics, and anticancer. Some examples include sulfadiazine, tetracyclines, phenobarbitone, rifampicin,vasicine, ethambutol, pyrazinamide, nimesulide, phenytoin, dapsone, carbamazepine, coenzyme Q 10, indomethacin, β-carotene, amino acids, ciprofloxacin glucose, curcumin, and numerous other medicines [10].

## 11.2.2 Antitubercular and antileprotic drugs

As mentioned earlier, the first reported bioenhancer, piperine, was employed in the treatment of tuberculosis in humans. Rifampicin is one of the first-line drugs for the treatment of both tuberculosis and leprosy. But this drug was effective in a much higher dose due to low bioavailability and, therefore, exhibited toxicity. After

combining piperine with this drug, the dose profile ( from 450 to 200 mg) was reduced along with the treatment period. Further, the bioavailability of rifampicin was increased by 60%. Rifampicin inhibits the transcription of the polymerase by acting on RNA polymerase in human cells, which is being catalyzed by *Mycobacterium smegmatis*. Piperine enhanced this inhibition activity of RNA polymerase, several folds. It also arouses the binding capacity of rifampicin in resistant strains of bacteria [11, 12].

### 11.2.3 Medical adjuvants for antibiotics/chemotherapy

Nowadays, the use of antibiotics and antimicrobials has highly increased; therefore, the problem of drug resistance and addiction has increased. Hence, a high dose of such drugs is required for exerting the same therapeutic effect due to reduced drug absorption and resisting efflux pumps.

Despite advances in the field of pharmacology and traditional chemistry, the production of novel synthetic antibiotics, modification of antimicrobial compounds, and identification of appropriate enzyme targets for inhibitor development, current worldwide medicate advancement endeavors may not be sufficient to supply spearheading antimicrobials for the coming decade [13]. Given the rise in acquired resistance to traditional antibiotics, it makes sense to attempt mixing traditional antibiotics with bioenhancing plant extracts to achieve antimicrobial synergism [14]. The use of such a conventional and herbal combination therapy against hard-to-eradicate bacteria may open up newer avenues for infectious disease treatment. Combination therapy may be used to broaden the antimicrobial spectrum, prevent resistant mutants from emerging, and reduce side effects [15].

The use of bioenhancer along with the main drug has led to increased bioavailability and minimized drug dosage. Piperine, the main alkaloid found in the plant's black piper (*Piper nigrum* Linn) and long pepper (*Piper longum* Linn) are well known for increasing bioavailability and, hence, improving medication and nutraceutical efficacy, in addition to being an efflux pump inhibitor [16–19]. Piperine used in the antituberculosis medicine "Risorine," has shown evidence of increasing bioavailability [20]. The studies explored the anticancer and cancer-protective activity of a piperine-free *P. nigrum* extract against breast cancer cells. The resistance of cancer cells to multiple chemotherapeutic agents and the side effects of some agents pose a problem for the successful treatment of breast cancer. Currently, the progress of multidrug resistance (MDR) is a major problem to chemotherapy. Over a long-term treatment, several patients suffer from MDR, which can decrease therapeutic efficiency and lead to treatment failure and a decrease chance of survival. Therefore, the search for new potent chemotherapeutic agents from natural compounds is one way to detect new compounds for cancer treatment [21]. Piperine

also reduced the cytotoxic aflatoxins by inhibiting CYP-P450 enzyme, which activates mycotoxins into harmful products [22].

Numerous medicinal plants have served as anticancer resources, and over 60% of current anticancer drugs, such as *topotecan, vinblastin*, *paclitaxel*, and *etotecan* are plant-derived compounds [23–25].

Antibiotics and an ethanolic extract of *Ficus exasperata* leaf have been shown to have synergistic efficacy against *E. coli* and *Staphylococcus albus* [26]. The harmful effects of an increasing number of mutagenic and environmental carcinogens can be prevented or minimized by using herbal bioenhancers. The antimutagenic properties of tulsi (*Ocimum tenuiflorum*) [27]; Haldi (*Curcuma longa*) [28]; amla (*Phyllamentus embelica*) [29]; and neem (*Azadirachta indica*) [30] have been scientifically established. These promising antimutagenic herbals could be applied to bacteria to prevent spontaneous mutations, thereby reducing bacterial antibiotic resistance. Certain Ayurvedic preparations such as Brahma Rasayana and Amalaki Rasayana have been shown to enhance the DNA repair mechanism [31, 32]. These preparations could be applied to counteract the spontaneous or induced mutations in bacteria. Another report revealed enhanced bioavailability for Nevirapine drug was found when combined with piperine. Nevirapine, a nucleoside inhibitor, is used with other antiretroviral agents for the treatment of HIV-1 [33].

### 11.2.4 Cardiovascular disease

Breviscapine, a familiar bioactive flavonoid extracted from traditional medicine, has been widely used in ischemic cerebrovascular and cardiovascular diseases, to prolong the duration of the drug in the circulation, reduce the frequency of injection administration, and subsequently afford patient compliance [34].

*Ginkgo biloba* phytosomes (GBP): It exhibits significant cardioprotective activity by lowering the levels of serum marker enzymes and lipid peroxidation and elevating the levels of catalase, glutathione, glutathione peroxidase, superoxide dismutase, and glutathione reductase [35].

### 11.2.5 Anti-inflammatory action

Triptolide (TP): It has been shown to have anti-inflammatory, antineoplastic, antifertility, and immunosuppressive activity. However, its clinical use was limited due to some serious toxicity. The mechanism for triptolide-induced hepatotoxicity was related to reactive oxygen species (ROS)-inducing lipid peroxidation and DNA damage.

Glycyrrhizic acid: It is a triterpene glycoside that possesses a wide range of biological and pharmacological activities. When extracted from the plant, it can be obtained

in the form of mono-ammonium glycyrrhizin and ammonium glycyrrhizin. Glycyrrhizic acid has been used in China and Japan as a hepatoprotective drug in cases of chronic hepatitis and it shows anti-inflammatory action [36].

### 11.2.6 Nutraceuticals

Bioenhancer has wide applications in the nutrition field in enhancing the absorption and bioavailability of foods or nutrients by acting on the gastrointestinal tract. As per a reported clinical study, the herbal bioenhancer, piperine, can increase the bioavailability of vitamins against placebo by 50–60%. Data suggested the reported mechanism is owing to the thermogenic properties of piperine [3, 37].

## 11.3 Recent advances of bioenhancers

### 11.3.1 Bioenhancer: piperine

Drug: 18β-glycyrrhizic acid

Delivery system: transdermal patches

Alsaad et al. prepared and evaluated patches of glycyrrhizic acid with a synthetic polymer, carbopol 934. It was a reservoir-type patch in which they used piperine as a bioenhancer. The result showed that the patch containing herbal bioenhancer had tremendous potential as compared to those without bioenhancer [38].

### 11.3.2 Bioenhancer: piperine

Drug: celecoxib

Delivery system: oral delivery

Srivastava et al. worked on the colon cancer cells to study the synergistic antiproliferative effect of piperine with celecoxib. They reported that, by using bioenhancer, oral bioavailability increased to 129%. Further, this formulation was expressively cytotoxic to HT-29 cells. They suggested it is a novel approach for the treatment of colon cancer [39].

### 11.3.3 Bioenhancer: *Artemisia annua* L

Drug: vancomycin, erythromycin, chloramphenicol and kanamycin

Delivery system: oral delivery
Rolta et al. worked on *A. annua* as bioenhancer with different antibacterial and antifungal agents to overcome the drug resistance. They found a methanolic extract of artemisia had a greater antioxidant effect as compared to petroleum ether extract. In an antimicrobial study against *Candida* strains, both the extracts produced potent inhibitory action as compared to plain drugs [40].

### 11.3.4 Bioenhancer: *Dunaliella salina* (*D. salina*)

Drug: β-carotene

Delivery system: oral delivery
El-Baz et al. developed oral tablets of *D. salina* powder by direct compression technique by using a novel solubilizer, Sepitrap™ 80, and crospovidone. Both these solubilizers and crospovidone helped in reducing the disintegration time and enhanced the dissolution rate of β-carotene. The authors found that the tablets of *D. salina* powder had a promising antifibrotic potential in rats [41].

### 11.3.5 Bioenhancer: naringin

Drug: resveratrol

Delivery system: oral delivery
Chakraborty et al. worked on a combination of resveratrol and naringin, which exhibited intense protection against ischemia injury-induced myocardial toxicity, as compared to resveratrol alone. Both the results of pharmacokinetic and pharmacodynamics were satisfactory [42, 43].

### 11.3.6 Bioenhancer: piperine

Drug: silybin

Delivery system: oral delivery
Bi et al. demonstrated the potential of piperine as a bioenhancer with silybin. This product boosted the therapeutic effect in a liver-injured rat model. Piperine enhanced

the absorption of silybin and inhibited the biliary excretion in sandwich-cultured rat hepatocytes. Further, they mentioned piperine did not affect the phase-2 metabolism of silybin [44].

## 11.4 The future of bioenhancers

### 11.4.1 Bioenhancing activity through different routes of drug administration

The bioavailability can be increased by different mechanisms including increasing the polarity of the drug through chemical modification, prodrug formation, film coating, targeted delivery, encapsulation in suitable delivery systems, micro or nanosization, etc. The mechanism of drug and bioenhancer, when administered through different routes, is summarized in Figure 11.1.

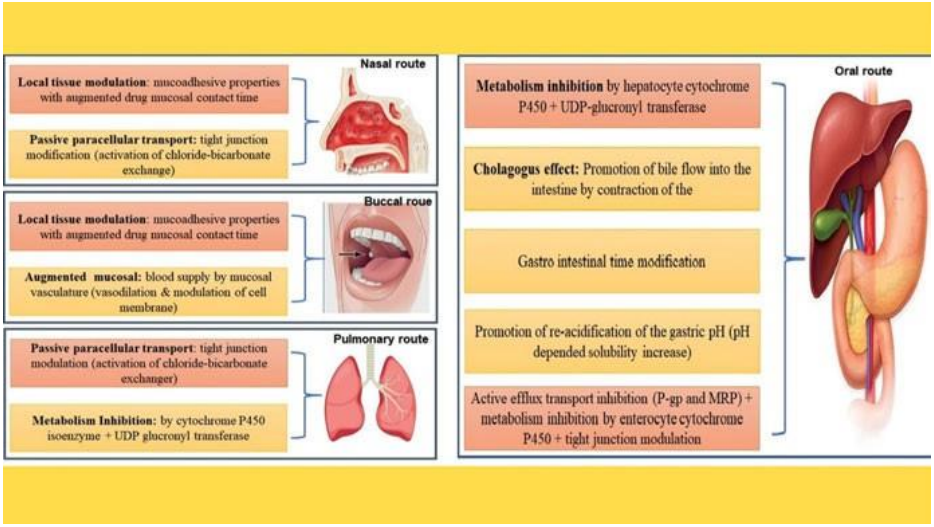


Figure 11.1: Illustration of the main mechanisms of action of bioenhancers for different routes of drug delivery.

### 11.4.2 New drug delivery systems for traditional bioenhancer

Table 11.1 depicts numerous examples of drugs and bioenhancers in different dosage forms for delivering through different routes [45-62].

Many researchers have worked on new delivery systems for entrapping bioavailability enhancers of herbal origin from a different route. New drug delivery systems like liposomes, nanoparticle, transferosomes, and many others are reported to increase the bioavailability of traditional bioenhancer. A few important examples are summarized here. Catechins liposome when delivered through the transdermal route increased permeation through the skin. It was prepared by the rotary evaporation sonication method with an encapsulation efficiency 93.0 ± 0.1%. When delivered through oral route, the water solubility of flavonoids and lignans nanoparticles, was increased. These nanoparticles were prepared by the nanosuspension method with 90% encapsulation. Flavonoid was entrapped in phytosomes for antioxidant activity by phospholipids complexation and also stabilized the ROS, when given by subcutaneous route. Similarly, when curcumin was entrapped in phytosomes, it increased antioxidant activity and bioavailability through the oral route. However, to date, many other novel delivery systems are unexplored for their efficiency in delivering bioenhancers. More researches should be focused on this area as it hasa wide scope of applications [63].

Table 11.1: Delivery of drugs by using natural bioenhancers through different routes.

| S. no. | Bioenhancer (class) | Research compound | Mode of action | Study design model | References |
|---|---|---|---|---|---|
| | | | Intranasal route for delivery of drugs with bioenhancer | | |
| 1. | Aloe vera (plant) | Didanosine | Intercellular modulation | *In vitro* (Franz diffusion cells) | [45] |
| 2. | Chitosan (deacetylated chitin) | FITC-dextran | Mucoadhesion; changes in lipid organization | *In vitro* (T146 cells 1) | [46] |
| 3. | Chitosan (deacetylated chitin) | Corticosteroid | Mucoadhesion | *In vivo* (pig), ex vivo (porcine buccal mucosa) | [47] |
| 4. | Cod-liver oil extract (cod fish) | Ergotamine tartrate | No mechanism specified | *Ex vivo* (hamster cheek pouch) | [48] |
| 5. | Oleic acid (cod fish) | Insulin | No mechanism specified | *In vitro* (dissolution test), *in vivo* (rat) | [49] |
| | | | Oral route for delivering drugs with bioenhancer | | |
| 1. | Aloe vera | Atenolol | Tight junction modulation | *Ex vivo* (rat intestinal tissue) | [50] |

Table 11.1 (continued)

| S. no. | Bioenhancer (class) | Research compound | Mode of action | Study design model | References |
|---|---|---|---|---|---|
| | | Oral route for delivering drugs with bioenhancer | | | |
| 2. | Caraway | Rifampicin, isoniazid, pyrazinamide | Local mucosal tissue modulation | *In vivo* (human) | [51] |
| 3. | Curcumin | Midazolam | Efflux transporter inhibition; CYP3A4 inhibition | *In vivo* (rat) | [52] |
| 4. | Emodin | Digoxin | Efflux transporter inhibition | *In vitro* (MDR1-MDCKII cells 6, Caco-2 cells2 | [53] |
| 5. | Gallic acid ester | Nifedipine | CYP3A metabolism inhibition | *In vitro* (human liver microsomes) | [54] |
| | | Buccal route for delivering drugs with bioenhancer | | | |
| 1. | Chitosan | Endogenous polypeptide hormone | Tight junction modulation | *In vivo* (sheep) | [55] |
| 2. | Chitosan | Morphine | Increased mucoadhesion | *In vivo* (sheep, human) | [56] |
| 3. | Chitosan–TBA (thiolated polymer | Insulin | Increased mucoadhesion | *In vivo* (rat) | [57] |
| 4. | TMC (chemically modified chitosan) | Mannitol, a sugar alcohol | Tight junction modulation, increased mucoadhesion | *In vivo* (rat) | [58] |
| | | Pulmonary route for delivering drugs with bioenhancer | | | |
| 1. | Aprotinin, bestatin (protease inhibitors) | Granulocyte-colony stimulating factor | Metabolism inhibition | *In vivo* (rat) | [59] |
| 2. | Chitosan (chemically modified biopolymer) | Somatostatin analog | Tight junction modulation | *In vitro* (Calu-3 cells 5); in vivo (rat) | [60] |

Table 11.1 (continued)

| S. no. | Bioenhancer (class) | Research compound | Mode of action | Study design model | References |
|---|---|---|---|---|---|
| | Pulmonary route for delivering drugs with bioenhancer | | | | |
| 3. | Citric acid (chelating agents) | Insulin | metabolism inhibition | *In vivo* (rat) | [61] |
| 4. | Sodium taurocholate (bile salt) | Insulin | Metabolism enhancement, enzymatic degradation inhibition | *In vitro* (Caco-2 cells 2), in vivo (dog) | [62] |
| 5. | TMC (cationic polymers) | Octreotide | Tight junction modulation | *In vitro* (Calu-3 cells 5); in vivo (rat) | [60] |

## 11.4.3 Reduce the cost of drug development

The high cost of drug development, as well as the imminent patent expiration of many bestselling drugs are major roadblocks to long-term commercial viability. In addition, intellectual property (IP) specifications that are related to trade, such as patenting of products have been extended to include a large number of countries, where generics have previously dominated [37]. Bioenhancers is a novel phenomenon discovered using Ayurveda, a traditional Indian medical method (as mentioned by Charaka, Sushruta, and other apothecaries in the traditional system of medicine). The idea may be useful not only in lowering the toxicity side effects but also, importantly, the drug development costs, which could have a very positive impact on the country's economy, as desired by the WHO. Ayurveda can greatly aid the drug discovery process by the use of reverse pharmacology. This may provide new ways of detecting active compounds and reduced drug development costs. A reduction in the cost of medication could make treatment accessible to a more extensive segment of society, including financially challenged patients [17]. When coadministered or pre-treated with a variety of medications and nutraceuticals, available scientific research studies on bioenhancers have shown to have a significant improving effect on bioavailability. Many natural agents such as piperine, curcumin, *Zingiber offcinale*, glycyrrhizin, niaziridin, *Aloe vera*, *Cuminum cyminum*, allicin, *Carum carvi*, lysergol, sinomenine, *Stevia rebaudiana*, genistein, *Ammanniamultiflora*, capmul, capsaicin, quercetin, and naringin [15] are potential bioenhancing agents and, thus, require urgent scientific attention.

### 11.4.4 Ecological aspect

The dosage of anticancer chemotherapeutic drugs such as taxol can be decreased, with the help of bioenhancers. This will also decrease the drug toxicity because of the lower dose of taxol given for treatment. The ecological implication of this is huge, as taxol is extracted from the bark of the Pacific yew tree, which is one of the world's slowest growing trees. Currently, several trees must be cut down for the treatment of one patient. With the integration of bioenhancers, fewer trees need to be sacrificed [3, 17].

### 11.4.5 Regulatory guidelines

The hurdles in the use of bioenhancers are that large-scale production of bioenhancers is not an easy task. Phytomolecules as bioenhancers are extracted in meager amounts from natural sources, and this imposes a big hurdle in their use. From the commercialization point of view, large-scale use of bioenhancers is needed, rather than laboratory scale. Secondly, it is important to get regulatory approval for them. Detailed study of their physicochemical and pharmacokinetic properties is required to ensure their safety profile. And lastly, without sufficient clinical studies, they cannot be incorporated into formulations and marketed directly for public use. The bioenhancing effect of phytochemicals as natural bioenhancers of the wide variety of drugs and nutraceuticals in animals and humans needs a lot of experimentation on animals. Lack of information on the mechanism of action, adverse effects, and evaluation of toxicity indices of the extracts have to be taken into account. Research should be focused on all these parameters of safety, compatibility with drugs and nutraceuticals, toxicity, efficacy, and mechanism of action of these bioenhancers. Finally, optimization of pharmacokinetics of these bioenhancers is required to establish them as effective bioenhancers.

Regulation is a difficult task when it comes to traditional drug products. The Quality Council of India and the Department of AYUSH together have developed two brands for traditional medicines: Premium mark and AYUSH mark [37]. This enactment of a product certification program initiated by the Department of AYUSH for several AYUSH goods is to gain consumer trust. The program is based on protocol implementation. The two levels of this program are a) AYUSH Standard Mark, based on compliance with domestic regulatory requirements; and b) AYUSH Premium Check, which is based on GMP prerequisites that comply with WHO rules and having stricter guidelines. In the case of products containing bioenhancers, the US-FDA and EMEA have set a few standards for physicochemical and pharmacological properties. But no comprehensive standards have been set for medicines containing herbal bioenhancers. The regulatory authorities should take the initiative to set standards for such products.

### 11.4.6 Industry and future of bioenhancers

In the last two decades, big pharmaceutical companies have become increasingly interested in therapeutic herbs. This is due to the increased awareness and interest in medicinal plants [64] among the public and scientific community. By 2050, global trade in medicinal plants and their products is estimated to be worth $5 trillion, with both China and India emerging as key players [65]. Looking to this projection, many biopharmaceutical giants have begun including herbal divisions in their drug development efforts. On the other hand, many mini- and micro-sized Ayurvedic firms that lack good laboratories and skilled personnel are not indulging in patents or new drug discovery research. It is also true that many Ayurvedic drug companies have avoided entering molecular research because they desire to remain firm to the traditional path, brand loyalty, and specialized consumer base. The majority of Ayurvedic enterprises focus on producing traditional Ayurvedic products (based on the classical Ayurvedic text). A novel proprietary product developed by a firm gives them exclusive marketing rights in an unchallenged competitive environment, and they might even have a commodity monopoly, in some cases. Without the required push from the big pharmaceutical companies, no medicine, be it traditional or herbal, can be successful in the market. Increased research work is, thus, needed to convince the international scientific community on the efficacy of herbal bioenhancers. Though many herbal bioenhancers do show tremendous promise in the lab and preclinical studies, the real impetus comes after the success of a properly designed clinical trial. The knowledge of Ayurvedic remedies has already resulted in many drugs or standardized extracts with identified active compounds, viz., *gum guggulu*, *brahmi*, *reserpine*, *flavopiridol*, etc. [66]. Proper coordination of the institution–industry-regulators may see many more herbal products getting international recognition in the future.

## 11.5 Conclusion

By using bioenhancers, the dosage of the drug is reduced and the hazards of drug resistance are curtailed. This concept is especially applicable for drugs like anticancer, antimicrobials, and other potent drugs. Herbal bioenhancer is less toxic, easily available, and has a wide mechanism of action. However, development of herbal bioenhancers has also created new challenges for regulatory control. Moreover, nanodrug products that use bioenhancers need to have separate regulations as they are different from traditional products. In this issue, the European Medicines Evaluation Agency and United States Food and Drug Administration have taken the initiative to recognize possible regulatory and scientific challenges. Another point to be considered is the evaluation of ecological aspects of using bioenhancer. This is

important because herbal enhancer is one of the essential parts of the ecological system, and therefore, may have a profound effect on it. Several researches are being conducted with bioenhancers, but very few of them are entering into clinical studies. To establish these products' potential and use, more clinical trials should be conducted. The reported data on bioenhancer research and clinical trial can further help commercialize these products. To date, commercialization of these products is limited due to lack of proper data, insufficient clinical trial results, and lower research interest among researchers and others. Proper coordination of the institution–industry-regulators may see many more herbal products getting international recognition in the future.

## List of abbreviations

| | |
|---|---|
| CNS | Central nervous system |
| MDR | Multidrug resistance |
| *D. salina* | *Dunaliella salina* |

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