

# Bioenhancers: Revolutionary concept to market

Navin Atal, K. L. Bedi<sup>1</sup>

Consultant Physician, Department of Internal Medicine, Pushpanjali Medical Center, Delhi, <sup>1</sup>Indian Institute of Integrative Medicine, Jammu Tawi, India

## ABSTRACT

Treatment cost is a major concern for modern medicine in developing countries like India and systematic innovative means to reduce these costs are needed. This article reviews the concept of bioenhancers to reduce treatment costs by increasing drug bioavailability. This concept, based on the Ayurvedic system of medicine, works for a wide range of ingested substances, and has been applied to modern drugs, particularly single chemicals. It offers a fine example of the benefit of integrating an ancient system with modern medicine in both theory and practice.

**Key words:** Bioenhancer, *Piper longum*, piperine

## INTRODUCTION

Modern pharmaceutical research is concerned with all aspects of identifying new chemical substances with new modes of action. In particular, economics of treatment linked to drug dosage has led to new drug development technologies. Ayurveda has made a major contribution to the drug discovery process<sup>[1]</sup> through reverse pharmacology, with new means of identifying active compounds and reduction of drug development costs. Recent developments of another Ayurveda-based technology, this time, enhancing bioavailability of drugs, have produced a revolutionary shift in the way medicines are administered. The global focus is now on methods aimed at reducing drug dosage, and thus drug treatment cost. As a result, treatments are now becoming more affordable for wide sections of society, including the financially challenged. One way to achieve reduction in drug dosage, and therefore drug toxicity and cost, is to increase drug bioavailability.

## BIOENHANCERS

Bioavailability is the rate and extent to which a therapeutically active substance enters systemic circulation and becomes available at the required site of action. Intravenous drugs

attain maximum bioavailability, while oral administration yields a reduced percentage due to incomplete drug absorption and first-pass metabolism. Methods of increasing bioavailability of a drug, correspondingly increase levels in the bloodstream, and thus the efficacy, which in turn reduces the drug dosage required to achieve a given therapeutic effect. Until now, methods of increasing drug bioavailability have operated within a narrow manipulative framework, mainly based on physical processes including micronization, deaggregation of micronized molecules, timed/site release preparations, solubilization of active drug and polymorphic/crystal form selection and nanotechnology (nanotechnology is at the experimental stage so it is a promising future method).

A bioenhancer is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used. The term bioavailability enhancer was first coined by Indian scientists at the Regional Research laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine), who discovered and scientifically validated Piperine as the world's first bioavailability enhancer in 1979.<sup>[2]</sup> C.K. Atal, the Director of the institute scrutinized a list of ancient Indian Ayurvedic formulations used in the treatment of a wide range of diseases. He observed that a majority of Ayurvedic formulations contained either Trikatu or else one of the ingredients of Trikatu, namely *Piper longum* (210 formulations out of 370 reviewed) used in a large variety of diseases. He posed two questions, 'Why is Trikatu used in so many different formulations?' and 'Is it effective against all those diseases?' He formed the working hypothesis that Trikatu increased the efficacy of formulations. Trikatu has three ingredients: black pepper (*Piper nigrum*), long pepper (*Piper longum*) and ginger (*Zingiber officinale*). Based on this

### Address for correspondence:

Dr. Navin Atal,  
Department of Internal Medicine, Consultant Physician, Pushpanjali  
Medical Center, Delhi - 110092, India.  
E-mail: navinatal@yahoo.co.in

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hypothesis, these ingredients were studied by a research team led by Usha Zutshi, which found that one of the ingredients, 'Piper longum', 'Piper' increased the bioavailability of many drugs.<sup>[3]</sup> Piperine, the active principal present in Piper longum was isolated and its bioavailability enhancing action was established. Further research on several<sup>[4]</sup> classes of drugs including antitubercular, leprosy, antibiotics, NSAIDS, CVS and CNS drugs showed similar results. Piperine was found to increase bioavailability of different drugs ranging from 30 to 200%. Subsequent research has shown that it increases curcumin bioavailability by almost ten-fold.<sup>[5]</sup> However it was also noted that piperine did not increase bioavailability of all drugs, while with some drugs the effect was found to be inconsistent.

Significant data was published by RRL in various national and international journals<sup>[6]</sup> and patents were filed in India, Europe and USA.<sup>[7]</sup> After the planned stepwise protocol of drug development, antitubercular formulations were made. After completion of Phase IIIb clinical trials, license was granted by Drug Control General of India (DCGI) for marketing in the Indian market as antitubercular formulations. The formulation named Risorine containing 200 mg of rifampicin, 300 mg of isoniazid (INH) and 10 mg of Piperine has already been launched in India by Cadila Pharma in November 2009. Piperine is the first and most potent bioenhancer to this date. Piperine increases bioavailability of rifampicin by about 60%. Therefore adding bioenhancer 'Piperine' reduces the dose of rifampicin from 450 to 200 mg. This reduces dosage, cost and toxicity of rifampicin.

Consider the economic benefits to poor patients needing prolonged and expensive antituberculosis treatment (ATT). When a bioenhancer has been added to the treatment, if dose requirement of rifampicin is reduced by about half, they only have to pay about half the original treatment cost. If applied to the world population suffering from tuberculosis, the economic benefit to the world economy would be tremendous. Furthermore, if bioenhancer action is applied to other drugs, benefit levels become astonishing. Internationally, many billions of dollars are wasted annually due to the poor bioavailability of many drugs.

The bioenhancing effects of piperine have been demonstrated in several other studies showing that piperine can improve the absorption of many nutrients. These include: vitamin C, selenium, beta-carotene, vitamin A, vitamin B6, coenzyme Q. Studies continue on its role to help combat malnutrition-associated diseases, and even malabsorption states. Chronic ailments and anemia might also benefit but studies need to be conducted to prove this. The ability to increase efficiency of absorption of nutrients may also have a beneficial effect in the reduction

of food and medication requirement (like vitamins), thereby contributing to reduced burden on resources of the country.

The benefits of adding a bioenhancer include reduced drug dosage, reduced cost of the drug, reduced incidence of drug resistance and reduced risk of adverse drug reaction/side effects. Moreover, efficacy is enhanced by increased bioavailability. Secondary beneficial effects include reduced requirement of raw material for drug manufacture. For example, this is especially beneficial and evident in anti-cancer drugs like Taxol used to treat breast cancer. This drug is obtained from the Yew tree, one of the slowest growing trees in the world, and to obtain taxol for one patient, six trees of 25–100 years need are to be chopped. Simply adding a bioenhancer to Taxol means that fewer trees need to be sacrificed. The great reduction in raw material is an added, ecological, benefit. With the discovery of the first bioavailability enhancer piperine in 1979, a new class of drug and a new concept was introduced into science. This revolutionary discovery opened up a new field, that of increasing drug bioavailability. Piperine still remains the most effective bioenhancer.

## MECHANISM OF ACTION OF BIOENHANCERS

Different mechanisms for the bioenhancer activity of piperine have been proposed including DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump.<sup>[8-10]</sup> In general, it inhibits drug metabolizing enzymes, stimulates absorption by stimulating gut amino acid transporters, inhibits the cell pump responsible for drug elimination from cells and inhibits intestinal production of glucuronic acid, thus permitting a more active form of drug to enter the body.

It may increase the absorption of drug in the GIT, or inhibit enzymes responsible for drug metabolism, especially in the liver when the drug passes through the liver after absorption from GIT. Oral administration of piperine in rats strongly inhibited the hepatic arylhydrocarbon hydroxylase (AHH) and UDP-glucuronyltransferase activities.<sup>[11]</sup> Pre-treatment with piperine prolonged hexobarbital sleeping time as well as zoxazolamine paralysis time in mice given at half the dose. These results demonstrate that piperine is a potent inhibitor of drug metabolism. Another study demonstrates that piperine modifies the rate of glucuronidation<sup>[12]</sup> by lowering the endogenous UDP-glucuronic acid content and also by inhibiting the transferase activity. Piperine inhibits human P-glycoprotein<sup>[13]</sup> and CYP3A4. Both the proteins are expressed in enterocytes and hepatocytes and contribute to a major extent to first-pass elimination of many drugs; this indicates that dietary piperine could affect plasma concentrations of P-glycoprotein and CYP3A4 substrates in humans, in particular if these drugs are administered

orally. Some of the metabolizing enzymes inhibited or induced by piperine include CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4 etc. Most of the drugs metabolized by these enzymes will therefore be influenced by bioenhancers. The detailed mechanism of action of bioenhancers is still being evaluated. Some other suggested mechanisms include making target receptors more responsive to drugs, acting as receptors for drug molecules, increasing GIT vasculature by vasodilation to increase absorption of drugs, modulation of the cell membrane dynamics to increase transport of drugs across cell membranes,<sup>[14,15]</sup> etc.

Major categories of drugs that have shown increased bioenhancement include cardiovascular, respiratory, CNS, GIT, antibiotics and anticancers. Some examples include tetracyclines, sulfadiazine, vasicine, rifampicin, INH, pyrazinamide, ethambutol, phenytoin, phenobarbitone, carbamazepine, nimesulide, indomethacin beta-carotene, coenzyme Q10 (CoQ10), ciprofloxacin, curcumin, dapsone, amino acids, glucose and several other classes of drugs<sup>[16-18]</sup> The aim of this technology is to target expensive, toxic and scarce drugs or drugs that exhibit poor bioavailability. It is interesting to note that Piperine is added in a dose of 10 mg in all formulations, irrespective of the dose of active combination.

Piperine is derived from pepper, which has been used since time immemorial as a food condiment and which as such is a very safe food item. However, since Piperine can influence drug levels of a number of drugs, care should be taken when using with other drugs whose levels are influenced by it. It can potentiate the efficacy of drugs hence, dose reduction is required to prevent toxicity. The list is still being researched and updated.

## CONCLUSION

Bioenhancers constitute an innovative concept the discovery of which was based on a traditional system of Indian medicine. They will lead to reductions in drug cost, toxicity, and other adverse effects, and have a beneficial influence on the national economy. Research aimed at developing powerful new Piperine derivatives and novel bioenhancers continues.

It satisfies all necessary criteria to be considered an ideal drug. It is safe, effective, economical, easily procured, non-addictive, and has a widely-based effect on several classes of drug. A synthetic process for its commercial production has been developed for industrial use.

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