Natural Bioenhancers in Drug Delivery: An Overview

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When the bioavailability of a drug increases, a corresponding increase in the levels of that drug in the bloodstream occurs. With this, drug efficacy is augmented and the dosage required to yield a specific therapeutic effect diminishes comparably. Until recently, only a few methods have proven effective in enhancing drug bioavailability, among which are the disaggregation of micronized molecules, the use of timed-release and topical preparations, mechanization, polymorph and crystal form selection, drug solubilisation, and the use of nanotechnology. (Though still at the experimental stage, nanotechnology promises to become a powerful pharmacological tool in the future.) Bioenhancers are agents not possessing any inherent therapeutic effects but that, when combined with active drugs, potentiate the pharmacological effects of those drugs. Hence the current article describes the enhancement of the bioavailability of drug molecules through the utilization of natural bioenhancers. [*P R Health Sci J 2018;37:12-18*]

Key words: Bioavailability, Bioenhancers, Bio-efficacy, Micronization, Nanotechnology

Currently, the high cost of drugs means that drug dose affects treatment economics, which in turn drives the development of novel drug technologies through pharmaceutical research. Pharmaceutical research is, at base, the identification of new chemical substances that provide new modalities of action. *Innovative* pharmaceutical research, on the other hand, restricts itself not merely to the identification of new materials and new approaches but also extends itself to shining new light on any relevant system of knowledge, contemporary or ancient. One such, the Ayurvedic system of medicine, contains a number of active medicinal elements that are even now being explored by modern researchers (1); it is anticipated that these elements will contribute to the reduction of drug-development costs by enhancing the bioavailability of current drugs, thereby transforming the way medicine is dispensed today. Global demand would have treatment costs be lowered, and one way of accomplishing this is by reducing drug doses. Increasing a given drug's bioavailability reduces the effective dosage of that drug—as well as its potential for toxicity—and thus lowers treatment costs; ideally, using a bioenhancer will result in decreasing the dosage of the drug whose activity it is intended to enhance, minimizing the risk of drug resistance and reducing the potential toxicity of the drug with which it is being combined—which is especially critical in the case of anticancer drugs. Recent successes in decreasing costs have resulted in treatments that are economically viable across broad populations, including those that include the financially challenged.

A subcategory of absorption, *bioavailability* represents the rate at and extent to which a substance reaches the systemic circulation in its unchanged form, thus becoming available at the target site (2–3). Drugs administered intravenously yield maximum bioavailability, whereas those that are administered orally have rather poorer bioavailability. Moreover, under- or unutilized drugs that remain within a patient's body augment that individual's risk of developing drug resistance and of susceptibility to adverse reactions. Augmenting the bioavailability of a drug or molecule benefits patients both by enhancing drug efficacy and by reducing treatment costs. Thus, developing non-therapeutic molecules that can be combined with specific drugs to enhance the bioavailability of those drugs represents a critical goal in the field of pharmacology.

An effective bioenhancer is nontoxic to both humans and animals, easy to concoct, and highly responsive, even when its concentration in a given enhancer/drug combination is low. The degree to which a bioenhancer improves the activity and the uptake or absorption of the molecules of a given drug is perhaps its most important characteristic (4). An important secondary characteristic of bioenhancers has to do with minimizing the need for raw materials. As an example, and specifically in the anticancer venue, the drug Taxol (paclitaxel), used to treat breast, lung, and ovarian cancer as well as Kaposi's sarcoma, is obtained from the Pacific yew tree *(Taxus brevifolia)*. The bark from as many as 6 trees must be harvested to provide sufficient

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paclitaxel for a single patient, and as the process of harvesting kills the slow-growing (100 or more years to reach adequate growth) trees, one can see that the life-giving treatment comes at a grievous ecological cost. And while new techniques and technologies, such as cultivating plant cell cultures in bioreactors (Phyton Biotech, USA; ESCAgenetics Corp., USA; Samyang Genex, South Korea; A. Nattermann& Cie. GmbH, Germany), are able to provide as much as an entire day's supply of the vital drug, augmenting the therapeutic effects of Taxol with a bioenhancer (piperine, but also glycyrrhizin) thus benefits patients and protects precious natural resources, both (5).

As explained above, increasing the bioavailability of a drug increases the levels of that drug in the bloodstream, which enhances drug efficacy and reduces drug dosage without diminishing the desired therapeutic effect. Up to now, the methods available for increasing drug bioavailability have been restricted primarily to processes and strategies of a more physical nature and include, among others, the disaggregation of micronized molecules, the use of timed-release and topical preparations, mechanization, polymorph and crystal form selection, drug solubilisation, and the use of nanotechnology. This last, while still at the experimental stage, promises to become a powerful pharmacological tool in the future. Bioenhancers are another such promising tool.

First used by a team of scientists at the Regional Research Laboratory in Jammu, India (now the Indian Institute of Integrative Medicine, IIIM), the term "bioavailability enhancers" refers to chemical agents (also called *bioenhancers*) that can be extracted from natural compounds found in a variety of medicinal plants; these bioenhancers work in concert with certain drugs, augmenting their bioavailability without having a specifically therapeutic effect (6-7). The world's first (and to date, most potent) bioenhancer is *piperine*, which was discovered and confirmed in its effectiveness by that same team of scientists in 1979 (8).

The piperine "story," centers on CK Atal, the director of IIIM at the time. In his perusal of ancient Indian Ayurvedic healing medicines, Atal realized that a majority of these medicines (210 of the 370 that were reviewed) contained either *Trikatu* or one of its primary components, *Piper longum*. This realization led to his wondering both why *Trikatu* was so prevalent in these concoctions and how effective it might be at fighting—or even preventing—disease. With time, he came to believe that while *Trikatu* was not curative, it was enhancive, that it intensified the effects of the formulas and medicines in which it was found.

The next step involved a close study of *Trikatu* and its 3 ingredients: black pepper *(Piper nigrum)*, long pepper *(Piper longum)*, and ginger *(Zingiber officinale)*. The research team, led by Usha Zutshi, discovered that *Piper longum* (*Piper* species), in particular, acted to increase the bioavailability of many drugs (9, 10). In time, the team isolated piperine, the active principle in *Piper longum*, and confirmed its role as a bioenhancer. Research from this team and others has shown that piperine can increase the bioavailability of different drugs and chemicals (e.g., rifampicin, oxytetracycline, carbamazepine, curcumin, nevirapine, epigallocatechin-3-gallate) from 30 to 200% (11, 12, 13), which drugs include antituberculars, leprostatic agents, antibiotics, and non-steroidal anti-inflammatories (e.g., nimesulide, diclofenac sodium, ibuprofen), as well as those that act on the central nervous system (e.g., carbamazepine, phenytoin, phenobarbital) and the cardiovascular system (e.g., propranolol, atenolol) (14); curcumin bioavailability has been shown to increase an amazing 2000% when administered concomitantly with piperine (15).

It should be noted, however, that some drugs do not see their bioavailability increased when used in combination with piperine, and some few others that do, inconsistently so. For example, Singh et al. found that when piperine alone was used against *Mycobacterium smegmatis* (a model for such mycobacterial species as *M. tuberculosis*), no beneficial result ensued; however, when it was used in combination with rifampicin, the inhibitory effect of the antitubercular was increased several fold (9). Further, the bioenhancing effect of piperine when used in conjunction with rifampicin (which can increase bioavailability by some 60%) led to significant dosage changes: reducing dosages of 450 mg to as low as 200 mg (16) (see Risorine, below). This kind of reduction benefits patients undergoing the prolonged and expensive antituberculosis therapy (ATT), not only by alleviating some the burden of cost but also by ameliorating the side effects suffered.

Adding a bioenhancer to a given treatment regimen—in this case, ATT with rifampicin—can cut dose requirements by as much as half, effectively halving treatment cost without weakening the effects of the therapy. Even if bioenhancers (piperine, in the above case) were to be prescribed only to the global population of tuberculosis patients, the presumed economic benefit to be accrued would be staggering. India, with—according to 2015 WHO estimates—the greatest TB burden in the world (17), would be correspondingly advantaged, both medically and economically.

To that end, an antitubercular formulation including piperine was developed. After successfully negotiating a phase IIIb trial, a license to market the antitubercular drug in India was granted by the Drug Controller General of India (DCGI). In 2009, Cadila Pharmaceuticals Ltd. began selling the piperine-enhanced formulation, called Risorine, to tuberculosis patients in India. Risorine contains 300 mg of isoniazid (INH), 200 mg of rifampicin, and 10 mg of piperine.

The bioenhancer piperine, then, might be presumed to be, if not a miracle drug in the literal sense, then a miracle component of any number of future miracle drugs, in that poor bioavailability leads to billions of dollars wasted every year, a plethora of side effects caused by the need for high drug doses, and even insufficient patient compliance.

It isn't only *drug* bioavailability that can be improved with piperine and other such bioenhancers: Studies have shown that nutrients such as vitamin A, vitamin B6, vitamin C, selenium, beta-carotene, and coenzyme Q all find their absorption rates

enhanced when administered concomitantly with piperine (17), to the degree that nations with endemic poverty and, thus, populations suffering from chronic malnutrition, might enjoy significant increases in available nutritional resources (relatively speaking, as the amount of food available would not actually increase) and equally significant reductions in the economic burden that attends widespread malnutrition. Ongoing research is exploring the potential roles of piperine in combating malnutrition- and malabsorption-associated conditions as well as, on the opposite end of the spectrum, obesity and those maladies either directly linked to or secondarily caused by obesity (e.g., metabolic syndrome) (18).

Enhancing drug bioavailability remains a relatively new idea, and piperine, a new class of drug employed to that end, remains the world's foremost bioavailability enhancer (11).

2. Enhancing Oral Bioavailability

2.1 Absorption enhancers

Various elements have been found to enhance or promote the gastrointestinal absorption of some orally administered drugs. Among these absorption enhancers are bile salts, surfactants, fatty acids, salicylates, chelating agents, and some polymers (chitosan and its derivatives) (19-20). The mechanics of each differ from those of the others, so while such agents as ethylene glycol tetra acetic acid and EDTA (ethylenediaminetetraacetic acid) enhance absorption by reducing extracellular concentrations of calcium, which leads to the disruption of cell–cell contact, chitosan—in particular trimethylated chitosan—works to the same effect by inducing the redistribution of cytoskeletal F-actin, resulting in increased paracellular permeability (21).

2.2 Pharmaceutical and dosage-form approaches

Modifying the physical properties of drug molecules can result in increased bioavailability: Co-crystallization is a technique for solubility enhancement; micronization and nanonization both approach the issue of improving bioavailability by reducing drug particle size; and complexation can affect a given molecule's solubility and thus its bioavailability. Novel formulations such as liposomes, solid dispersion, liquisolid techniques, self-nanoemulsifying drug delivery systems (SNEDDS), self-microemulsifying drug delivery systems (SMEDDS), phytosomes, transferosomes, nanocrystals, nanoparticles, and ethosomes are some of the different drug-delivery systems that are useful in the bioavailability enhancement of both lipophilic and hydrophilic drug moieties (22-25, 26, 27).

2.3 Prodrugs

Prodrugs are pharmacologically inactive compounds that are metabolized within the body, becoming, as a result, active. Therapeutic strategies that incorporate prodrugs are intended to enhance a drug's bioavailability by improving the absorption, distribution, metabolism, and excretion of that drug; this particular approach is effective for both lipophilic and hydrophilic drug molecules (28). For example, the ampicillin prodrugs pivampicillin, bacampicillin, and talampicillin are synthesized by the esterification of the carboxyl group of ampicillin.

2.4 P-glycoprotein inhibitors

Inhibitors of P-glycoprotein (P-gp) affect drug–drug interactions, altering pharmacokinetic properties, metabolism, and the eventual excretion of active drugs; concentration (by retention in the body) is thus indirectly enhanced (19, 29).

3. Medicinal Plants That Enhance Drug Bioavailability

3.1 *Piper nigrum*

Piperine (1-piperoyl piperidine), an alkaloidal component of both *Piper nigrum* Linn. and *Piper longum* Linn. (or mixtures containing same), enhances the bioavailability and efficacy of a number of drugs and other substances, including vasaka leaves, vasicine, sparteine, phenytoin, rifampicin, sulfadiazine, and propranolol (30-31).

Piperine's bioenhancing effect was first noted in the treatment of human tuberculosis. We know now that when given in conjunction with piperine, the bioavailability of the anti-tuberculosis drug rifampicin increases by about 60%, resulting in significant reductions in drug dosages (31, 32).

Piperine, in addition, has been demonstrated to bolster the effects of the non-nucleoside HIV-1 reverse transcriptase inhibitor nevirapine, as well as those of other antiretroviral agents (33).

3.2 *Curcuma longa*

Curcumin, the active principle of turmeric *(Curcuma longa)* (itself a natural bioenhancer similar to piperine), has long played a curative role in several traditional medicinal systems. The yellow compound is isolated from the plant *Curcuma longa* and sees regular use in traditional Indian medicine to combat various respiratory conditions (asthma, bronchial hyperactivity, allergies and sinusitis, coryza, cough) but is also commonly employed to treat anorexia and hepatic disease. Evidence from numerous sources shows this agent to promote anti-inflammatory, antioxidant, antimicrobial, and wound-healing activities. Documented also are it radio sensitizing, chemotherapeutic, and chemosensitizing properties (34, 35). Notably, its bioavailability is increased in the presence of piperine: A 20 mg dose of piperine co-administered with curcumin has been found to increase the bioavailability of the latter as much as 20-fold in humans (36).

3.3 *Zingiber officinale*

A member of the Zingiberaceae family, ginger *(Zingiber officinale)* has a powerful effect on the mucous membrane of the GI tract. By regulating intestinal function, ginger facilitates absorption, making it a very good bioenhancer; its effective dose is from 10 to 30 mg/kg of body weight. It has been observed, as well, that ginger can increase the bioavailability of the drug moieties of several drug classes, including antibiotics

(erythromycin, 105%; azithromycin, 85%; cefadroxil, 65%; cephalexin, 85%; cloxacillin, 90%; amoxicillin, 90%; rifampicin, 65%; ethionamide, 56%), antifungals (ketoconazole, 125%), antiretrovirals (zidovudine, 105%), and anticancer drugs (5-fluorouracil, 110%) (37).

3.4 *Glycyrrhiza glabra*

The active component of licorice, glycyrrhizin, is a known bioenhancer, intensifying the cell-division inhibitory activity of Taxol by 5-fold, thereby hindering the growth and multiplication of the MCF-7 cancer cell line (4); the inhibition of cancer cell growth using Taxol was found to be greater when used in conjunction with glycyrrhizin than it was when Taxol was used alone. Glycyrrhizin has been reported to enhance, as well, the transport across the gut membrane of several antibiotics (rifampicin, tetracycline, nalidixic acid, and ampicillin), vitamin B1, and vitamin B12 (38, 39).

3.5 *Moringa oleifera*

Isolated from *Moringa oleifera* pods (6), the nitrile glycoside niaziridin enhances the bioactivity of commonly used antibiotics against such Gram-positive bacteria as *Mycobacterium smegmatis* and *Bacillus subtilis* and such Gram-negative bacteria as *Escherichia coli* (6). Coupled with niaziridin, the anti–Gram-positive properties of rifampicin, ampicillin, and nalidixic acid are enhanced by 1.2- to 19-fold (31); the potency of the azole antifungal drug clotrimazole against *Candida albicans* is increased by 5- to 6-fold. Lastly, niaziridin increases the absorption of vitamin B12 (40).

An *in vitro* study that used fractioned hydroalcoholic extracts of *M. oleifera* to investigate this glycoside's protective effect against *Mycobacterium tuberculosis* (H37Ra) determined first that it has no such effect but instead that it enhances the bioactivity of such commonly used antibiotics as rifampicin, tetracycline, and ampicillin, which are themselves biologically active against Gram-positive and Gram-negative bacteria (40).

3.6 *Cuminum cyminum*

The active components present in hydroalcoholic extracts obtained from black cumin (*Cuminum cyminum*) have been shown to enhance the bioavailability of erythromycin, cephalexin, amoxicillin, fluconazole, ketoconazole, zidovudine, and 5-fluorouracil within a dose range of 0.5 to 25 mg/kg body weight. Not just an effective bioenhancer, black cumin has been successfully employed as a gastric stimulant, a carminative, and an anthelmintic. Other therapeutic uses are as an anti-diarrheal, a galactagogue, and a diuretic; finally, it has been found to be beneficial in treating hoarseness (41, 42).

3.7 *Allium sativum*

Amphotericin B is a commonly prescribed antifungal agent used to treat such pathogenic fungi as *Candida albicans, Aspergillus fumigatus,* and *Saccharomyces cerevisiae* (yeast); the fungicidal activity of Amphotericin B against *S. cerevisiae* is enhanced by allicin, one of the active phytomolecules in garlic (*Allium sativum*) (43, 44).

3.8 *Quercetin*

Ubiquitous throughout nature, the plant-derived flavonoid quercetin is the aglycone form of several other flavonoid glycosides (e.g., rutin, quercitrin, kaempferol) and is found in *Thuja occidentalis*, *Morus alba*, and *Quercus tinctoria*. Possessing antioxidant, radical scavenging, anti-inflammatory, and anti-atherosclerotic capabilities, quercetin is also an inhibitor of CYP3A4 as well as a modulator of P-glycoprotein. Quercetin has been observed to enhance the bioavailability of and—therefore—increase the therapeutic efficacy of a number of drugs: epigallocatechin gallate (an anticancer component of green tea), diltiazem (used to treat angina pectoris, hypertension, and some types of arrhythmia), and digoxin (widely used for atrial fibrillation, atrial flutter, and heart failure) to name a few (45-48).

3.9 *Lysergol*

Isolated from such plants as *Rivea corymbosa*, *Ipomoea violacea*, and *Ipomoea muricata*, the bioactive alkaloid lysergol enhances the antimicrobial effects of different antibiotics, thus showing promise as an herbal bioenhancer (49).

3.10 *Aloe vera*

In their 2005 study, Vinson et al. combined 2 different *Aloe vera* preparations (an inner-fillet gel and a whole-leaf extract) with either vitamin C or vitamin E. Their results showed that the 2 preparations improved the absorption of both vitamins, leading to their longer retention in blood plasma; that being the case, it seems probable that *Aloe vera* has role as a nutritional herbal bioenhancer (50).

3.11 *Genistein*

Such dietary plants as soybean *(Glycine max)* and kudzu *(Pueraria lobata)* are among the many in which are found genistein, a phytoestrogen belonging to the isoflavone class of flavonoids (51). Genistein's reported effects include the ability to inhibit multidrug resistance protein 2 (MRP2) efflux function, breast cancer resistance protein (BCRP), and P-gp. The intestinal absorption of paclitaxel—a substrate for efflux transports such as P-gp and MRP2—was significantly increased when it was co-administered with genistein (52, 53).

3.12 *Sinomenium acutum*

Though paeoniflorin is a wonderful anti-arthritic as well as an anti-inflammatory agent, its absorption rate on oral administration is low, as is its bioavailability (3–4%) (42). However, when co-administered (in rats) with sinomenine, an alkaloid extracted from *Sinomenium acutum* (Thunb.) (54), paeoniflorin's pharmacokinetic behavior was drastically altered (55).

3.13 *Naringin*

Naringin, the primary flavonoid glycoside found in grapefruit, apples, onions, and tea, is well known for its anti-ulcer, antioxidant, antiallergic, and blood-lipid lowering properties; in addition, it has been reported to inhibit intestinal CYP3A1/2 and P-gp in rats. However, another property of naringin is as a bioenhancer: Pretreatment with oral naringin (3.3 to 10 mg/kg body weight) has been shown to enhance the bioavailability of intravenous paclitaxel (56, 57).

3.14 *Carum carvi*

Extracted from the dried ripe fruit of *Carum carvi* (of the family Apiaceae), caraway (also known variously as Persian cumin and meridian fennel) is an effective P-gp efflux pump inhibitor that has been shown to possess antioxidant, antimicrobial, diuretic, and carminative properties but that also has a role as a bioenhancer. While this plant contains approximately 30 different compounds, the main constituents are carvone and limonene, which account for about 95% of the total (58). In doses of 5 to 100 mg/kg of body weight, caraway extract has been found to be a highly efficacious bioenhancer, boosting the potency of cycloserine by 75%, of rifampicin by 110%, and of ethionamide by 68%. Other chemical elements that experience an enhancement of their bioavailability when co-administered with caraway are the antibiotics cefdinir (89%) and cloxacillin (100%), the antifungal amphotericin B (78%), the antiviral zidovudine (92%), and the anticancer drug 5-fluorouracil (90%) (59).

3.15 *Stevia*

Besides being used as a sweetener, stevia *(Stevia rebaudiana)* is an anti-hypertensive agent that stimulates insulin secretion and a bioenhancing agent that increases the bioavailability of anti-tubercular, anti-leprotic, anti-cancer, antifungal, and antiviral drugs; it contains several compounds, of which stevioside forms the greatest percentage (60). At the time of this writing, the mechanism of action remains unknown, but as a bioenhancer, dosages in the range of 0.01 to 50 mg/kg body weight have been found to be effective (61).

3.16 *Mentha piperita*

Obtained from *Mentha piperita*, peppermint oil significantly improves the oral bioavailability of cyclosporine, to the degree that, in a study by Wacher et al., the co-administration of 100 mg/kg of peppermint oil almost tripled the maximum serum concentration (C_{MAX}) and area under the serum curve (AUC) of the drug. Wacher and his team theorized that the mechanism of action probably involved the inhibition of CYP3A by the oil (62).

3.17 *Rhus chinensis*

To reduce beryllium-induced hepatorenal dysfunction and protect against the consequences of oxidative stress, the co-administering of piperine and gallic acid (*Rhus chinensis*—from the nutgall tree, also known as Chinese sumac) has been found to have a synergistic effect, demonstrating a pronounced therapeutic potential (63). Propyl gallate, octylgallate, and laurylgallate, among other gallic acid esters, have been found to enhance the bioavailability of nifedipine and other, similar, drugs (64).

3.18 *Capsicum annum*

Isolated from chili peppers *(Capsicum annum)*, capsaicin is an irritant that causes a burning sensation when coming into contact with mammalian—including human—tissue. According to one 1988 study, capsaicin enhances the bioavailability of theophylline (65). Interestingly, it has been observed that on oral administration in rats, *Capsicum annum* reduces the bioavailability of aspirin (66).

3.19 *Capmul*®

Though commonly used in lip products, capmul MCM C10—a glycerylmonocaprylate derived from edible fats and oils—given concomitantly with the antibiotic ceftriaxone increased the bioavailability of the latter by 80% (16).

3.20 *Ammannia multiflora*

The novel compound ammaniol is a methanolic extract of *Ammannia multiflora* (Lythraceae); the bioenhancing properties of this compound augment the effects of the antibiotic nalidixic acid (as well as those of several other antibiotics), especially against CA8000 and DH5a, 2 strains of *Escherichia coli* (67).

3.21 *Cow urine distillate (Kamdhenu ark)*

Cow urine distillate (more than simple cow urine) is an effective bioenhancer; in its presence, the transportation of such antibiotics as rifampicin and ampicillin through the gut wall can be enhanced, boosting bioavailability by 80-fold and 11.6-fold, respectively (68). The bioavailability of the antifungal clotrimazole can be augmented by 5-fold. Additionally, cow urine acts as an agent against cadmium chloride toxicity and can be used as a bioenhancer of zinc. This substance's bioenhancing ability is that it can facilitate the absorption of drugs across the cell membrane (69, 70).

Resumen

Los métodos para aumentar la biodisponibilidad de un fármaco aumentan correspondientemente los niveles en el torrente sanguíneo y, por tanto, la eficacia, que a su vez reduce la dosis de fármaco necesaria para lograr un efecto terapéutico dado. Hoy en día se ha observado que los métodos para aumentar la biodisponibilidad de fármacos poseen un trabajo de marco muy limitado que está asociado con varios procesos físicos, incluyendo desagregación de moléculas micronizadas, preparaciones de liberación temporizada / sitio, mecanización, nanotecnología etapa experimental por lo que es un método futuro prometedory la solubilización del fármaco activo y la selección de forma

polimórfica / cristalina. Un biotensor se considera así como un agente que tiene la capacidad de potenciar la biodisponibilidad y la bioeficacia de un fármaco particular con el que se combina, sin ninguna actividad farmacológica típica propia a la dosificación aplicada. Por lo tanto, el artículo actual hace hincapié en la mejora de la biodisponibilidad de las moléculas de fármacos mediante la utilización de bio-nutrientes naturales.

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