



## Natural Bioenhancers: Current Outlook

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Pharmaceutical companies around the globe have always been in the urge of discovering innovative blockbuster drugs for various ailments by spending billions of dollars for the drug discovery programmes. Although identification of new chemical entities (NCEs) with alternate mode of actions for diseases is a primary concern for the pharmaceutical companies, application of innovative techniques and technologies to increase the bioavailability, efficacy and safety of the already existing drugs are of no less concern as well. In fact, enhancing bioavailability of therapeutically potent but poorly bioavailable molecules has always been a crucial aspect of drug development programmes, as it reduces the drug dosage and frequency resulting in reduced toxicity and cost for the patients [1]. Among the various factors responsible for poor bioavailability of drugs, physicochemical properties of the drug itself and biological barriers are two predominant factors [2]. While physicochemical properties of the drug include poor aqueous solubility, poor intestinal membrane permeability, and poor stability of drug in gastrointestinal tract (GIT), biological barrier constitutes hepatic and intestinal drug metabolizing enzymes (DMEs) and efflux drug transporters (EDTs). The metabolism of drugs by cytochrome P450 (CYP) DMEs in the gut wall and in the liver is the major contributors of reduced bioavailability of drugs that are substrate to these DMEs [3]. In addition to this, EDTs such as P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), multidrug resistant-associated protein (MRP) are also responsible for reduced bioavailability of the therapeutically active drugs, especially anticancer drugs [3].

Until now, myriad of strategies have been exploited to address the problems associated with the physicochemical properties of the drug including but not limited to a) physical modification approaches like particle size reduction (micronization or nanonization), crystal habit modification, amorphousization, inclusion complexation, etc. b) chemical modification processes such as salt formation, pH modification, etc., c) formulation techniques such as co-solvency, co-crystallization, modified (delayed/extended/sustained), targeted, and encapsulation techniques, etc. [4,5]. However, methods for circumventing biological barriers have often been overlooked given its complex physiological nature and unavailability of safe and effective facilitators. Enhancing the absorption of drugs and/or inhibition of DMEs and EDTs responsible for the biotransformation of the drugs are most effective ways to overcome the biological barriers [6]. Although absorption enhancers such as surfactants, bile salts, fatty acids, cyclodextrins, chelating agents, etc., are a type of synthetic facilitator molecules that enhance the permeation of drugs through the intestinal walls, they are often inefficient in inhibition of DMEs or EDTs. Besides, their toxicity and necessity of higher concentration to produce the permeation enhancement are of big concern to the scientists hindering their use as efficient bioavailability enhancers [4,7]. Interestingly, use of natural biopotentiators or bioactives of plant or animal origin have been found to be of use given their nontoxic safety profile, bioenhancing effect even at lower concentrations, and formulation compatibility [1,3,8]

Although most of the bioenhancers possess several pharmacological activities at different concentrations, to be considered as a novel

bioenhancer, one must be capable of enhancing the bioavailability and bioefficacy of the therapeutically active agents (drugs) and nutraceuticals upon co-administration, without any significant pharmacological activity of its own at the dose used [3]. Despite the fact that the use of bioenhancers dates back to a period between 700 BC and 600 AD, the first scientifically validated report was found only in 1979 [9]. Since then, the idea of utilization of bioenhancers has been gaining interest and myriad of bioactives of natural origin have been reported to be effective as bioenhancers. Bioenhancers help to reduce the dose and frequency of drug, to reduce duration of drug treatment significantly, to prevent drug resistance, enhance safety profile of the drug by reducing toxicities, and most of all reduce the burden on the patient through cost reduction [1-3,8]. This has propelled the scientific community to explore the potential possibilities of bioavailability enhancement using these natural agents. As a result several natural bioenhancers of both plant and animal origins such as piperine, quercetin, genistein, naringin, sinomenine, glycyrrhizin, curcumin, lysergol, allicin, niaziridin, cow urine distillate, etc. have been investigated and reported to possess pharmacological and/or bioenhancer activities. Several mechanisms of actions for the bioavailability enhancement of these bioenhancers have been proposed including, but not limited to, 1) modification of acid secretion and blood supply to the GIT, 2) modification of bile acid secretion, 3) modification of gastric emptying time, GIT motility and transit, 4) modification of GIT membrane permeability, 5) inhibition of DMEs in gut wall and liver 6) inhibition of EDTs, 7) stimulation of specific enzymes and/or transporters, etc. [1,3,8]. However, predominant mechanisms of action of these bioenhancers are enhancing the absorption by increased blood supply of the GIT and reducing biotransformation and efflux by modulation of DMEs and EDTs, respectively [3]. Subsequently, this literature presents a glimpse of currently available bioenhancers and their current outlook.

Piperine, one of the first and most intensively investigated bioenhancers, is an alkaloid obtained from black and long peppers (*P. nigrum* Linn and *P. longum* Linn). Piperine has been reported to enhance the bioavailability of various drugs and nutraceuticals [1,3,8]. The mechanism of action of piperine is manifold including inhibition of DMEs, EDTs, stimulation of gut amino acid transporters, increased intestinal glucuronic acid secretion, etc. The DMEs inhibited by piperine include arylhydrocarbon hydroxylase (AHH), uridine diphosphate-glucuronyl transferase (UDP-GT), ethylmorphine-N-demethylase, 7-ethoxycoumarin-O-deethylase, 3-hydroxy-benzo(a) pyrene glucuronidation, UDP-glucose dehydrogenase (UDP-GDH), 5-lipoxygenase, cyclooxygenase-1, and cytochrome P450 [10,11].

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Most importantly, piperine inhibits P-gp and CYP3A4 that are expressed in enterocytes of the gut wall and hepatocytes of the liver that contribute to a major extent of pre-systemic elimination of many drugs resulting in poor bioavailability. Sinomenine, another alkaloid extracted from *Sinomenium acutum* Thumb, was reported to enhance the bioavailability of a monoterpene glucoside used for inflammation and arthritis. The underlying mechanism of this effect was specific inhibition P-gp transporters responsible for efflux [12]. Quercetin is a plant derived flavonoid that is found mainly in citrus fruits, vegetables, leaves, and grains that has been reported to enhance the bioavailability of various drugs including, pioglitazone, diltiazem, digoxin, and epigallocatechin-3-gallate (EGCG) [13,14]. It exhibited the bioenhancing property by inhibition of CYP3A4 enzymes and/or P-gp and MDR transporters.

Naringin, a flavonoid glycoside found in grapefruit, apples, onions, and tea also act by the inhibition of CYP3A4, CYP3A1/2, and P-gp and enhanced bioavailability of various drugs including diltiazem, verapamil, paclitaxel, etc. in vivo [15-18]. Genistein, an intense phytoestrogen, is an isoflavone flavonoid found in dietary plants such as soybean and kudzu (*Glycine max* and *Pueraria lobata*). It exhibits its bioenhancing properties on various drugs including paclitaxel and EGCG through inhibition of CYP3A, P-gp, MRP2, and BCRP transporters [19]. Although this bioenhancer could be used with anticancer drugs given its efflux transporter and CYP enzyme inhibitory activities, genistein enhanced intestinal tumorigenesis in male mice in combination with EGCG in one study and should be seriously investigated for its safety [20]. Glycyrrhizin is a triterpenoid saponin glycoside found in liquorice (*Glycyrrhiza glabra L.*) and demonstrated bioenhancing activity for various antimicrobial agents including rifampicin, tetracycline, nalidixic acid, etc. and the bioenhancing activity of the tested compounds were due to the inhibition of intestinal P-gp transporters [3,8]. However, the major determinant of its action is the rate and extent of biotransformation of glycyrrhizin to glycyrrhizic acid by intestinal  $\beta$ -glucuronidase [21]. Curcumin, a curcuminoid obtained from turmeric (*Curcuma longa*), has been used as bioenhancer for antimicrobial and anticancer drugs such as norfloxacin and docetaxel, respectively, and the bioavailability of these drugs were enhanced by its inhibitory effect of CYP3A4 DMEs in the liver and P-gp transporters in the gut wall. It has also been reported to inhibit the DMEs non-specifically [22,23].

Niaziridin, a nitrile glycoside, is a good bioenhancer that has been isolated from the bark, pods, and leaves of Drumstick (*Moringa oleifera*) and enhances bioavailability of antibiotics such as rifampicin, ampicillin, tetracycline, and nalidixic acid, and antifungal drugs such as clotrimazole. It regulated the GIT functions to facilitate better absorption of the drugs and nutraceuticals [24]. Lysergol is a natural bioenhancer obtained from Morning Glory plant (*Ipomoea spp.*) and higher plants such as *Rivea corymbosa*, *Ipomoea violacea*, and *Ipomoea muricata* and lower fungi like *Claviceps* and *Rhizopus*. It has been reported to enhance the bioavailability of various broad-spectrum antibiotics such as rifampicin, tetracycline, ampicillin, etc. However, its mechanism of action is still under investigation [25]. Cow urine distillate obtained from urine of cow has also been shown to enhance the bioavailability of antimicrobial, antifungal, and anticancer drugs by enhancing the transport across the GIT [26]. In addition to these above-discussed bioenhancers, several other bioenhancers of natural origin such as alliin from garlic (*Allium sativum*), capsaicin from chilli peppers (*Capsicum annuum*) extract of ginger (*Zingiber officinale*), caraway oil (*Carum carvi.*), Aloe vera gel and whole leaf extract, Stevia from honey leaf (*Stevia rebaudiana*), extract of *Ammannia multiflora*,

etc. have also been under investigation for bioenhancing effect [1,3,8].

Incorporation of natural bioenhancers in the formulation to enhance the bioavailability and bioefficacy of poorly bioavailable compounds opens up new horizons in the therapeutic arena in terms of dose and cost reduction coupled with enhanced safety and efficacy. Until now, few bioactive compounds have been explored thoroughly for bioenhancing effect of actives, and very few bioactives have entered clinical studies, let alone commercialization and clinical practice. Availability of these compounds for large scale production and regulatory approval are other major hurdles faced by these natural bioenhancers. Despite these hurdles, the outlook and ability of these natural bioenhancers look promising, and further investigations of these compounds in terms of exact mechanism of action, toxicity and safety evaluation, selection of suitable drug or nutraceuticals, etc. are necessary. Hence, the scientific community has the responsibility of exploring these promising compounds for making better therapeutic options.

## References

- Dudhatra GB, Mody SK, Awale MM, Patel HB, Modi CM, et al. (2012) A comprehensive review on pharmacotherapeutics of herbal bioenhancers. *ScientificWorldJournal* 2012: 637953.
- Atal N, Bedi KL (2010) Bioenhancers: Revolutionary concept to market. *J Ayurveda Integr Med* 1: 96-99.
- Kesarwani K, Gupta R, Mukerjee A (2013) Bioavailability enhancers of herbal origin: an overview. *Asian Pac J Trop Biomed* 3: 253-266.
- Beg S, Swain S, Rizwan M, Irfanuddin M, Malini DS (2011) Bioavailability enhancement strategies: basics, formulation approaches and regulatory considerations. *Curr Drug Deliv* 8: 691-702.
- Fasinu P, Pillay V, Ndesendo VM, du Toit LC, Choonara YE (2011) Diverse approaches for the enhancement of oral drug bioavailability. *Biopharm Drug Dispos* 32: 185-209.
- Aqil F, Munagala R, Jeyabalan J, Vadhanam MV (2013) Bioavailability of phytochemicals and its enhancement by drug delivery systems. *Cancer lett* 334: 133-141.
- Lemmer HJ, Hamman JH (2013) Paracellular drug absorption enhancement through tight junction modulation. *Expert Opin Drug Deliv* 10: 103-114.
- Randhawa GK, Kullar JS, Rajkumar (2011) Bioenhancers from mother nature and their applicability in modern medicine. *Int J Appl Basic Med Res* 1: 5-10.
- Atal C (1979) A breakthrough in drug bioavailability-a clue from age old wisdom of Ayurveda. *IDMA Bulletin* 10: 483-484.
- Atal CK, Dubey RK, Singh J (1985) Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. *J Pharmacol Exp Ther* 232: 258-262.
- Singh J, Dubey RK, Atal CK (1986) Piperine-mediated inhibition of glucuronidation activity in isolated epithelial cells of the guinea-pig small intestine: evidence that piperine lowers the endogenous UDP-glucuronic acid content. *J Pharmacol Exp Ther* 236: 488-493.
- Chan K, Liu ZQ, Jiang ZH, Zhou H, Wong YF, et al. (2006) The effects of sinomenine on intestinal absorption of paeoniflorin by the everted rat gut sac model. *J Ethnopharmacol* 103: 425-432.
- Choi JS, Li X (2005) Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. *Int J Pharm* 297: 1-8.
- Wong CC, Akiyama Y, Abe T, Lipiat JD, Orfila C, et al. (2012) Carrier-mediated transport of quercetin conjugates: involvement of organic anion transporters and organic anion transporting polypeptides. *Biochem Pharmacol* 84: 564-570.
- Choi JS, Shin SC (2005) Enhanced paclitaxel bioavailability after oral coadministration of paclitaxel prodrug with naringin to rats. *Int J Pharm* 292: 149-156.
- Ali MM, Agha FG, El-Sammad NM, Hassan SK (2009) Modulation of anticancer drug-induced P-glycoprotein expression by naringin. *Zeitschrift fur Naturforschung C. Journal of biosciences* 64: 109-116.

17. Yeum CH, Choi JS (2006) Effect of naringin pretreatment on bioavailability of verapamil in rabbits. Arch Pharm Res 29: 102-107.
18. Tourniaire F, Hassan M, Andre M, Ghiringhelli O, Alquier C, et al (2005) Molecular mechanisms of the naringin low uptake by intestinal Caco-2 cells. Mol Nutr Food Res 49: 957-962.
19. Li X, Choi JS (2007) Effect of genistein on the pharmacokinetics of paclitaxel administered orally or intravenously in rats. Int J Pharm 337: 188-193.
20. Lambert JD, Kwon SJ, Ju J, Bose M, Lee MJ, et al. (2008) Effect of genistein on the bioavailability and intestinal cancer chemopreventive activity of (-)-epigallocatechin-3-gallate. Carcinogenesis 29: 2019-2024.
21. Wang Z, Kurosaki Y, Nakayama T, Kimura T (1994) Mechanism of gastrointestinal absorption of glycyrrhizin in rats. Biol Pharm Bull 17: 1399-1403.
22. Pavithra BH, Prakash N, Jayakumar K (2009) Modification of pharmacokinetics of norfloxacin following oral administration of curcumin in rabbits. J Vet Sci 10: 293-297.
23. Yan YD, Kim DH, Sung JH, Yong CS, Choi HG (2010) Enhanced oral bioavailability of docetaxel in rats by four consecutive days of pre-treatment with curcumin. Int J Pharm 399: 116-120.
24. Khanuja SPS, Arya JS, Tiruppadiripuliyur RSK, Saikia D, Kaur H, et al.(2005) Nitrile glycoside useful as a bioenhancer of drugs and nutrients, process of its isolation from moringa oleifera. Google Patents US 6858588.
25. Arya JS, Darokar MP, Khanuja SPS, Kumar S, Kumar TR, et al. (2003) Antibiotic pharmaceutical composition with lysergol as bio-enhancer and method of treatment. Google Patents WO 2003080059 A1.
26. Randhawa GK (2010) Cow urine distillate as bioenhancer. J Ayurveda Integr Med 1: 240-241.