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Phytomolecules: A potential bioenhancer for pharmaceutical drugs

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Abstract
Phyto-bioenhancer is an agent of herbal origin, which is capable of enhancing bio-availability and bio-efficacy of a particular drug or nutrient with which it is combined, without any typical pharmacological activity of its own at the dose used. These phyto-bioenhancers reduce the dose, decrease the treatment duration and increase the recovery rate. They also reduce the drug resistance or related adverse reactions which have economical implications in human, livestock and pet medicine. The main mechanisms involved for these phyto-bioenhancers are related to drug absorption *i.e.* effect on solubility, drug efflux and transport proteins, increased permeability in gastrointestinal system and drug metabolism *i.e.* inhibition/induction of drug metabolizing enzymes and thermogenic effect. The concept of bioenhancer is to achieve better therapeutic response in appropriate dose using phytomolecules like ginger, caraway, aloe, quercetin, glycyrrhizin piperine, curcumin etc. The use of phyto-bioenhancer is the most reliable means for bioavailability enhancement because these are safe, non-toxic, economical, easily procured, non-addictive, pharmacologically inert and non-allergenic in nature etc. Phyto-bioenhancers are used for various categories of drug like neutraceuticals, antibiotics, antitubercular, anticancer and cardiovascular for immediate effects. Therefore, there is a need to carry out extensive research on these phyto-bioenhancer so that they could be utilized in the marketed formulation in future prospective. Researchers must solve some issues of drug toxicity to deliver a safe and effective dose of drugs to attain desired pharmacological response.

Keywords: Phytomolecule, bioenhancer, bio-availability, drugs, dose

Introduction
Medicinal plants are major components of all indigenous or alternative systems of medicines like Ayurveda, Homeopathy, Naturopathy, Siddha, Unani, etc. Demand of herbal drug and natural plant based products has increased throughout the world due to its nontoxic, no side effect, low cost and affordable availability to poor (Jhanwar and Gupta, 2014) [1]. Many synthetic and herbal drugs suffer from the problem of low bioavailability due to low membrane permeability, lower lipo-philicity, ionic characteristics, poor water solubility or P-glycoprotein (P-gp) pumps, it is efflux pump and avoid it from reaching the target site. Bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action (Brahmankar and Jaiswal, 1995) [2]. Maximum bio-availability is attained by drugs administered via intravenous route, whereas drugs administered orally are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs/molecules enhance their bio-availability. Many natural compounds from medicinal plants have capacity to augment the bio-availability when co-administered with another drug (Gopal *et al.*, 2016) [3]. "The phenomenon of increasing the total availability of any chemical entity (nutrient or drug molecule) in biological fluid or systemic circulation is called bio-potentiation or bio-enhancement and the secondary agents which are responsible for this augmentation of plasma concentration of principle ingredient are termed as bio-potentiers or bio-availability enhancers" (Jhanwar and Gupta, 2014) [1].
Concept of bio-potentiation is not so novel, it has been so far used in old times by ayurvedic peoples so called as "*Yogvahi"* that meant to use herbs to increase or potentiate plasma concentration of drug. Piperine of black pepper was the first in this series as the major part of "*Yogvahi"*. According to the available literature, it is revealed that bio-potentiator shows bio-availability enhancement if administered at lower dose with active ingredient and it do not

introduce its own therapeutic action with the actual active principle at the therapeutic dose used. Piperine, naringin, quercetin, glycyrrhizin, genistein, sinomenine, nitrile glycoside and cow urine distillate have capability to augment and enhance the bio-availability. Augmentation of bio-efficacy reduces dose, toxicity and adverse effects so in return shorten the time and cost of treatment. These concept covers drug categories like antibiotics, anti-tubercular and anticancer, which are so potent in nature and require quite immediate effects. Bio-enhancers are recently used in many novel drug delivery formulations such as liposomes, transferosomes, ethosomes etc (Gopal *et al.,* 2016) [3].

Ideal properties of the phyto-bioenhancer

The bio-enhancers should be nontoxic, non-allergenic and non-irritating. It should be rapid-acting with predictable, reproducible activity and unidirectional in action. It must be compatible with other active pharmaceutical ingredients and stable with time and environment. It must be easily formulated into a various dosage form and easily available and cost effective (Jain and Patil, 2015) [4].

Concept of phyto-bioenhancer

The concept of bio-enhancers of herbal origin can be tracked back from the ancient knowledge of Ayurveda system of medicine. Use of Ayurvedic preparation "Trikatu" from the period between the 7th century B.C. and the 6th century A.D., which is a Sanskrit, word meaning three acrids. It refers to a combination of black pepper (*Piper nigrum* Linn.), long pepper (*Piper longum* Linn.), and ginger (*Zingiber officinale* Rosc.), which contains active component piperine, which enhances the bioavailability of drugs, nutrients, and vitamins (Khanuja *et al.,* 2007) [5].

Phyto-bioenhancer is an agent of herbal origin, which is capable of enhancing bio-availability and bio-efficacy of a particular drug or nutrient with which it is combined, without any typical pharmacological activity of its own at the dose used. The action of bio-availability enhancer was first discovered by Bose (1929) [6], an acknowledged author of "Pharmacographia Indica," reported an enhanced anti-asthmatic effect of an ayurvedic formula containing *vasaka* (*Adhatoda vasica*) when administered with long pepper. The term bio-availability enhancer was first coined by Indian scientists at the Regional Research laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine). They discovered and scientifically validated piperine as the world's first bio-availability enhancer (Atal, 1979) [7]. Phyto-bioenhancer offers comfortable, convenient, and non-invasive way to administer drugs due to dose reduction, minimization of drug resistance, minimization of drug (especially true in case of anti-cancer drug), ecological benefit and safety of the environment (Jain and Patil, 2015) [4].

Mechanisms of action of phyto-bioenhancers

Different phyto-bioenhancers may have same or different mechanism of action. Nutritional bio-enhancers enhance absorption by acting on gastrointestinal tract. Antimicrobial bio-enhancers mostly act on drug metabolism process. It increases the absorption of drug molecule in gastrointestinal region because of its vasodilator action that results in higher extent of perfusion in the area (Khajuria *et al.,* 2002) [8] and alteration of drug transporters such as inhibition of P-glycoprotein efflux pump (Tatiraju *et al.,* 2013) [9]. It increases gastrointestinal blood supply and reduces hydrochloric acid secretion (Annamalai and Manavalan, 1990) [10] and suppresses the first pass metabolism (Tatiraju *et al.,* 2013; Bhardwaj *et al.,* 2002) [9, 11].

It may also decrease gastric emptying time, gastrointestinal transit time (Bajad *et al.,* 2001) [12] and increase bile secretion, termed as cholagogue or cholerectics effect (Majeed *et al.,* 1996) [13]. It enhances the sensitivity of receptors and also modulates cell transduction pathways so decrease the efflux signals (Balakrishnan *et al.,* 2001) [14]. It interferes with the extent of glucuronidation in gut. Mainly it lowers the endogenous UDP-glucuronic acid content and also by inhibiting the UDP-glucuronyl-transferase (Atal *et al.,* 1985) [18]. It has thermogenic, bioenergetics properties (Majeed *et al.,* 1996; Reanmongkol *et al.,* 1988; Jamwal and Singh 1993) [13, 15, 16] and modulates the dynamics of cell barrier or blood brain barrier ultimately ends in enhancement of transportation of drugs (Balakrishnan *et al.,* 2001) [14]. It stimulate the γ-glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids (Johri *et al.,* 1992) [17] and inhibit the drug metabolizing enzymes such as suppression of cytochrome P450 enzymes and its iso-enzymes (Atal *et al.,* 1985; Reen *et al.,* 1993) [18, 19].

Classification of phyto-bioenhancers

The bioenhancer can be classified according to source (Gopal *et al.,* 2016) [3]. It may be plant origin (eg: Piperine. Turmeric, Naringin, Allicin, Quercetin, Genistein, Caraway, Black Cumin, Niaziridin, Lysergol, Gingerol, Stevioside) and animal origin (eg: Cow urine distillate). The phyto-bioenhancers can also be classified based on mechanism of action (Tatiraju *et al.,* 2013) [9]. It may inhibit the P-gp efflux pump and other efflux pump (eg: Genistein, Cuminum cyminum, naringin etc. It may also suppress the CYP-450 enzyme and its isoenzyme (eg: Narigin, Gallic acid and its esters etc). It may regulate the gastrointestinal tract function to facilitate better absorption (eg: Aloe, Niaziridin, Ginger etc).

Challenges with phyto-bioenhancers

Although bio-enhancers in drug delivery have been successful, not all approaches have met with the same success. New bio-enhancers being developed come with challenges which have to be surmounted. One of the challenges is to improve on properties of drug formulations such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site specific targeting. Another challenge of research and development of herbal bioenhancers is large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization.

Examples of phyto-bioenhancers

Since then phyto-bioenhancers have generated global interest and research in the field and has led to discovery of many other new bioenhancers. Piperine remains the most potent and extensively researched bioenhancer till date. It is safe, effective, extremely economical and easily manufactured for commercial use. It is also a broad spectrum bioenhancer acting on several classes of modern drugs as noted elsewhere (Kesarwani *et al.,* 2013) [37]. A detailed description of some of the bioenhancers based on the above classification system is as follows:

Piperine (Black pepper)

Piperine (1-piperoyl piperidine) is an amide alkaloid found in plants of Piperaceae family like *Piper longum* (long pepper), *Piper nigrum* (black pepper). The bioenhancing property of piperine was first utilized in the treatment of tuberculosis in human. Piperine was found to increase the bioavailability of rifampicin by about 60% and hence reduce the dose from 450 to 200mg (Atal and Bedi, 2010) [20]. In human medicine piperine is approved to be combined with antitubercular drugs. Piperine also showed enhanced bioavailability when combined with Nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase which is used in combination with other antiretroviral agents for the treatment of HIV-1 infection (Kashibhatta and Naidu, 2007) [21]. Piperine also increases the bioavailability of curcumin, the active principle of turmeric (*Curcuma longa*). A 20 mg dose of piperine can increase the bioavailability of curcumin by 20 fold in humans (Shoba *et al.,* 2008) [22]. Several animal studies on piperine have shown promising results in bioenhancing capacity of piperine for various drugs (Singh *et al.,* 2005; Janakiraman and Manavalan, 2008; Singh *et al.,* 2010) [23, 24, 25].

Aloein and Emodin (*Aloe vera*)

Aloe, a perennial and succulent xerophyte has widely been used in both human and veterinary medicine for its immune-modulatory, wound and burn healing, hypoglycemic, anticancer, gastro-protective, antifungal, and anti-inflammatory effects (Maan *et al.,* 2018) [26]. *Aloe vera* may be a promising future nutritional herbal bioenhancer. It contains aloein and emodin which are responsible for improvement of the absorption of vitamin C and E (Vinson *et al.,* 2005) [27]. The ethanolic extract of *Aloe vera* was found to augment the hypoglycemic effect of glipizide in streptozotocin induced diabetic rats (Naveen *et al.,* 2016) [28]. Due to its cyto-protective effects on gastric mucosa through induction of endogenous prostaglandin production, concomitant use of *Aloe vera* and pantoprazole for the gastro-esophageal reflux symptoms in mustard gas victims were found to be improved compared to single treatments (Panahi *et al.,* 2006) [29]. Meanwhile, aloe ingestion was found to activate the functions of P-gp and CYP3A, decreasing the cyclosporine bioavailability in a rat model, therefore a decrease in the bioavailability of the related absorbed/metabolized drugs could be expected (Yang *et al.,* 2017) [30].

Niaziridin (Drumstick pods)

Drumstick pods contain niaziridin, a nitrile glycoside which is a powerful bioenhancer. It regulates gastrointestinal functions to facilitate better absorption. It enhances the bioavailability of rifampicin by 38.8 folds at 1.00 µg/ml. It also enhances the bioavailability of Clotrimazole by 5-6 folds. An *in-vitro* study of active fraction of *M. oleifera* pods against *Mycobacterium tuberculosis* (H37Ra) exhibited no anti-tuberculosis activity at the concentration at which it enhanced the anti-tubercular activity of rifampicin (Pal *et al.,* 2010; Khanuja *et al*., 2005) [31, 32] performed a pre-clinical study to evaluate the influence of *M. oleifera* on pharmacokinetic disposition of rifampicin using HPLC method. They orally administered to Swiss albino mice a dose of 20 mg/kg body weight of rifampicin along with a dose of 0.10 mg/kg body weight of the active fraction of *M. oleifera* (*viz.* Niaziridin). They observed the bioavailability pattern shown in the following figure thereby proving the success of Niaziridin as an effective bioenhancer for rifampicin (Pal *et al.,* 2010) [31].

Flavonoid glycoside (Black cumin)

Black cumin (*Cuminum cyminum*) is a carminative, estrogenic, anti-nociceptive, anti-inflammatory, anti-oxidant and anti-microbial. The bioenhancer flavonoid glycoside present in cumin is 3,5-dihydroxyflavone-7-O-β-D-galactouronide-4-β-O-Dglucopyranoside. The effective dose of the bioenhancer extract is in the range of 0.5-25.00 mg/kg body weight. Percentage enhancement of bioavailability for Rifampicin is 250%, Cycloserine is 89%, Ethionamide is 78%. The results obtained revealed that the Cmax of rifampicin was enhanced by 35% and the AUC was enhanced by 53%. Apart from the above bioenhancing effects, black cumin also enhances the bioavailability of antibiotics (Cefadroxil-90% and Cloxacillin-94%), antifungal (Fluconazole -170%), antiviral (Zidovudine-330%) and anticancer (5-Fluorouracil-335%) drugs (Bedi *et al.,* 2006; Qazi *et al.,* 2009) [33, 34].

Curcumin (Turmeric)

Turmeric (*Curcuma longa*) is a common household item used as remedy for various ailments. Curcumin, a flavonoid from turmeric suppresses drug metabolizing enzymes like CYP3A4 in liver and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of Celiprolol and Midazolam in rats. The bioenhancer nature of curcumin is similar to piperine (Singh *et al.,* 2005) [23]. Curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues (Basu, 2004) [35]. It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs.

Allicin (Garlic)

Active bioenhancer phytomolecule in garlic is Allicin. It enhances the fungicidal activity of Amphotericin B against pathogenic fungi such as *Candida albicans* and *Aspergillus fumigatus* in addition to yeast *Saccharomyces cerevisiae*. Amphotericin B exhibits enchanced antifungal activity against *S. cerevisiae* when given along with Allicin (Ogita *et al.,* 2006; Kesarwani and Gupta, 2013) [36, 37]. Gallic acid esters like propyl gallate, octyl gallate, aluryl gallate etc. have been found to enhance bioavailability of several drugs like nifedipine (Wacher and Benet, 2001) [38].

Naringin (Grape/Apples)

Naringin is the major flavonoid glycoside found in grape fruit, apples, onions and tea. It exhibits pharmacological actions like anti-oxidant, anti-ulcer, anti-allergic and blood lipid lowering. Naringin is capable of inhibiting intestinal CYP3A4, CYP3A1, CYP3A2, P-gp and thus acts as a bioenhancer. Pretreatment with oral ingestion of naringin (3.30 and 10.00 mg/kg body weight) improves the AUC for intravenous paclitaxel (3.00 mg/kg body weight) in a dose dependent manner (Lim and Choi, 2006) [39]. Other drugs bio-enhanced are Diltiazem, Verapamil, Saquinavir and Cyclosporine A (Dudhatra *et al.,* 2012; Mekala and Arivuchelvan, 2012) [40, 41].

Quercetin (Citrus Fruits)

Quercetin is a flavonoid; an aglycone form of a number of other flavonoid glycosides found in citrus fruits. It exhibits anti-oxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic activities. It works by inhibiting CYP3A4 and P-gp efflux pump. Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including Diltiazem, Digoxin, Verapamil, Etoposide, and

Paclitaxel (Lim and Choi, 2006; Dudhatra *et al.*, 2012; Mekala and Arivuchelvan, 2012) [39, 40, 41].

Genistein (Soyabean)

Genistein is a phytoestrogen belongs to the isoflavone class of flavonoids found in a number of dietary plants like soyabean (*Glycine max*) and kudzu (*Pueraria lobata*). It is a P-gp and BCRP efflux pump inhibitor. The presence of genistein (10 mg/kg body weight) causes an increase in AUC by 54.70% and a decrease in total plasma clearance by 35.20% after oral administration of paclitaxel at dose of 30 mg/kg body weight (Lim and Choi, 2006; Dudhatra *et al.*, 2012; Mekala and Arivuchelvan, 2012) [39, 40, 41].

Carvone and Limonene (Caraway/cumin)

Caraway/cumin which is a P-gp efflux pump inhibitor consists of the dried ripe fruits of *Carum carvi* of family umbelliferae. It shows anti-oxidant, anti-microbial, diuretic and carminative. The main constituents are carvone and limonene. The effective dose of the bioenhancer extract is in the range of 5-100 mg/kg body weight. Percentage enhancement of bioavailability for rifampicin is 110.00%, for cycloserine is 75.00%, for ethionamide is 68.00%. Apart from the above bioenhancing effects, caraway also enhances the bioavailability of antibiotics (Cefdinir-89.00% and Cloxacillin-100%), antifungal (Amphotericin B-78.00%), antiviral (Zidovudine-92%) and anticancer (5-Fluorouracil-90%) drugs at the dose of 1-55 mg/kg body weight (Qazi *et al.*, 2006) [42].

Lysergol (**Morning glory plant)**

Morning glory plant is a source of lysergol that enhances the bioavailability of rifampicin by 4.5-6 folds at 0.2 µg/ml concentration. It also enhances the bioavailability of antibiotics in the range of 2-12 folds. It's mechanism of bioenhancer action is not yet clearly known (Mekala and Arivuchelvan, 2012) [41].

Glycyrrhizin (Liquorice)

Liquorice consists of dried, peeled or unpeeled, root and stolon of *Glycyrrhiza glabra* and exhibits anti-hepatotoxic, anti-fertility, anti-inflammatory, expectorant and anti-oxidant activity. It contains glycyrrhizin which enhances the bioavailability of rifampicin by 6.5 fold at the concentration of 1 µg/ml. It also enhances the bioavailability of taxol by 5 fold at the concentration of 1 µg/ml (Khanuja *et al.*, 2005) [43].

Gingerol (Ginger)

Ginger contains Gingerol which facilitates better absorption by regulating GI tract function. The effective dose of the bioenhancer extract is in the range of 10-30 mg/kg body weight. It enhances the bioavailability of Rifampicin by 65% and Ethionamide by 56%. It also enhances the bioavailability of antibiotics (Azithromycin-78%), antifungal (Ketoconazole-125%), antiviral (Zidovudine-105%) and anticancer (5-Fluorouracil-110%) drugs (Qazi *et al.*, 2002) [44].

Stevioside (Stevia/Honey leaf)

Stevia is anti-hypertensive agent and also promotes insulin secretion. The bioenhancing chemical constituent present in *Stevia* is stevioside. Though the mechanism of action is not known, it enhances the bioavailability of anti-tubercular, anti-leprotic, anticancer, antifungal and antiviral drugs. The effective dose of the bioenhancer extract is in the range of 0.01-50 mg/kg body weight (Gokaraju *et al.*, 2010) [45].

Sinomenine (*Sinomenium acutum*)

Sinomenine is an alkaloid extracted from *Sinomenium acutum*. It is found to increase the bioavailability of paeoniflorin by inhibition of P-gp efflux pumps. Paeoniflorin is used in the treatment of inflammation and arthritic conditions but has a poor absorption rate and thus a very low bioavailability (3-4%) when administered orally (Cheng *et al.*, 1964; Takeda *et al.*, 1995) [46, 47].

Capsaicin (Chili pepper)

It is commonly known as Chili pepper (*Capsicum annum*) which gives capsaicin that enhances the bioavailability of theophylline and ciprofloxacin. In an experiment on rabbits, oral dose of theophylline with or without capsaicin was given the second maintenance dose of bioenhancer after 11 hours raised the plasma levels of theophylline (Bouraoui *et al.*, 1988; Lopez *et al.*, 2007) [48, 49].

Peppermint oil (Mentha piperita)

Peppermint oil significantly improves the oral bioavailability of cyclosporine. Co-administration of 100 mg/kg body weight peppermint oil almost tripled the Cmax and AUC of Cyclosporine. It exerts its mechanism of action probably by CYP3A inhibition (Wacher *et al.*, 2002) [50].

Applications of phyto-bioenhancers

The bioenhancer is primarily targeted for toxic drugs, expensive drugs, scarce drugs, poorly bioavailable drugs or drugs which need to be given for prolonged periods. However, it can also be used in any drugs influenced by bioenhancers. The discovery and characterization of bioenhancers has led to several patent applications. Piperine is marketed as bioenhancer in mono preparations and as a component of dietary supplements that contain different vitamins curcumin, resveratrol or Coenzyme Q_{10}. Since, bioenhancer can reduce the dosage and cost of expensive medication while making treatment safer, its application has for the first time been done in humans in treating tuberculosis for which the existing drugs are toxic and expensive and need to be administered over prolonged periods. In India where low treatment costs for medical care are essential, the drug Risorine is approved against tuberculosis. Besides the antibiotics rifampicin and isoniazid it contains piperine (Atal and Bedi, 2010) [20].

Additional functions of phyto-bioenhancers

Even though phyto-bioenhancers are not pharmacologically active, they can have added benefits such as reduction of gastrointestinal side effects and hepatotoxicity of primary active drug which further makes formulation safer, better tolerated and again reduces drug toxicity and drug resistance. For example, by reducing the required dose of expensive toxic Rifampicin by 60 percent, it correspondingly reduces the cost and side effects of Rifampicin while treating the dreaded tuberculosis disease. This is a great advantage to poor patients, poor countries and for dreaded diseases of man (Randhawa *et al.*, 2011) [51].

Conclusions

The development of phyto-bioenhancer is to be targeted for drugs that are poorly bioavailable, given for longer period of time, highly toxic and expensive. Phyto-bioenhancers may have non-uniform or selective pattern of their action. This may be due to different efficacy power of phytomolecules on pharmacokinetics and pharmacodynamics of drugs.

Researches are needed to know the possible use of phyto-bioenhancers with antimicrobials via parentral routes in veterinary medicine. Nutritional phyto-bioenhancers can be used as domestic and wild animal/bird feed supplement. Further, research should be carried out to evaluate clinical application of phyto-bioenhancers with antimicrobials in modern human and veterinary therapeutics.

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