Bioenhancer for Animal Health and Production: a Review

P. Mekala and A. Arivuchelvan

Department of Veterinary Pharmacology and Toxicology, Veterinary College and Research Institute Namakkal Tamil Nadu INDIA

Abstract

The combined use of drugs has become mandatory in the current scenario both in human and animals. In veterinary medicine, most commonly prescribed category of drugs are different classes of antibiotics, anti-inflammatory and antihistaminic agents. There is a wide difference in bioavailability of these agents when given under different pathological conditions by different routes to different species. In order to achieve the required therapeutic concentration, high concentration of drugs is used which ends up in high cost, drug associated toxicity and development of resistance among the pathogens. A search for an alternative opened up research on isolation of active principles from plants which could act as bioenhancers. Hence the application of these compounds in veterinary medicine would necessarily be a solution to the current problems as well as augment the health and production in animals and thereby contribute to the development of health and wealth of the nation.

Keywords: Bioenhancer, piperine, bioavailability, animal production.

INTRODUCTION:

The knowledge on the use of bioenhancer is new to modern science but it was very familiar as yogvahi in Ayurveda. Yogvahi was used to enhance the bioavailability, tissue distribution, and efficacy of drugs, especially those with poor oral bioavailability and also decreasing the adverse effects (Randhawa et al., 2011). Trikatu is one such preparation used in ayurveda which is a mixture of Piper longum (long pepper), Piper nigrum (black pepper) and Zingiber officinale (ginger). The application of bioenhancer was first reported by Bose in 1929, who described the increase in antiasthmatic effect of vasaka (Adhatoda vasica) leaves by the addition of long pepper to it (Varshneya). The scientific validation of piperine as worlds first bioenhancer was done only in 1979 by Indian Scientists at Regional Research laboratory, Jammu (Atal et al., 1979) through adoption of reverse pharmacology. Since then a number of phytomolecules have been screened, reported and patented for their bioenhancing potential. The accidental discovery of penicillin by Alexander Fleming in 1928 was a landmark in the history of antibiotics. Since then variety of antibiotics were added to the list by way of meticulous screening and research. Of them, sulphonamides were the first antibacterial to be used for treatment and the credit goes to Greghard Domagk. The quinolones were the last category to occupy the astonishing list of antibacterial and after the advent of fluoroquinolones in 1980s so far there is no new antibiotic with unique mechanism of action. With the available antibiotics which played a key role in increasing the life expectancy of human beings, we still have a long way to go. Hence judicious use of these antibiotics is the need of the hour. It is estimated that globally humans consume above 250 million doses of antibiotics annually and 20-50% of that use is unnecessary depending on the class of antibiotics (Khamija et al., 2007). Indiscriminate use of antibiotics may be attributed to improper diagnosis, unnecessary use of broad spectrum antibiotics, and use of either too high or too low dose of antibiotic which in turn introduces selection pressure and ends up in development of antibiotic resistance among the microbes. Several approaches have been suggested to overcome the problem of antimicrobial resistance like combination therapy but again there is every possibility of misuse. Hence, the recent approach is to utilize the compounds that by themselves do not posses any pharmacological activity but capable of modifying the action of concurrently administered drugs. This led to the emergence of the concept of bioenhancer or biopotentiator.
They can also be called as drug facilitators since they improve the bioavailability of not only antibiotics but also anti-inflammatory agents, anti-cancer agents and nutritional compounds.

MECHANISM OF ACTION OF BIOENHANCERS:

Bioenhancers are molecules which do not possess inherent pharmacological activity of their own but promote and augment the biological activity or bioavailability of other drugs which are combined with them. They can be used in combination therapy with drugs and nutrients resulting in reduced drug associated toxicity, cost and also shorten the treatment course. A bioenhancer may act by interfering with the various stages in pharmacokinetics of a drug viz. absorption, distribution and elimination. They may act by 1. Enhancing the absorption of orally administered drugs from gastrointestinal tract by increase in blood supply (Annamalai and Manavalan, 1989). 2. Modulating the active transporters located in various locations eg. P-glycoprotein (P-gp) is an efflux pump which pumps out drugs and prevent it from reaching the target site. Bioenhancers in such case act by inhibiting the P-gp (Hayashi et al., 2006). 3. Decreasing the elimination process thereby extending the sojourn in the body. a. Inhibiting the drug metabolizing enzymes like CYP 3A4, CYP1A1, CYP 1B2, CYP2E1, in the liver, gut, lungs, and various other locations. This will in addition help to overcome the first pass effect administered drugs (Atal et al., 1985). b. Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibiting P-gp and facilitating passive tubular reabsorption. Sometimes biliary clearance is also affected by inhibiting the UDP-glucuronyl transferase enzyme which conjugates and inactivates the drug (Srinivasan, 2007).

BIOENHANCERS FROM HERBAL ORIGIN: PIPERINE

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). This not only reduces dosage, drug cost, toxicity but can also prevent rapid development of resistance to rifampicin by Mycobacterium. In human medicine piperine is approved to be combined with antitubercular drugs. The bioavailability of protease inhibitors used in management of HIV like Saquinavir, Indinavir, Nelfinavir, Lopinavir, Amprenavir were improved by administration of 30mg of piperine per dosage but it was not possible to improve bioavailability of Ritanovir (Bakulesh, 2005). 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). Piperine increased elimination half life (t1/2). The total body clearance (CIB) reduced by 21% where as total duration of pharmacological effect (td) increased by 29 per cent. Treatment with P. longum reduced the loading and maintenance dose by 33.3% respectively (Singh et al., 2005). Further, piperine administration to healthy broiler chicken prior to administration of ofloxacin enhanced the relative bioavailability of ofloxacin from 95.28 to 131.46% (Parthiban, 2007). Trikatu administration in mountain gaddi goats revealed higher values of AUC, AUMC and MRT for pefloxacin. The enhanced bioavailability was not due to increased absorption but because of decreased elimination as evidenced by the higher values of t. Based on MIC data, only marginal reduction in the dose (6-15%) was possible following trikatu administration but the duration of antimicrobial action was enhanced by about 22% (Dama et al., 2008). In rabbits the AUC for ampicillin and norfloxacin was increased by 333.8% and 174.6% respectively when piperine was coadministered (Janakiraman et al., 2008). Similarly, piperine significantly increased the absorption of metronidazole and retarded its metabolism in New Zealand white rabbits. The combination may result in reduced dose as well as dose dependent side effects (Singh et al., 2010). The standard dose of piperine used in majority of the
studies was 10-20mg oral. The LD50 of piperine in mice and rats were found to be 330 and 514mg/kg respectively. A dosage of 100mg/kg was found to be nontoxic in subacute toxicity studies (Piyachaturawat et al., 1983). In case of broiler chicken oral administration of piperine @ 1.12 mg/kg for 14 days was found to be nontoxic whereas 2.25mg/kg of piperine seems to increase the total number of leukocytes (Cardoso et al., 2009). Piperine also increases the bioavailability of antibacterials like tetracycline, ciprofloxacin, sulphadiazine; antiepileptics like phenytoin, phenobarbitone, carbamazepine; NSAID like nimesulide, diclofenac and indomethacin. Piperine in most instances inhibits the drug metabolising enzyme, CYP3A4 and thereby enhances the bioavailability. On the contrary, it is also capable of inducing certain enzymes. This may be useful in case of prodrug which needs metabolic conversion to become active drug. The opposite could also be true if it inhibits the drug metabolising enzyme required for its conversion. Hence, piperine cannot be taken as a universal bioenhancer., The pharmacokinetics of individual drugs must be studied along with coadministration or preadministration of piperine to arrive at a conclusion. But in majority of the cases it has proven to be a potent bioenhancer.

**TURMERIC:**

Turmeric (Curcuma longa) is a common house hold item used as remedy for various ailments. Curcumin, a flavonoid from turmeric suppresses drug metabolizing enzymes like CYP3A4 in liver (Zhang et al., 2008) and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of celeprolol and mida- zolam in rats (Zhang et al., 2007). The bioenhancer nature of curcumin is comparable to piperine (Singh et al., 2005) and pretreatment of curcumin at the rate of 60 mg/kg po for 3 days at 24h interval increased elimination half life and volume of distribution of norfloxacin(100mg/kg, po single dose) in rabbits. It also reduced the loading and maintenance does by 26 and 24% respectively. Curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues (Basu et al., 2004). It also modifies the physiological activity in the gastrointestinal tract leading to better absorption of drugs. It can probably delay the excretory mechanism of norfloxacin, since P-gp exists in the proximal convoluted tubule (Pavithra et al., 2009).

**GRAPE FRUIT**

Grape fruit contains naringin, a flavonoid glycoside responsible for the bitter taste of grape juice is capable of inhibiting intestinal CYP3A4, CYP3A1, CYP3A2, P-gp and thus acts as a bioenhancer. Pretreatment with oral ingestion of naringin @ 3.3 and 10mg/kg improves the AUC for intravenous paclitaxel (3 mg/kg) in a dose dependent manner (Lim et al., 2006). Ingestion of grapefruit juice increased plasma concentrations of felodipine, nitrendipine, saquinavir, cyclosporine A, terfenadine, and other compounds (Bailey et al., 1998).

**CITRUS FRUITS**

Quercetin found in citrus fruit and also in red onion is a dual inhibitor of CYP3A4 and P-gp. Pretreatment / cotreatment of quercetin @ 5-15mg/kg, through oral route half an hour before verapamil increase the absolute and relative bioavailability in rabbits. It also influences the bioavailability of diliziaem, paclitaxel, digoxin, doxorubicin and tamoxifen (Randa et al., 2011). Quercetin significantly increases the bioavailability of epigallocatechin gallate (EGGG), a main anticancer component in green tea with poor bioavailability in rats and humans due to oxidation, metabolism and its efflux (Kale et al., 2010).

**GINGER**

Ginger (Zingiber officinale) is a component of trikatu and its role is to regulate the intestinal function so as to facilitate absorption. It is used in the range of 10-30 mg/kg body weight by oral route and significantly increases the bioavailability of different antibiotics like amoxicillin, cloxacinil, cepahlexin, cefadroxil, erythromycin and azithromycin (Qazi et al., 2002).

**CUMIN/CARAWAY**

Cumin (Carum carvi) seeds are widely used as spice for culinary purpose and as flavouring agent. It is more effective as a bioenhancer when combined with ginger (10-150mg/kg) and piperine (3-15mg/kg). This composite bioenhancer increases the bioavailability (50-180%) of not only antibiotics but also other category of drugs. Cumin at the rate of 1-55 mg/kg enhances the bioavailability of antibiotics, antifungal, antiviral and anticancerous drugs. Sometimes the extracts / fractions of Carum carvi either in presence of absence of Zingiber officinale and/or piperine have been found to be highly selective in their bioavailability/bioefficacy enhancing action (Qazi et al., 2006).

**BLACK CUMIN**

Black cumin (Cuminum cyminum) at the rate of 0.5 to 2.5 mg/kg enhances the bioavailability of antibiotics (erythromycin, cepahlexin, amoxicillin), antifungal agents (fluconazole, ketoconozaloe) and antiviral drugs (Zidovudine, 5-fluorouracil) (Qazi et al., 2003). It contains vari-
ous volatile oils, luteolin and flavonoids of which bioenhancing activity is mainly attributed to the luteolin portion, a potent P-gp inhibitor.

**GARLIC**

Allicin, the phytomolecule in garlic (Allium sativum) enhances the activity of amphotericin B against yeast (Sacchromyces cerevisiae) and fungal (Candida albicans, Aspergillus fumigatus) infection (Ogita et al., 2006).

**INDIAN ALOE**

Indian aloe (Aloe vera) with its rich source of phytomolecules enhances the absorption of vitamin C and E (Vinson et al., 2005) and hence it can be used to improve the production performance in animals as well as in promoting recovery from any disease ailments.

**DRUMSTICK PODS**

Niaziridin, a novel nitrile glycoside isolated from the pods of Moringa oleifera enhances the absorption of drugs, vitamins and nutrients through the gastrointestinal membrane and thus increase the bioavailability. It enhances the bioactivity of commonly used antibiotics such as tetracycline and ampicillin against gram positive and gram negative bacteria and also antitubercular drugs like rifampicin and isoniazid. The molecule also enhances the activity of antifungal drugs against Candida albicans. The bioactive fraction enhances the activity of antibacterial, antifungal and antitubercular agents from 2 to 80 folds (Khanuja et al., 2005).

**LICORICE**

Glycyrrhizin, a plant glycoside found in licorice, the root extract of Glycyrrhiza glabra facilitates the transport/uptake of various compounds including antibiotics, antifungal and anticancer agents, vitamins and amino acids across the membrane thereby increasing the bioavailability. The activity of rifampicin, tetracycline, nalidixic acid, ampicillin, vitamin B1 and B12 increases from 2-6 fold. Glycyr rhizin also enhanced the antitumor activity of taxol in terms of inhibiting growth and multiplication of MCF-7 cancer cells by atleast 5 folds. Hence the natural glycoside glycyr rhizin which is nontoxic to humans and animals and effective at very low concentration can be readily used for therapeutic and nutraceutical applications (Khanuja et al., 2000).

**BIOENHANCER FROM ANIMAL ORIGIN: COW URINE DISTILLATE**

Cow urine/ gomutra has been elaborately explained in Ayurveda as effective medicinal substance with innumerable therapeutic properties. Cow urine has bioenhancing activity for rifampicin, and also increases action against E. coli (5-7 fold) and gram positive bacteria (3-11 fold). Cow urine distillate is more effective as a bioenhancer than cow urine. It enhances the transport of antibiotics like rifampicin, tetracycline and ampicillin across the gut wall by 2-7 folds (Khanuja et al., 2007). It also enhances the potency of taxol against MCF-7 cell lines (US Patent No. 6,410,059). Cow urine @ 1 ml per bird (White Leghorn layers) showed increase in feed intake, better feed conversion efficiency. The nutrient utilisation was also improved and thus it can be used as a growth promoter and bioenhancer in poultry (Garg et al., 2005).

**CONCLUSION:**

The bioenhancer properties of phytochemicals can be clinically exploited after appropriate dose titration studies in the species of animal in which it is intended to be used. Piperine is the only bioenhancer that has been widely studied in animals. There are a wide variety of other bioenhancers as discussed above need to be studied in animals so that their application in veterinary field can improve the health as well as production. The use of bioenhancers in veterinary medicine will help in reducing the dose, shorten the course of treatment and thereby the cost of medicine. Bioenhancer reduce the toxicity associated with over dosage due to poor bioavailability, and minimize the development of drug resistance by microbes which are not only a problem to animals but also to human beings. Above all they also improve the utilization of nutrients and hence their potential should be utilized for improving the production performance of animals.

**REFERENCES:**


A. Arivuchelvan


