USE OF HERBAL BIO-ENHANCERS IN ANIMAL HEALTH CARE

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Bio enhancers are the substances which when mixed with drug enhance the effectiveness of the drug without taking away its properties.

Advantages:

1. With bioenhancers the dosage are reduced and dangers of drug resistance are minimized.
2. Toxicity of drug will be minimized because of reduced dosage. This is especially true of anticancer drugs like Taxol.
3. There are ecological benefits too. Toxol used to treat ovarian cancer or breast cancer is derived from bark of Pacific yew tree, one of the slowest growing trees in the world. At present to treat one patient, six trees, 25-100 years old need to be felled. With bioenhancers fewer trees will be destroyed.

The concept of bioenhancers is derived the traditional age old system of Ayurveda (Science of life). In ayurveda, black pepper, long pepper and ginger are collectively termed as “Trikatu”. In sanskrit “Trikatu” means three acrids.

The action of bioenhancers first documented by Bose (1929) who described that addition of long pepper to Vasaka (*Adhatoda vasica*) leaves increased the antiasthmatic properties of vasaka leaves. The list of drugs whose bio availability is enhanced by black pepper or long pepper or its alkaloid, piperine are given below:

Sr.	**Drug**	**Bioenhancer**	**Species**	**Reference**
1.	Tetracycline	*Piper chaba*	Dog	Atal *et.al*. (1980)
2.	Sulfadiazine	*Piper chaba*	Dog, rat	Atal *et.al*. (1980)
3.	Vasicine	Piperine	rats	Zutshi & Kaul (1982)
4.	Sulfadiazine pyra zinamide Rifampicin, Isoniazid	Piperine	Human volunteers	Zutshi (1985)
5.	Phenytoin	Piperine	Human volunteers	Bano & coworkers (1987)
6.	Pentobarbitone	Piperine	Rats	Majumdar *et.al*. (1990)
7.	Nimesulide	Piperine	Human volunteers	Mathur *et.al*. (1998)
8.	Indomethacin Carbamazepine	Trikatu	Rabbits	Karan *et.al.* (1999)

Bioenhancers are drug facilitators they are the molecules which by themselves do not show typical drug activity, but when used in combination enhance the activity of drug molecules in several ways including:

a) Increased bio availability of the drug across the membrane.
b) Potentiating the drug molecule by conformational interaction.
c) Acting as receptor for drug molecule.
d) Making target cells more receptive to drugs & so on.

Piperine has been found to possess bio enhancing properties. Adding this to Anti-TB and leprosy drugs has been found to enhance their effectiveness. With the use of piperine, dose of anti-TB drugs can be reduced to half. The piperine has been granted patent and phase I, II, III clinical trials have been completed. Phase III-B trials are yet to be completed.

Failurs:

Not in all cases, bio-enhancers increase the blood levels of the drugs. A few failures noticed include: Streptomycin sulfate, Benzyl penicillin, Aspirin (Atal *et.al*., 1980).

Mechanism of Action of Piperine:

The action of mechanism of action of piperine has recently been elucidated at Indian Institute of Science, Banglore using *Mycobacterium smegmatis* as the test organism (Bal Krishnan *et.al.*, 2001). Piperine has shown remarkable growth inhibitory effect on the microorganism and this inhibition is higher than that of rifampicin alone. Interestingly, piper alone, even at higher concentration, does not inhibit growth of mycobacteria. As RNA poly merase is the site of action of rifampicin and piperine was found to abrogate non specific transcription catalysed by *M. smegmatis* RNA polymerase. When RNA polymerase was purified from a rifampicin- resistant strains of *M. smegmatis*, the enzymatic activity, otherwise resistant to rifampicin, significantly decreased in presence of piperine alongwith rifampicin.

The studies of Atal and Coworkers (1984) reveal that enhancement of *in vivo* drug bio availability is possibly due to inhibition of hepatic and non hepatic drug metabolizing enzymes. Glucuronyl transferase activity is known to be inhibited by lowering of the endogenous UDP glucuronic acid contents and decreased transferase activity (Atal *et.al*., 1985; Singh *et.al*., 1986).

Further, inhibition of aryl hydrocarbon hydroxylase (AHH) and 7-ethoxycoumarin deethylase (7 ECDE)) activities were also inhibited both under *in vitro* and in vivo conditions (Atal *et.al.,* 1985, Reen and Singh *et.al.,* 1991). Methylenedioxyphenyl ring in piperine has been found to be responsible for inhibition of drug metabolizing enzymes and piperine mediated inhibition of AHH activity is consequent to suppression of the procarcinogen as a result of direct interaction of piperine with CyP_1A_1 (Reen *et.al*., 1996).

Bioavailability enhancing action of drugs is also partly due to enhancement of blood supply in enteric vessels as a result of local vasodilatation.(Annamalai & Manavalan, 1989).

A recent work conducted in Regional Research Laboratory, Jammu has shown that piperine acts as modulator of cell membrane dynamics and help the transport of drugs across these barriers. A complex with drugs and help them reach the target site rather than spread out non specifically.

Toxicity:

The LD_{50} of piperine in mice and rat was 330 mg Kg^{-1} and 514 mg Kg^{-1}, respectively. In sub acute toxicity studies, piperine at the dose rate of 100 mg Kg^{-1} for 7 days was reported to be non toxic. (Piyachaturawt *et.al*., 1983).

Bio-availability Enhancing Action on Nutrients:

Increase in glucose absorption from gastrointestinal tract of rabbits has been observed following piperine administration (Annamalai & Manavalan, 1989). Piperine has also been found to reduce the acid secretion and the decrease in the intestinal motility.

In another study, Piperine supplementation in diet for 14 days in male human volunteers resulted in 60% increase in area under the serum beta- carotene curve (AUC) than observed during supplementation with beta carotene plus placebo. (Badmaev *et.al*., 1999).

The improved bio availability of nutrients by the piperine is perhaps due to its thermo nutrient action.

Other herbal bioenhancers:

Other herbal bio-enhancers which have been obtained from the

Sr	Name	Source	Action
1.	5^1 methoxy hydnocarpin (MHC)	*Barberis fremontii*	Incapacitates MDR pump (Balasubramanian, 2006)
2.	Hydnocarpoic acid	Chaulmoogra oil	Useful in leprosy (Balasubramanium,2000)
3.	MHC analogues	Diverse sources	Useful in cancer therapy by incapacitating MDR *(*Balsubramanian, 2000)
4.	Kamdhenu Ark (cow urine distillate)	Gomutra	Bioenhancing action of anticancer drugs (Govigyan Anusandhan Kendra)
5.	Lysergol Glycyrrhizin Niaziridin	Herbal sources	Efficacy of anti cancer drugs increased (CIMAP)

Bio-enhancers in Animal Health Care

The drugs patented for bioenhancing action of human drugs can also be used in increasing efficacy bio-availability in case of veterinary drugs.

The studies conducted in our department have revealed that absorption of oxytetracycline is enhanced by oral administration of *Piper longum* (long pepper). Use of Piper longum increased elimination half life, total duration of pharmacological action. Further loading and maintenance doses were reduced upto 30-40 % in poultry birds (Singh, *et.al*., 2005).

Conclusion

The work conducted so far reveals that tradition wisdom of Ayurveda can be of immense utility in enhancing the bioavailability of allopathic drugs which have proven pharmacotherapeutic action but their therapeutic utility is marred on account of poor bio availability. Hopefully, the tradition wisdom coupled with modern technology would open new vistas in Animal Health Care. Let the traditional wisdom, modern science, modern Veterinary Science and industry come together to reap the fruits of plant biodiversity for better animal health care.

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