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Indian Herbal Bioenhancers: A Review

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ABSTRACT
Herbal bioenhancers are phytomolecules that at low doses promote and augment the bioavailability or biological activity of drugs. Their development is based on ancient knowledge of Ayurveda. They reduce the dose, shorten the treatment period and thus reduce drug-resistance problems. Due to dose-economy, they make treatment cost effective, minimize drug toxicity and adverse reactions. They are effective when used in combination with number of drug classes such as antibiotics, antituberculosis, antiviral, antifungal and anticancerous drugs. They improve oral absorption of wide range of nutrients such as vitamins, minerals, herbal extracts and amino acids. They act through several mechanisms of action affecting mainly absorption process, drug metabolism or action on drug-target. Since, bioavailability of drugs and nutrients is of equal relevant to animal health as for as human health, uses of bioenhancers are also applicable in veterinary practice. This review highlights some of the herbal bioenhancers and their applications in human and veterinary practices.
KEYWORDS: - Bioavailability, Drugs, Herbal bioenhancers, Nutrients

INTRODUCTION

It is estimated globally that there is consumption of 250 million doses of antibiotics annually and 20-50% of its use is unnecessary or irrational. Indiscriminate use of antibiotics promotes multiple drug resistance and infected individuals have to consume more amount of antibiotics may be due to reduced absorption in gut membrane, restrictive uptake by target microbe and operation of efflux pump (1). One of the possible ways to reduce drug dosage is synergism between two therapeutic agents, i.e. combination therapy. However, if both drugs used concurrently have antimicrobial property, the problem of selection pressure and drug toxicity will continue. Thus, there is need of molecules, which are not antimicrobial or target drugs but enhance activity and availability of main drugs in combination therapy.

Herbal bioenhancers are agents of herbal origin or any phytomolecule, which is capable of enhancing bioavailability and/or bioefficacy of a specified drug or nutrient at the low dose but it do not show typical pharmacological activity. The concept of bioenhancers (herbal origin) can be tracked back from the ancient knowledge of Ayurveda system of medicine. 'Trikatu' is an Ayurvedic preparation containing black pepper, long pepper and ginger, which are prescribed routinely for a variety of diseases as part of a multidrug prescription. Herbal bioenhancers have properties like non-toxic to humans and animals, effective at low concentrations, easy to formulate and enhance absorption and bioactivity of the drug or nutrient.

MECHANISMS OF ACTION

Herbal bioenhancers act through several mechanisms of action. Different herbal bioenhancers may have same or different mechanism of action. Nutritional bioenhancers mostly acts on gastrointestinal tract to enhance absorption, whereas antimicrobial bioenhancers mostly act on drug metabolism process. Various mechanisms of action postulated for herbal bioenhancers include (a) increase in gastrointestinal blood supply and reduction in hydrochloric acid secretion (2), (b) inhibition of gastric emptying time, gastrointestinal transit and intestinal motility (2,3), (c) modifications in GIT epithelial cell membrane permeability (4,5), (d) cholagogous effect (4), e) thermogenic and bioenergetics properties (4,6), (f) inhibition of drug metabolizing enzymes and suppression of first pass metabolism (7-9) and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids (10).

IMPORTANT INDIAN HERBAL BIOENHANCERS

Long pepper (*Piper longum*) and Black pepper (*Piper nigrum*)

Active compound in both *Piper longum* and *Piper nigrum* is piperine (1-piperoyl piperidine) which is responsible for bioenhancing effect. Various drugs and nutrients bioenhanced by piperine are listed in Table 1. Piperine augments transcription inhibitory activity of rifampicin by several fold against *Mycobacterium smegmatis*. Rifampicin inhibits transcription of DNA template exclusively by binding to the β-subunit of RNA polymerase. Piperine alone shows no inhibitory effect for the growth of *M. smegmatis* even at higher concentration of 50 µg/ml but increases inhibitory potential of rifampicin when given with it in ratio of 24:1, at the lower concentrations of 0.125 – 0.5 µg/ml. Piperine enhances the binding ability of rifampicin to RNA polymerase (11).

In White Leghorn (2-2.8 kg) hens, pharmacokinetic profile of orally administered oxytetracycline (10 mg/kg body weight) was studied 7 days post-oral treatment of *Piper longum* (piperine

Table 1 : Typical examples of drugs and nutrients bioenhanced by piperine.

Drug	Class of drug	Experimental model	Reference
Rifampicin	Antituberculous	Human (*In vitro)*	(11,12)
Phenytoin,	Anticonvulsant		(13,14)
Propranolol	Antihypertensive	Human	(13,14)
Theophyllin	Antiasthmatic		(13,14)
Nimesulide	NSAID	Mice	(15)
Beta lactams [1]	Antibiotics	Rats	(16)
EGCG [2]	Anticancerous	Mice	(17)
Oxytetracycline	Antibiotics	WLH hens	(18)
Ciprofloxacin	Antibiotics	*In vitro*	(19)
Beta carotene	Nutrient	Human	(20)
Vitamin B6	Nutrient	Human	(4)

1 = Amoxycillin trihydrate and cefotaxime; 2 = (-)-epigallocatechin-3-gallate; a polyphenol derived from green tea (Camellia sinensis).

equivalent to 15 mg/kg). Prior treatment of *P. longum* significantly reduced elimination rate constant (β) and increased elimination half life ($t_{1/2\beta}$) of oxytetracycline. The total body clearance (Cl_B) reduced by 21%, whereas total duration of pharmacological effect (t_d) increased by 29%. Loading and maintenance dose were reduced by 33.26% and 39%, respectively (18).

Ginger (*Zingiber officinale*)

Ginger acts powerfully on GIT mucous membrane. The role of ginger is to regulate intestinal function to facilitate absorption. Ginger is used in the range of 10-30 mg/kg body weight as bioenhancer. It exhibited significant increasing in bioavailability of different antibiotics like Azithromycin (85%), Erythromycin (105%), Cephalexin (85%), Cefadroxil (65%), Amoxycillin (90%) and Cloxacillin (90%) (21).

Drumstick pods (*Moringa oleifera*)

A new nitrile glycoside, Niaziridin has been isolated from the pods of *Moringa oleifera*. It enhances bioactivity of commonly used antibiotics against gram-positive bacteria like *Myobacterium smegmatis*, *M. tuberculosis* H37Rv (ATCC 27294) and *Bacillus subtilis* and gram-negative bacteria like *Escherichia coli* (CA 8000). It enhances activity of rifampicin, ampicillin, nalidixic acid by 1.2 - 19 folds against the gram-positive strains (22). It enhances the activity of azole antifungal drugs such as clotrimazole against *Candida albicans* by 5 - 6 folds. It also enhances absorption of Vitamin B_{12} (22).

Liquorice (*Glycyrrhiza glabra*)

Active component of liquorice responsible for its bioenhancing activity is Glycyrrhizin. It enhances cell division inhibitory activity of anticancerous drug `Taxol` (paclitxel®) by 5 folds against the growth and multiplication of breast cancer cell line MCF-7. Cancerous cells growth inhibition by Taxol (0.01 µg/ml) in presence of glycyrrhizin (1 µg/ml) was higher than treatment with taxol alone (0.05 µg/ml) (23). Glycyrrhizin is also reported to enchance (2 to 6 fold) transport of antibiotics like rifampicin, tetracycline, nalidixic acid, ampicillin and vitamins B_1 and B_{12} across the gut membrane (23).

Black cumin (*Cuminum cyminum*)

It is an effective gastric stimulant, carminative and anthelmintic. The doses of its fractions responsible for the bioavailability enhancement activity ranged from 0.5 to 25 mg/kg body weight. Bioactive fraction of *Cuminum cyminum* enhanced bioavailability of Erythromycin (105%), Cephalexin (75%), Amoxycillin (111%), Fluconazole (126%), Ketoconazole (156%), Zidovudine (270%) and 5-Fluorouracil (290%) (24).

Cumin/Caraway (*Carum carvi*)

Cumin seeds have carminative, mild stomachic, aromatic and diuretic actions. The effective dose for the *Carum carvi* bioactive fraction as bioenhancer is in the range of 1-55 mg/kg body weight. It has been reported to enhance bioavailability of antibiotics, antifungal, antiviral and anticancerous drug. It is also found to be more effective as bioenhancers when used in combination with bioenhancer from *Zingiber officinale* (10-150 mg/kg body weight) and piperine (3-15 mg/kg body weight) (25).

Garlic (*Allium sativum*)

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 exhibited enchanced antifungal activity against *S. cerevisiae* when given along with Allicin (26).

Morning glory plant (*Ipomoea spp.*)

Lysergol, a phytomolecule, enhances the killing activities of different antibiotics on bacteria and is a promising herbal bioenhancer. Bioenhancing activities of lysergol are under investigation. It has been isolated from higher plants like *Rivea corymbosa*, *Ipomoea violacea* and *Ipomoea muricata* (1).

Indian Aloe (*Aloe vera*)

Effect of two different *Aloe vera* preparations, i.e. whole leaf extract and inner fillet gel was studied on the absorption of vitamin C and E. Results indicate that the aloes improve the absorption of both the vitamin C and E. The absorption is slower and vitamins last longer in the plasma with aloes and increases bioavailability of Vitamin C and E in human (27). *Aloe vera* may be a promising future nutritional herbal bioenhancer.

CONCLUSIONS

The development of plant-based bioenhancers is to be targeted for drugs that are poorly bioavailable, given for longer

period of time, highly toxic and expensive. Herbal 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 herbal bioenhancers with antimicrobials via parentral routes in veterinary medicine. Nutritional bioenhancers can be used as animal/bird feed supplement. Further, research should be carried out to evaluate clinical application of herbal bioenhancers with antimicrobials in modern human and veterinary therapeutics.

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