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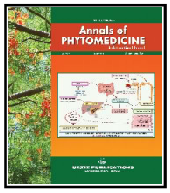

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Exploring the pharmacological properties of herbal bioenhancers: An overview

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Abstract

The global scenario of unnecessary or irrational antibiotic consumption is leading to the alarming rise of multiple drug resistance. This review introduces the concept of herbal bioenhancers as a potential solution. Herbal bioenhancers are defined as agents capable of improving the bioavailability and efficacy of co-administered drugs without possessing antimicrobial properties. The ideal characteristics of such substances include safety, compatibility with other active pharmaceutical ingredients, stability, ease of formulation, accessibility and cost-effectiveness. The mechanisms include inhibition of P-glycoprotein efflux pump, stimulation of gamma-glutamyl transpeptidase activity, and regulation of the gastrointestinal tract. Furthermore, specific herbal bioenhancers like piperine, gingerol, and curcumin are examined for their effects on cytochrome P-450 enzymes, uridine diphosphate (UDP) enzymes, and P-glycoprotein. Piperine inhibits cytochrome P-450 enzymes and drug-metabolizing enzymes which promotes enhanced blood supply to the gastrointestinal tract, and modulates proteins and enzymes associated with drug transport, resulting in increased bioavailability. These bioenhancers influence the pharmacokinetics of various drugs, enhancing their therapeutic efficacy. Various research studies were conducted to find out how the pharmacokinetic modulation of drugs in veterinary medicine, emphasizing the versatility and widespread applicability of herbal bioenhancers.

1. Introduction

Globally, an estimated 250 million doses of antibiotics are consumed each year, and it is reported that 20-50% of this usage is deemed unnecessary or irrational. The indiscriminate use of antibiotics contributes to the development of multiple drug resistance. In cases of infection, individuals may find themselves needing higher amounts of antibiotics, possibly attributed to factors such as reduced absorption in the gut membrane, limited uptake by the target microbe, and the operation of efflux pumps. Health professionals are increasingly challenged by the growing significance of bacterial infections due to the multidrug resistance exhibited by pharmaceuticals (Dhama *et al.,* 2022). A potential strategy for minimizing drug-dosage involves the synergistic interaction between two therapeutic agents, known as combination therapy. However, when both drugs concurrently exhibit antimicrobial properties, issues such as selection pressure and drug toxicity may persist. Therefore, there is a demand for molecules that do not possess antimicrobial or target drug properties but instead enhance the activity and availability of primary drugs in combination therapy. Herbs and spices include bioactive chemicals with a wide range of biological activities (Soni *et al.,* 2022). Herbal bioenhancers are agents of herbal origin or any phytomolecules, which is capable of enhancing bioavailability and/or bioefficacy of a specified drug or nutrient at the low dose but it does not show typical pharmacological activity.

"A bioenhancer is a substance that can improve the bioavailability and effectiveness of a co-administered drug, without exhibiting any pharmacological activity at the therapeutic dose employed."

Yogvahi is an ancient word of Ayurveda, which means the combination of compounds used to increase the effect of drug. Determining the biological properties of plants used in traditional medicine is helpful to the rural communities (Nayanabhirama, 2016). The concept of bioenhancer which has started from the use of "trikatu" from Ayurveda has successfully taken the lead to different modern medicines to improve their bioavailability. "Trikatu" is a Sanskrit word of ayurvedic preparations in which three acrid combinations of long pepper, black pepper and ginger was used for the treatment of many diseases. The bioenhancer term was firstly coined by Bose in 1929 who observed that there was improvement in the antihistaminic property of vasaka (*Adhatoda vasica*) leaves when it was given in combination along with long pepper (Alexander *et al.,* 2014).

2. Properties and benefits bioenhancers

The ideal substance should possess characteristics that prioritize safety and well-being, being non-toxic, non-allergenic, and non-irritating to both humans and animals. It is crucial that the substance does not generate its own pharmacological effects. Compatibility with other active pharmaceutical ingredients is a fundamental requirement. Stability, both over time and in diverse environmental

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conditions, is imperative. Furthermore, the substance should facilitate easy formulation into various dosage forms, promoting versatility in its application. Accessibility and cost-effectiveness are additional considerations to ensure its practical utility. Lastly, an enhanced activity of the drug molecule is a desirable quality, contributing to the overall efficacy of the substance (Iswariya *et al.,* 2019). The use of a bioenhancer may contribute to a reduction in the drug dosage, minimizing the cost of the drug. It also decreases the chances of the development of resistance and lowers the risk of harmful effects of drug, ultimately enhancing efficacy through increased bioavailability (Muttepawar *et al.,* 2014).

3. Herbal bioenhancer

Herbal bioenhancers refer to non-therapeutic, biologically active phytochemicals capable of enhancing the bioavailability and efficacy of various drugs. Several authors are currently being undertaken to isolate the active compounds by bioassay guided fractionation from the spices that showed high biological activity during screening. The utilization of herbs has been incorporated into traditional practices, constituting a prevalent approach to promoting health across a significant portion of the globe. In order to catalyze their utilization, researchers are actively involved in efforts to find out the bioactive compounds present in herbs and spices and comprehend their contributions to the promotion of health (Mehrotra, 2021). Determining the biological properties of plants utilized in traditional medicine is essential for the development of drugs with various applications (Nayanabhirama, 2016).

4. Source of herbal bioenhancers

Bioenhancers can be categorized into two primary classes, distinguished either by their origin or their mechanism of action:

4.1 Origin-based classification

a. **Plant origin**: Piperine (*Piper longum / Piper nigrum*), Gingerol (*Zingiber officinale*), Curcumin (*Curcuma longa*), Caraway (*Carum carvi*), Black cumin (*Cuminum cyminum*), Allicin (*Allium sativum*), Glycyrrhizin (*Glycyrrhiza glabra*), Aloe (*Aloe vera*), Quercetin (*Citrus fruits*), Niaziridin (*Moringa oleifera*).

b. **Animal origin**: Cow urine distillate.

5. Mechanisms of action of herbal bioenhancer

Various mechanisms underlie the efficacy of herbal bioenhancers. Individual herbal bioenhancers may manifest either similar or disparate mechanisms of action. Nutritional bioenhancers potentiate absorption by modulating gastrointestinal tract functions. Antimicrobial bioenhancers predominantly influence drug metabolism pathways. Regulation of gastrointestinal tract function encompasses the inhibition of hydrochloric acid secretion mediated by agents such as aloes, niaziridin, ginger, and liquorice. Furthermore, there is observed augmentation in gastrointestinal blood perfusion (Annamalai and Manavalan, 1989). Moreover, the inhibition of gastric emptying time, gastrointestinal transit, and intestinal motility can be attained through the administration of substances such as alliums, tea, and liquorice (Bajad *et al.,* 2001). It exemplified as cholagogues substances like liquorice, stimulate bile secretion in the intestine. Additionally, thermogenic/bioenergetic effects from ingredients such as garlic, ginger, and turmeric contribute to an increased metabolism rate and heightened gastric motility, alongside modifications in the permeability of gastrointestinal tract epithelial cell membranes (Khajuria *et al.,* 2002). The suppression of first-pass metabolism represents pharmacokinetic mechanisms by which certain substances alter the bioavailability and metabolism of drugs within the body (Atal *et al.,* 1985). Altering enzymatic system's activity involves the suppression of cytochrome P-450 enzymes and their isoforms (piperine, naringin, gallic acid, quercetin), as well as the stimulation of gamma-glutamyl transpeptidase (GGT) activity, leading to the enhanced uptake of amino acids. Drug transporter modification involves inhibiting the P-glycoprotein efflux pump with substances such as caraway, sinomenine, and genistein. It is possible to alter physicochemical properties, including hydrophobicity, pKa and solubility (Johri *et al.,* 1992).

5.1 Mechanism of action-based classification:

a. **Inhibitors of P-glycoprotein (P-gp) efflux pump**: Piperine**,** Caraway, Naringin**,** Quercetin**,** Cumin.

b. **Suppressors of CYP-450 and its isoenzyme**: Quercetin, Piperine**,** Naringin**,** Gallic acid.

c. **Enhancers of GIT function to improve absorption**: Aloe**,** Niaziridin**,** Glycyrrhizin**,** Ginger.

5.1.1 Enhancement of bioavailability *via* enzymatic modulation

Cytochrome P450 (CYP) and Uridine diphosphate (UDPs) play a fundamental role in the phase I metabolism of a wide range of drugs, nutrients, endogenous substances, and environmental toxins. The modification of CYP and UDP enzymes by various herbs plays a pivotal role in determining the effectiveness of therapy or the development of toxicity (Teo *et al.,* 2015). The initial exploration of the isolated bioenhancer molecule piperine revealed its ability to suppress various forms of cytochrome P450 (especially CYP3A4) and hepatic/intestinal uridine diphosphates (UDPs) (Mhaske *et al.,* 2018). Grapefruit juice, containing furanocoumarin, has been observed to enhance the bioavailability of several drugs, like calcium channel blockers, benzodiazepines, and statins. This effect is ascribed to the irreversible inhibition of cytochrome P450 3A (CYP3A) enzymes (Hanley *et al.,* 2011).

5.1.2 Enhancing bioavailability through alterations in transporter proteins

P-glycoprotein (P-gp) serves as the primary efflux pump in cells, predominantly located in epithelial cells with excretory functions. It is prominently present on the apical surfaces of epithelial cells lining various organs, including the colon, small intestine, pancreatic ductules, bile ductules, kidney proximal tubules, adrenal gland, and endothelial cells of the blood-brain barrier (BBB). Additionally, P-gp is found on the surface of numerous neoplastic cells, playing a crucial role in transporting many drugs from the blood into the intestinal lumen (Amin, 2013). Piperine, naringin, silymarin, quercetin, caraway and cumin are known herbal bioenhancers which alters the transporter proteins (Yu *et al.,* 2016).

5.1.3 Enhancing bioavailability through cholagogue effects

Cholagogues stimulate the release and secretion of bile from the gallbladder, facilitating the digestion and absorption of lipids as well as aiding in the absorption of drugs from the GIT. Primarily, choleretics enhance bile stream, while cholagogues activate gallbladder motility. These agents find application in conditions such as

cholecystitis and cholelithiasis, as well as in cases where spasmolytic activity is needed in the intestines. Liquorice is known for its cholagogue effect (Holm *et al.,* 2013).

5.1.4 Enhancing bioavailability through thermogenesis

Herbal bioenhancers, possessing thermogenic properties, elevate the metabolism rate by inducing a rise in temperature. This, in turn, enhances gastric motility and impedes the absorption of cholesterol. The thermogenic effects also result in heightened cellular energy levels and improved nutrient utilization through diverse mechanisms in digestion and GIT absorption. Natural compounds with recognized thermogenic effects incorporate garlic, ginger, and turmeric (Song *et al.,* 2017).

6. Commonly used herbal bioenhancers

6.1 Black pepper

- Plant: *Piper nigrum* (Figure 1)
- Hindi name: Kali mirch
- Gujarati name: Kala mari
- Part used: Dried fruit
- Active compound: Piperine

Figure 1: Black pepper.

Piperine elicits bioenhancing effects by inhibiting P-glycoprotein (P-gp) and drug-metabolizing enzymes, including arylhydrocarbon hydroxylase, uridine diphosphate glucuronyl transferase, UDP-glucose dehydrogenase, 5-lipoxygenase, cyclooxygenase-1, and cytochrome P450. Additionally, piperine promotes enhanced blood circulation to the GIT tract, reduces hcl secretion, and modulates other enzymes and proteins associated with their transport, ultimately resulting in heightened bioavailability. Piperine demonstrates bioenhancing properties for various pharmaceutical agents utilized in veterinary medicine, including pyrazinamide, propranolol, theophylline, curcumin, rifampicin, amoxicillin, oxytetracycline, and ciprofloxacin. This bioenhancement is attributed to the modulation of drug absorption and metabolism, resulting in improved therapeutic efficacy of these agents in veterinary applications (Kesarwani and Gupta, 2013). *In vitro* studies reveal that piperine attenuates the cytotoxic and genotoxic effects induced by aflatoxin B1 by inhibiting its metabolization pathways (Reen *et al*., 1997).

Balakrishnan *et al*. (2001) reported piperine enhances transcription inhibitory action of rifampicin. Rifampicin selectively inhibits DNA template transcription by binding exclusively to the â-subunit of RNA polymerase. Piperine in isolation does not demonstrate any inhibitory impact on the growth of *Mycobacterium smegmatis*, even at a higher concentration of 50 mg/ml. However, it significantly enhances the transcription inhibitory activity of rifampicin by several folds in *M. smegmatis*. Difference in the inhibitory potential of rifampicin and rifampicin with piperine is more pronounced at a lower concentration (Figure 2). The results indicate that rifampicin alone has a significantly lower growth-suppressive effect on *M. smegmatis* compared to the combination of rifampicin with piperine.

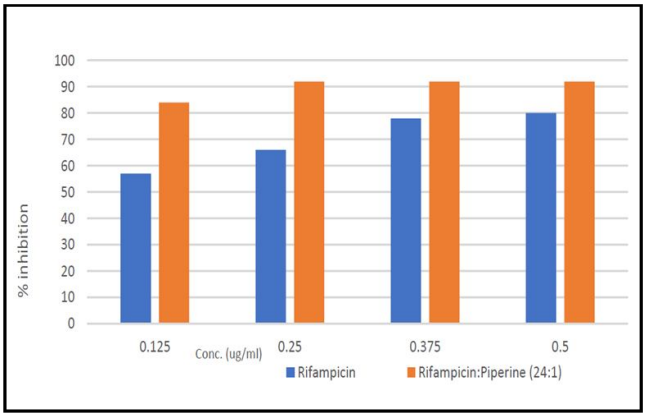

Figure 2: Effect of rifampicin and rifampicin + piperine on RNA polymerase from *M. smegmatis*.

Singh *et al*. (2005) evaluated changes in pharmacokinetics of Oxytetracycline following oral administration of *Piper longum* in poultry. The pharmacokinetic profile of over-the-counter (OTC) medication was investigated seven days after oral administration of *P. longum* extract, containing piperine equivalent to 15 mg/kg. The study was performed on layer birds, divided into two groups, each comprising eight birds with a body weight ranging from 2 to 2.8 kg. The birds in group I were administered oxytetracycline orally at the dose rate of 10 mg/kg b.w. The birds in group II were fed *P. longum* for 7 days and on day 8, oxytetracycline was administered orally as in group I. The results indicated a significantly elevated plasma concentration of OTC medication in birds treated with *P. longum* throughout the entire absorption phase (Figure 3). Pre-treatment with *P. longum* significantly decreased the elimination rate constant (β) and concurrently extended the elimination half-life. Total body clearance (Cl_B) exhibited a reduction of 21%, while the total duration of pharmacological effect (td) concurrently increased by 29% following the intervention (Table 1).

Table 1: Comparative pharmacokinetics of oxytetracycline administered orally (10 mg/kg) in control and *P. longum* treated birds (Mean ± SE)

Parameters (unit)	Control (OTC alone)	OTC + Piperine
β(/h)	0.147 ± 0.011	0.112 ± 0.006**
t1/2β (h)	4.934 ± 0.422	6.370 ± 0.438**
AUC (µg/ml/h)	5.055 ± 0.689	6.417 ± 0.317*
td (h)	16.38 ± 1.4	21.142 ± 1.453**
Cl_B (ml/kg/h)	184.63 ± 7.7	145.97 ± 14.42**

*Significant at $p<0.05$, **Highly significant at $p<0.01$.

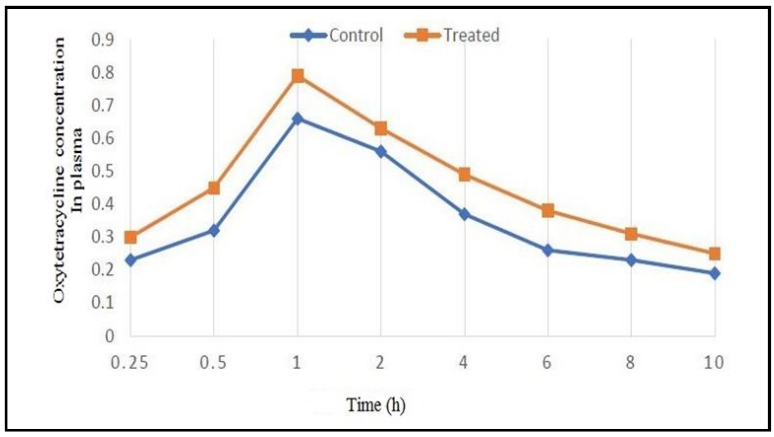

Figure 3: Comparison of mean plasma levels of oxytetracycline (µg/ml) at different time intervals following oral administration in control and *P. longum* treated layer birds (n=8).

Sadariya *et al.* (2018) investigated the pharmacokinetics of gemifloxacin both in isolation and in combination with piperine in layer birds. The findings revealed that piperine significantly augmented the oral bioavailability of gemifloxacin, approximately doubling its bioavailability in layer birds after the oral co-administration of gemifloxacin with piperine (Table 2).

Table 2: Comparative pharmacokinetics of gemifloxacin administered orally in control and piperine treated and pretreated birds (Mean ± SE)

PK parameter	Gemifloxacin	Gemifloxacin + Piperine	Piperine pre-treatment + Gemifloxacin
C_{max} (ng/ml)	181.71 ± 3.80	214.02 ± 2.25**	236.67 ± 1.73**
AUC_{0-t} (ng.h/ml)	811.20 ± 13.12	1311.40 ± 11.58**	1394.42 ± 11.61**
$AUC_{0-\infty}$(ng.h/ml)	870.18 ± 14.81	1390.77 ± 12.36**	1499.30 ± 14.59**
$AUMC_{0-\infty}$(ng.h^2/ml)	4969.77 ± 97.86	7648.84 ± 86.63**	8552.86 ± 134.09**
Vdarea (ml)	61888.73 ± 3151.53	36370.14 ± 839.67**	37809.93 ± 2177.18**
Cl_B (ml/h)	18244.54 ± 863.51	10700.37 ± 182.83**	10152.75 ± 570.45**
F (%)	15.50 ± 0.90	25.79 ± 0.65**	30.22 ± 2.95**

*Significant at $p<0.05$, **Highly significant at $p<0.01$.

6.2 Ginger

- Plant: *Zingiber officinale* (Figure 4)
- Hindi name: Adrak
- Gujarati name: Adu, Sunth
- Part used: Rhizome
- Active compound: Gingerol

Figure 4: Ginger.

Gingerols are present in the rhizome extract of *Zingiber officinale*, which can undergo further conversion into shogaols, zingerone, and paradol. These compounds play a regulatory role in intestinal functions, facilitating the absorption of drugs and exhibiting cholagogue effects (Yurdakok- Dikmen *et al.,* 2018). The co-administration of ginger significantly altered the pharmacokinetic attributes of pefloxacin in rabbits, resulting in increased maximal concentration, area under the curve (AUC), and half-life (Naduka *et al.,* 2013). It was demonstrated to enhance the bioavailability of methotrexate, 5-fluorouracil, and acyclovir (Alexander *et al.,* 2014).

Naduka *et al.* (2013) conducted a study comparing the pharmacokinetic attributes of orally administered pefloxacin alone and in conjunction with ginger in rabbits. In the initial phase, rabbits received oral pefloxacin at a dose of 100 mg/kg body weight. In the subsequent phase, 30 min after the administration of 4 ml of ginger extract, the animals were again administered the same dose of pefloxacin as in phase one. The inclusion of ginger resulted in increased maximal concentration and a significant elevation in both area under the curve (AUC) and area under the moment curve (AUMC) of pefloxacin (Figure 5 and Table 3).

Table 3: Comparative pharmacokinetics of pefloxacin administered orally (100 mg/kg) alone and in the ginger treated rabbits (Mean ± SEM)

PK parameter	Pefloxacin alone	Ginger pretreatment + Pefloxacin
C_{max} (µg/ml)	2.55 ± 0.794	2.96 ± 0.746*
AUC (µg.h/ml)	21.37 ± 7.442	36.84 ± 4.856**
AUMC (µg.h²/ml)	217.73 ± 66.513	417.86 ± 41.038**
$T_{1/2}$ (h)	10.02 ± 3.548	15.64 ± 1.187**
Cl (ml/kg/h)	0.79 ± 0.183	0.21 ± 0.017*

*Significant at $p<0.05$, **Highly significant at $p<0.01$.

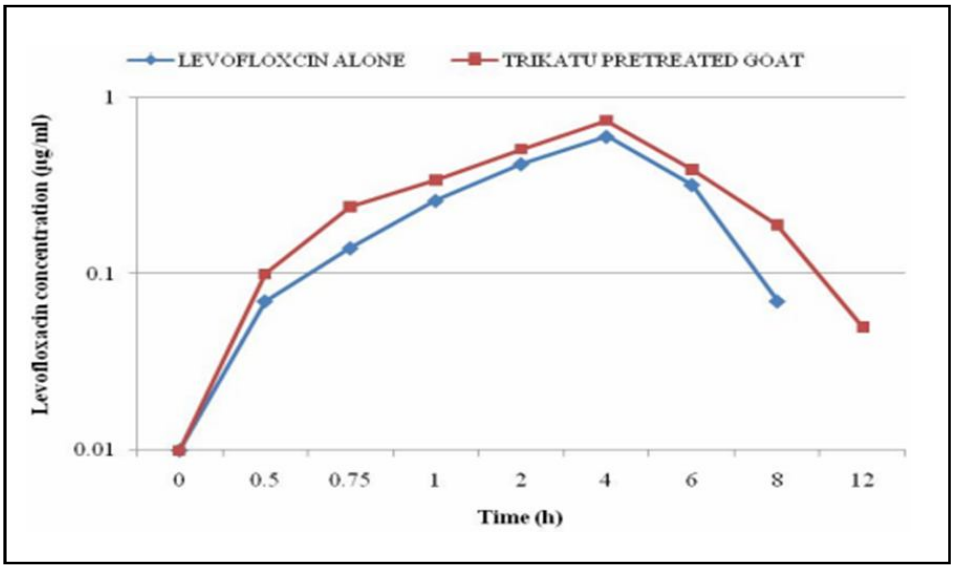

Figure 5: Plasma concentration-time profile of pefloxacin alone and in the presence of ginger in rabbits following a single oral administration (Perf is Pefloxacin and Gin is Ginger).

Patel *et al.* (2019) documented the pharmacokinetics of levofloxacin in goats pre-treated with trikatu. Levofloxacin was orally administered at a dose rate of 4 mg/kg of body weight in a randomized manner among six goats. The powdered form of trikatu was suspended in water, and piperine equivalent to 20 mg/kg body weight was orally administered through an esophageal tube for 7 days as pretreatment before the administration of levofloxacin. In trikatu-pre-treated goats, significant increases were observed in pharmacokinetic parameters, including maximum plasma concentration (C_{max}), area under the curve (AUC), and bioavailability (Figure 6 and Table 4).

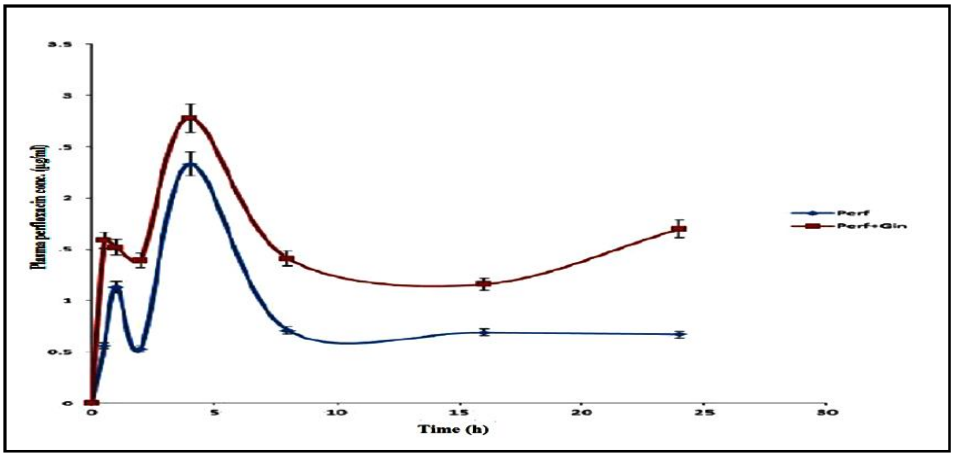

Figure 6: Plasma concentration vs. time profile of levofloxacin (4 mg/kg, orally) in normal and trikatu pretreated goat (n = 6).

Table 4: Pharmacokinetic parameters (Mean ± SE) of levofloxacin (at a dose rate of 4 mg/kg of body weight) in normal and trikatu pretreated goat after oral administration (n = 6)

Pharmacokinetic parameters	Levofloxacin	Trikatu pretreatment + Levofloxacin
C_{max} (µg/ml)	0.60 ± 0.03	0.74 ± 0.03 **
AUC (µg.h/ml)	2.86 ± 0.14	4.15 ± 0.10 **
AUMC (µg.h^2/ml)	11.62 ± 0.70	20.53 ± 0.65 **
F (%)	21.49 ± 1.60	1.31*

*Significant at $p<0.05$, **Highly significant at $p<0.01$.

Dama *et al.* (2008) evaluated the effect of trikatu pretreatment on PK of pefloxacin in goats. The research involved six healthy adult mountain Gaddi goats with body weights ranging from 18 to 22 kg. The same set of animals was utilized for both treatments, with a washout period of 15 days. During the initial treatment phase, pefloxacin was administered at a dose rate of 20 mg/kg body weight. In the subsequent treatment phase, the animals received oral administration of trikatu at a dose rate of 2 g/kg for 14 days. On the 15th day, pefloxacin was administered at a dose rate of 20 mg/kg body weight. The administration of trikatu resulted in an increased bioavailability in the pharmacokinetic profile of pefloxacin (Table 5).

Table 5: Comparative pharmacokinetic profile of pefloxacin in goats: oral administration (20 mg/kg) in control and trikatu-treated groups (Mean ± SE)

Pharmacokinetic parameters	Control (Pefloxacin alone)	Trikatu treated
t1/2β (h)	2.5 ± 0.12	3.30 ± 0.19**
AUC (µg.h/ml)	27.10 ± 0.38	30.85 ±1.39**
AUMC (µg.h^2/ml)	121.10 ± 4.07	164.25 ± 15.62*
F (%)	38.83 ± 1.80	44.18 ± 2.90*

*Significant at $p<0.05$, **Highly significant at $p<0.01$.

6.3 Turmeric

- Plant: *Curcuma longa* (Figure 7)
- Hindi name: Haldi
- Gujarati name: Haldar
- Part used: Rhizome
- Active compound: Curcumin

Figure 7: Turmeric.

Turmeric, commonly known as Haldi, possesses substantial antimicrobial and herbal properties (Barman *et al.,* 2021). Curcumin is the natural phenolic pigment of *Curcuma longa*, exerts its bioenhancing properties by suppressing drug-metabolizing enzymes and P-glycoprotein (P-gp) (Hatcher *et al.,* 2008). The rhizome portion of the *C. longa* plant used medicinally (Bhavsar *et al.,* 2022). Curcumin was observed to regulate the pharmacokinetics of drugs that serve as P-gp substrates. This effect was observed in studies where celiprolol, midazolam, and paclitaxel were orally given to rats, along with marbofloxacin in broilers (Sharma *et al.,* 2017).

Abo-El-Sooud *et al.* (2017) reported that pharmacokinetics of marbofloxacin in broiler; following oral administration (100 mg/kg) was evaluated in curcumin pretreated broilers. Group I was subjected to the oral administration of marbofloxacin at a dosage of 5 mg/kg body weight. While, birds in Group II were orally administered the same dosage of marbofloxacin (5 mg/kg b.w.), following a 10-day oral pre-treatment with curcumin at a dose of 100 mg/kg b.w./day. Each treatment group consisted of twenty animals, primary treatment group orally received curcumin at a dosage of 100 mg/kg for four consecutive days. On the fifth day, both curcumin-pretreated animals and a second group of animals (administered oral paclitaxel without curcumin) received an oral dose of paclitaxel at 35 mg/kg. The results indicated a significant difference in the majority of pharmacokinetic data for marbofloxacin between curcumin-pretreated chickens and those treated solely with marbofloxacin. Curcumin pretreatment in broilers led to a significant increase in the bioavailability of marbofloxacin (Figure 8 and Table 6).

Sharma *et al.* (2017) evaluated enhancement oral bioavailability of paclitaxel by pre-treatment with curcumin in Swiss mice. In two treatment groups, each comprising twenty animals, the first group was orally administered curcumin at a dosage of 100 mg/kg for four consecutive days. On the fifth day, curcumin-pretreated animals in this group received an oral dose of paclitaxel at 35 mg/kg, while the second group received oral paclitaxel without curcumin. The results demonstrated a 1.4 to 1.5-fold increase in both C_{max} and AUC in the curcumin pre-treated group was compared to the group treated solely with oral paclitaxel. This enhancement suggests an improvement in the oral bioavailability of paclitaxel (Table 7).

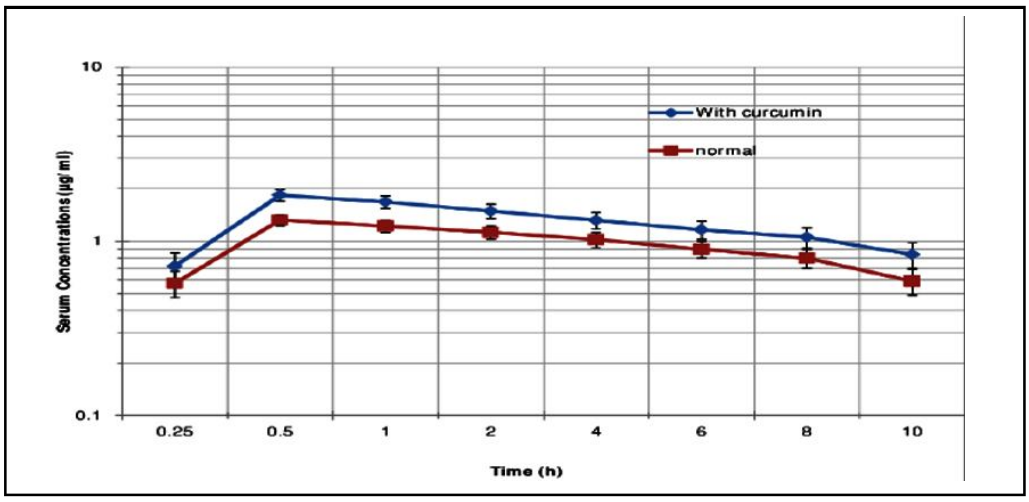

Figure 8: The serum concentrations in curcumin pre-treated group of chickens were significantly higher than marbofloxacin treated group.

Table 6: Comparative pharmacokinetic parameters of marbofloxacin administered orally (5 mg/kg) in control and curcumin treated birds (Mean ± SD)

Pharmacokinetic parameters	Control (Marbofloxacin alone)	Marbofloxacin + Curcumin
C_{max} (µg/ml)	1.32 ± 0.14	1.92 ± 0.12*
AUC (µg.h/ml)	13.22 ± 1.87	18.02 ± 2.71**
AUMC (µg.h^2/ml)	142.08 ± 10.24	217.47 ± 12.47**
F (%)	86.70 ± 4.22	>100 %

*Significant at $p<0.05$, **Highly significant at $p<0.01$.

Table 7: Comparative pharmacokinetic parameters of paclitaxel alone as well as paclitaxel in combination with curcumin

Pharmacokinetic parameters	Paclitaxel alone	Paclitaxel + Curcumin
C_{max} (µg/ml)	2.3	3.4
AUC_{0-t} (µg.h/ml)	9.9	14.3
$AUC_{0-\infty}$ (µg.h/ml)	10.6	15.0

Table 8: Percentage enhancement in bioavailability of important drug classes due to bioactive fraction of *Carum carvi*

S. No.	Drug class	Range (%)
1	**Antibiotics** (Erythromycin, cephalexin, amoxicillin)	50-110%
2	**Antifungal Agents** (Fluconazole, amphotericin B, ketoconazole)	50-80%
3	**Antiviral Agents** (Acyclovir, zidovudine)	70-95%
4	**Anticancerous** Agents (Methotrexate, 5-fluorouracil)	70-90%
5	**Anti TB/Antileprosy agents** (Rifampicin, isoniazid, pyrazinamide)	40-110%

6.4 Caraway

- Plant: *Carum carvi* (Figure 9)
- Hindi name: Jeera
- Gujarati name: Jeeru
- Part used: Seeds
- Active compound: Carvone

Figure 9: Caraway.

Caraway seed administration was observed to increase plasma levels of antitubercular drugs (rifampicin, pyrazinamide, and isoniazid) in Wistar rats when given together (Sachin *et al.,* 2009). The bioenhancing effect of caraway was associated with its permeation-enhancing properties across the absorptive surface of the small intestine. *Carum carvi* extracts were also observed to influence drugs metabolized by CYP1A1, such as bufuralol and theophylline (Naderi-Kalali *et al.,* 2005). Qazi *et al*. (2009) reported that percentage enhancement in bioavailability of important drug classes due to bioactive fraction of *Carum carvi* (Table 8).

6.5 Black cumin

- Plant: *Nigella sativa* (Figure 10)
- Hindi name: Kala Jeera
- Gujarati name: Kali Jeeri
- Part used: Seeds
- Active compound: Thymoquinone

Figure 10: Black cumin.

The alcoholic extracts of *Nigella sativa* was found to increase the intestinal permeability of amoxicillin in *in vitro* experiments using excised laboratory rat intestinal segments in a dose-dependent manner (Ali *et al.,* 2018). In addition to enhancing intestinal permeability, the fatty acids present in *N. sativa*, particularly eicosadienoic acid, were identified to computationally hinder P-gp activity against the primary amino acid sequence of P-gp from rats. This inhibition potentially contributes to an increased bioavailability of drugs (Ali *et al.,* 2015). In the context of co-administration, it was observed that the bioavailability of cyclosporine, a cyclic polypeptide employed as an immunosuppressant in organ transplantation, was reduced with the inclusion of black cumin. This reduction is attributed to its ability to activate CYP3A4 (Al-Jenoobi *et al.,* 2013). Theophylline pharmacokinetics in Beagle dogs remained unaffected by the administration of black cumin, indicating the absence of a significant impact and suggesting no discernible affinity for CYP1A2 activity (Al-Jenoobi *et al.,* 2015).

Ali *et al.* (2018) reported that bioavailability enhancement of Amoxicillin with hexane extracts of *N. sativa*. Two groups of animals (n=6) were randomly assigned. One group was administered amoxicillin (25 mg/kg body weight, po), while the other group received a combination of amoxicillin (25 mg/kg b.w., po) and *N. sativa* hexane extract (25 mg/kg b.w., po).There is enhancement of C_{max} and AUC in *N. sativa* extract treated group compared with amoxicillin treated group (Tables 9 and 10).

Table 9: There was a significantly increased (p<0.001) in amoxicillin concentration in rat plasma in presence of hexane extract (25 mg/kg po)

Time (h)	Concentration of amoxicillin (ng/ml)	Conc. amoxicillin + Hexane extract (ng/ml)
0.000	0.000	0.000
0.250	151.780 ± 8.96	439.043 ± 28.91*
0.500	527.912 ± 23.43	992.92 ± 62.73*
0.750	2152.613 ± 91.26	3091.239 ± 139.02*
1.000	4138.251 ± 156.93	5995.045 ± 196.28*
1.500	3140.012 ± 124.29	4049.738 ± 162.67*
2.000	2049.160 ± 84.51	2904.583 ± 119.28*
4.000	982.030 ± 53.75	1604.674 ± 63.61*
6.000	241.818 ± 10.41	558.281 ± 34.75
8.000	51.342 ± 0.991	123.015 ± 1.102*

*Significant at p<0.05, **Highly significant at p<0.01.

Table 10: Comparative PK parameters of amoxicillin alone as well as amoxicillin in combination with *N. sativa* hexane extract

Parameters	Amoxicillin alone	Amoxicillin + *N. sativa* hexane extract
C_{max} (ng/ml)	4138.251 ± 156.93	5995.045 ± 196.28**
AUC (ng/ml.h)	8890.40 ± 143.33	13483.46 ± 152.45**

*Significant at p<0.05, **Highly significant at p<0.01.

6.6 Garlic

- Plant: *Allium sativum* (Figure 11)
- Hindi name: Lahsun
- Gujarati name: Lasan
- Part used: Whole part
- Active compound: Allicin

Figure 11: Garlic.

Allicin is an important allyl sulfur metabolite (isolated from garlic) that enhances the fungicidal activity of amphotericin B against pathogenic fungi, including *Candida albicans, Aspergillus fumigatus*, and the yeast *Saccharomyces cerevisiae* (Jamindar *et al.,* 2014). The antibacterial activity of β-lactams, namely cefazolin, oxacillin, and cefaperazone, against *Staphylococcus* spp. and *Pseudomonas aeruginosa* was observed to be improved by allicin when tested at sub-inhibitory concentrations (Cai *et al.,* 2007). Garlic oils exhibited synergistic antifungal effects when combined with ketoconazole *in vitro* (Pyun and Shin, 2006). Reports indicate that garlic extracts inhibit certain CYP enzymes, namely CYP2C9, CYP2C19, CYP3A4, and CYP3A5, while not affecting P-gp. The bioenhancing effects of garlic are primarily attributed to its inhibitory impact on these CYP enzymes, coupled with physiological changes in circulation that decline the clearance and removal of drugs (Foster *et al.,* 2001).

Ogita *et al*. (2006) evaluated improvement of the fungicidal activity of amphotericin B (AmB) by allicin against the yeast *Saccharomyces cerevisiae.* Allicin was found to enhance AmB-induced structural damage to the vacuolar membrane, even at a non-lethal dose of AmB. This potent enhancing effect extends to the fungicidal activity of AmB against pathogenic fungi, including *Candida albicans*, *Aspergillus fumigatus*, and the yeast *S. cerevisiae* (Table 11).

Table 11: Enhanced *in vitro* fungicidal activity of amphotericin B by allicin against *S. cerevisiae*

Drug/Compound	Conc. (μM)	Action against *S. cerevisiae*
AmB alone	1	Mostly resistance
AmB alone	5	Subjected to lethal damage
Allicin alone	120	Not lethal
AmB + Allicin	0.5 + 120	More susceptible

6.7 *Glycyrrhiza glabra* (Liquorice)

- Plant: *Glycyrrhiza glabra* (Figure 12)
- Hindi name: Mulethi
- Gujarati name: Jethimadh
- Part used: Dried root and stolon
- Active compound: Glycoside glycyrrhizin

Figure 12: *Glycyrrhiza glabra* (Liquorice).

Glycyrrhiza glabra or liquorice is used to cure peptic ulcer (Menegazzi *et al.,* 2008). Glycyrrhizin, an active substance derived from licorice, has been identified as a compound that enhances the transport of certain antimicrobials (such as rifampicin, tetracycline, nalidixic acid, and ampicillin), as well as vitamins B1 and B12, across the intestinal membrane (Jain and Patil, 2015). Additionally, glycyrrhizin has been reported to enhance the activity of azole antifungal drugs, including clotrimazole, against *Candida albicans* (Khanuja *et al.,* 2006).

Khanuja *et al.* (2006) reported glycyrrhizin (1 μg/ml) *in vitro* improves activity of commonly used antibiotics such as rifampicin, ampicillin, tetracycline and nalidixic acids against *E. coli*, *B. subtilis* and *M. smegmatis* (Table 12).

Table 12: Enhancing antibiotic activity through glycyrrhizin (1 μg/ml) in conjunction with antibiotics against various organisms

Organisms	Antibiotics	Concentration (μg/ml)	Fold enhancement of activity
E. coli (CA8000)	Rifampicin rifampicin ampicillin tetracycline tetracycline nalidixic acid	20.030.06.01.02.06.0	38.812.65.32.35.250.0
B. subtilis (MTCC121)	Rifampicin ampicillin tetracycline nalidixic acid	0.050.013.52.0	19.45.13.57.0
M. smegmatis (MC2 155)	Rifampicin ampicillin tetracycline nalidixic acid	0.050.011.02.0	1.94.74.01.2

6.8 Aloe

- Plant: *Aloe vera* (Figure 13)
- Hindi Name: Gwarpatha or Dhrutkumari
- Gujarati Name: Kunvarpathu
- Part Used: Leaves
- Active Compound: Aloin

Figure 13: ***Aloe vera.***

Aloe is a perennial succulent xerophyte, has found extensive use in both human and veterinary medicine due to their diverse range of effects, including immunomodulatory, wound and burn healing, hypoglycemic, anticancer, gastroprotective, antifungal, and anti-inflammatory properties (Maan *et al.,* 2018). The hypoglycemic effect of glipizide in streptozotocin induced diabetic rats was augmented by the ethanolic extract of *Aloe vera* (Naveen *et al.,* 2016). The concomitant use of *Aloe vera* and pantoprazole for managing gastroesophageal reflux symptoms in mustard gas victims was found to be more effective compared to single treatments. This improvement is attributed to the cytoprotective effects of *Aloe vera* on gastric mucosa, achieved *via* initiation of endogenous prostaglandin production (Panahi *et al.,* 2006).

Vinson *et al.* (2005) evaluated the impact of *Aloe vera* preparations on bioavailability of vitamins C and E in human. The investigation into the plasma bioavailability of vitamins C and E involved eight subjects for vitamin C and ten subjects for vitamin E in normal fasting humans. In a random crossover design, subjects consumed either 500 mg of ascorbic acid or 420 mg of vitamin E acetate alone as a control or in combination with Aloe preparations, specifically an inner fillet gel. The results revealed an enhancement in the area under the curve (AUC) for both vitamin C & E when combined with aloe gel (Table 13).

Table 13: Areas under the plasma concentration-time curves for vitamins C and E in the presence of Aloe gel

Supplement	AUC (µM/h)
Vitamin C (500 mg)	339 ± 124
Vitamin C + Aloe gel	1031 ± 513
Vitamin E (420 mg)	19.3 ± 23.2
Vitamin E + Aloe gel	71.3 ± 22.5

7. Conclusion

Herbal bioenhancers are non-therapeutic, biologically active phytochemicals that can augment the bioavailability and efficacy of different drugs. Top of Form It helps to reduce adverse reactions/ toxicity of drugs and also minimize chances of development of drug resistance against antimicrobials. Bioenhancers operate by inhibiting the P-glycoprotein efflux pump, suppressing the activity of the CYP-450 enzyme and its isoenzymes, and regulating gastrointestinal (GIT) function, thereby facilitating improved drug absorption. Trikatu is an Ayurvedic formulation comprising long pepper, black pepper, and ginger, frequently employed as a bioenhancer for numerous drugs. Piperine, a constituent of trikatu, induces bioenhancement by inhibiting P-glycoprotein (P-gp) and drug-metabolizing enzymes. Additionally, it augments blood supply to the gastrointestinal tract (GIT) and reduces hydrochloric acid secretion, culminating in heightened drug bioavailability. Piperine demonstrated a notable enhancement in the oral bioavailability of gemifloxacin, achieving a twofold increase in layer birds. Meanwhile, gingerol, derived from *Zingiber officinale* (ginger), exerts its influence on intestinal functions, primarily amplifying drug absorption and exhibiting cholagogic effects. Trikatu significantly increased C_{max}, AUC and bioavailability of levofloxacin in trikatu pretreated goats. Curcumin derived from *Curcuma longa*, exerts its bioenhancing properties by suppressing drug-metabolizing enzymes and P-glycoprotein (P-gp). Curcumin pretreatment in broilers significantly increased bioavailability of marbofloxacin. Caraway seed has been observed to augment the plasma levels of antitubercular drugs and enhance permeation properties across the absorptive surface of the small intestine. Allicin (garlic) boosts the fungicidal activity of amphotericin B and enhances the antibacterial activity of β-lactams. Glycyrrhizin (*Glycyrrhiza glabra)* enhances the bioavailability of tetracycline, rifampicin, nalidixic acid and ampicillin (antimicrobial), vitamin B_1 & B_{12} and clotrimazole (antifungal).

The exploration of medicinal plants and their active principles with bio-enhancing potential is imperative and warrants comprehensive scientific investigation, particularly within target animal species. Herbal bioenhancers like capsaicin, quercetin and naringin are yet to be explored for their mechanism of action, therapeutics and its drug interactions.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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