



Herbal Bioenhancers in Veterinary Phytomedicine

Begum Yurdakok-Dikmen*, Yagmur Turgut and Ayhan Filazi

Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Ankara University, Ankara, Turkey

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*Correspondence:

Begum Yurdakok-Dikmen
byurdakok@yahoo.com

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Herbal bioenhancers are active phytomolecules that increase the bioavailability, bioefficacy and biological activity of various drugs when coadministered at low concentrations. These valuable compounds reduce the dose, increase the treatment rate, decrease the treatment duration, drug resistance or related adverse reactions which have economical implications in livestock and pet medicine. Eventhough the concept of herbal bioenhancers are known for years through Ayurvedic medicine, the underlying mechanisms remains unclear. The main mechanisms involved are related to drug absorption (effect on solubility, drug efflux and transport proteins, increased permeability in gastrointestinal system) and drug metabolism (inhibition/induction of drug metabolising enzymes, thermogenic effect). Due to species specific differences in these mechanisms, corresponding data on human and laboratory animal could not be attributed. As multidrug resistance is a major treat to both human and animal health, within “One Health” concept, efficient therapeutical strategies are encouraged by authorities, where focus on herbal supplements as a vast unexploited field remains to be researched within “Bioenhancement Concept.” This review brings insight to mechanisms involved in bioenhancing effect, examples of herbal extracts and phytoactive compounds and their potential in the veterinary medicine including different classes of drugs such as antibiotics, anticancerous, antiviral, and antituberculosis.

Keywords: herbal bioenhancers, veterinary medicine, bioenhancing mechanisms, herb-drug interactions, phytomedicine

INTRODUCTION

Herbal bioenhancers (biopotentiators) are facilitating phytomolecules, which are able to promote and augment the biological activity including the bioavailability and bioefficacy of a particular drug or nutrient at low doses; where no typical pharmacological activity of its own at the dose used is present (1).

From the available literature, the concept of herbal bioenhancers is mainly attributed to Ayurvedic medicine (2). In Ayurveda, the term “Yogvahi” is referred as herbs that are able to increase or potentiate the plasma concentration of drug. Piperine from black pepper is the first example of Yogvahi which is scientifically validated. As in form of Trikatu (an Ayurvedic preparation) a mixture of black pepper, long pepper and ginger is prescribed as an ailment for various diseases (3).

As herbal drugs are mainly administered through oral routes, biodegradation in stomach or gut lumen occurs where membrane permeability and metabolism are the key contributors. This eventually lowers the free drug/pharmacologically active compound concentration in the systemic circulation and the efficacy is decreased. In order to

increase the bioavailability rate, change in molecular structure and constituents of dosage form effect are studied extensively especially for oral route administered drugs (4). For this, formulation scientists adopted various strategies to enhance drug absorption; such as micronization, nanocrystals (ball-milling, dense gas), solid solutions, self dispersing solid solutions with surfactants, nanoparticles, lipid solutions, self-emulsifying drug delivery systems, surfactant-cosolvent systems (5). Meanwhile, these formulation systems are mainly designed for isolated active compounds as formulations and not for whole plant extracts. Therefore, herbal bioenhancers with different mechanism of action are favored for increasing the bioavailability of herbal preparations. Besides increase in bioavailability, bioenhancers act receptor for drug molecules, potentiate conformational interaction and make the target cells more receptive to drugs (6).

MECHANISM OF ACTION

The major mechanisms involved in bioenhancing property of plant extracts and phytochemicals are summarized as follows:

1. Alteration in the activity of enzymatic systems such as suppression of cytochrome P450 enzymes and its isoenzymes (piperine, naringin, gallic acid, quercetin) or stimulation of gamma glutamyl transpeptidase (GGT) activity (resulting uptake of aminoacids)
2. Alteration of drug transporters such as inhibition of P-glycoprotein efflux pump (caraway, sinomenine, genistein)
3. Chologogues effect (promotion of bile into intestine) such as liquorice
4. Thermogenic/Bioenergetic effects leading increased metabolism rate and increased gastric motility such as garlic, ginger, turmeric
5. Regulation of gastrointestinal tract through reduction of hydrochloric acid secretion (Aloes, niaziridin, ginger, liquorice), inhibition of gastric emptying time, gastrointestinal transit and intestinal motility (Alliums, tea, liquorice), increase in gastrointestinal blood supply, modification in gastrointestinal tract epithelial cell membrane permeability.
6. Change physicochemical properties (hydrophobicity, pKa, solubility) such as phytosome formulations
7. Effect target drug receptors

Bioenhancing Through Enzymatic Alterations

Herbal medicines are combination of biologically active compounds; where metabolism of these several compounds might occur with the similar mechanism of the administered drug; leading interaction and eventually inhibition/increase of free drug metabolizing enzymes or transporters. The change in the expression of these proteins, or physical/chemical/pharmacological competition, eventually effects the free drug/metabolite concentration and the pharmacokinetic parameters leading altered pharmacological effects. Several herbs were found to interact cytochrome p450, the major microsomal enzyme for drug metabolism/detoxification, which has high polymorphisms in both human and companion

animals (7). As CYP and UDPs are the core for phase I metabolism of many drugs, nutrients, endogenous substances, and environmental toxins; alteration of the expression or the functionality of these enzymes plays a crucial role in the efficacy of the therapy or the progress of the toxicity (8). Inhibition will lead fewer drug molecules to be metabolized with an increased concentration of untransformed drug passing from gut into the blood. Major isoenzymes among CYPs, involved in the metabolism of drugs in humans are CYP3A4, 2D6 and 2C9 family (9). Eventhough orthologue families are present in different animal species with structural similarities and substrate ranges comparable to humans; the species specific differences should be well considered for bioenhancing through enzymatic alterations. For instance, the orthologue enzyme to CYP3A4 in humans, is CYP3A12 in dogs and for CYP2D6 is CYP2D15. Also, polymorphism/genotypic variations (leading deficiencies or fold expressions) are common in different dog breeds for CYP1A, CYP2B11, CYP2C, CYP2D15 families (10). Therefore the clinically proven bioenhancing phytochemicals in human might not resemble veterinary medicine.

First purified bioenhancer molecule piperine were found to inhibit different forms of cytochrome p450 (CYP) (especially CYP3A4) (11) and hepatic/intestinal UDP-glucuronosyltransferases (UDP); while this inhibition is dependent on the administration route, dose and duration of exposure (12). Various studies reveal the potentiating effect of piperine in drug bioavailability and bioefficacy for laboratory animals such as rats, mice and rabbit along with human volunteers (11); while few are available for veterinary medicine. Oral administration of Trikatu, an Ayurvedic blend of equal parts of the fruits of Black Pepper (*Piper nigrum*), Long Pepper (*Piper longum*), and the rhizomes of Ginger (*Zingiber officinale*), increased the plasma concentration and the bioavailability of pefloxacin (fluoroquinolone antibiotic) in Gaddi goats (13). Similar increase in bioavailability and alterations of pharmacokinetics was observed for oxytetracycline treated hens which received oral *Piper longum* administration seven days prior to treatment (14).

St. John's wort (*SJW-Hypericum perforatum*), promising anxiolytic in pets were found to induce CYP3A4, CYP2C19, CYP2C9, CYP1A2, CYP2B6, CYP2E1; where decreased plasma levels of the substrates of many common drugs including antihistamines, antivirals, CNS drugs, immunosuppressants, statins, and chemotherapeutics are present with co or pretreatments such as increased warfarin and nifedipine clearance (15). The repeated administration of SJW were found to affect the pharmacokinetic profile with decreased maximum whole-blood concentration and area under the curve (AUC) in dogs treated by cyclosporine (16).

Homeopathic tinctures of *Ginkgo biloba* is used in all food producing species for improving the growth, slaughter performance and immune index; and pets for various ailments including neurological conditions and hormonal imbalances (17). *G. biloba* were found to induce various hepatic CYP enzymes, especially CYP2B-type enzymes in rats (18). *G. biloba* exerting a significant inductive effect on CYP2C19, were found

to induce omeprazole hydroxylation in a CYP2C19 genotype-dependent manner decreasing its potential efficacy in human (19). *G. biloba* increased the AUC of raltegravir, an HIV integrase inhibitor in humans by 21% and C_{max} by 44% which is favorable (20). Meanwhile, these examples with reduced AUCs in humans are mainly at doses higher than the recommended standardized extracts by European Pharmacopeia (21). In an *in vitro* microsomal study using male Beagle dogs, *G. biloba* extract inhibited CYP2C8, CYP2C9, and CYP2C19 enzyme, while no significant effect was present with coadministration of cilostazol where CYP2C is responsible for its metabolism (22).

The increase of bioavailability of several drugs including calcium channel blockers, benzodiazepines, and statins by grapefruit juice is mainly attributed to its furanocoumarin content which irreversibly inhibits CYP3A; where normal consumption inhibits only in the enterocyte cells lining the small intestine; while hepatic CYP remain unaffected unless at high concentrations (23). Meanwhile grapefruit juice has still potential on some orally-administered drugs that are metabolized by CYP3A and normally undergo extensive presystemic extraction like cyclosporine to increase the efficacy and reduce the costs. *In vitro* study using Beagle dog liver microsomes showed that grapefruit juice, lyophilized grapefruit juice, and powdered whole grapefruit inhibit cytochrome P450-mediated triazolam hydroxylation which is used as a surrogate for cyclosporine oxidation (23).

Bioenhancing Using Phytosome Formulations

Among herbal drug formulations, phytosomes as facilitating bioenhancing phytomolecules were recently introduced. Phytosomes, form a complex between a natural product and natural phospholipids; where the plant component and phosphatidylcholine form 1:1 or 1:2 molecular complex involving hydrogen bonds. The dual solubility property of this complex results in an increase in absorption and bioavailability compared to liposomes. Standardized plant extracts or polar active compounds (flavonoids, terpenoids, tannins, xanthenes) in phytosome has improved lipid solubility. They also protect the active ingredients from destruction in stomach by gastric juice and gut bacteria leading better bioavailability (24, 25). Therefore, overall phytosomes improve absorption, increase biological activity and delivery to target tissue (26).

Silybum marianum (milk thistle) contains beneficial flavonoids (silybin, silydianin and silchristin) used for hepatoprotective effects, but it is poorly absorbed through oral routes. Meanwhile; phytosomal silybin (silybin-phospholipid complex) is more rapidly absorbed, lowering the conventional dose of silymarin; which improves the biological effects with reduced adverse/toxic effects. This compound is also used in cancer prevention and treatment (prostate cancer) and management of chronic iron overload (27, 28). Another example is centenella (*Centella asiatica* L.); where the triterpenes form complex with soyphospholipids a phytosome form which increases the oral bioavailability and decrease interaction with bile salts. Centenella phytosomes are used especially in cosmetics

for its properties such as stimulation of collagen biosynthesis and modulate the metabolism in connective tissue along with reduction of increased capillary permeability. Centenella phytosomes were also found to induce antiinflammatory effect through NF- κ B signaling inhibition in a mouse model of phthalic anhydride-induced atopic dermatitis; confirming its potential use in atopic dermatitis treatment (29).

Bioenhancing Through Transporter Protein Alterations

Among transporter proteins P-glycoprotein (P-gp) acts as a physiological barrier found in the apical surface of epithelial cells adrenal gland, endothelial cells of the blood brain barrier (BBB) and in the surface of many neoplastic cells where it contributes of many drugs from the blood into the intestinal lumen. The inhibition of this efflux pump as an attractive therapeutic strategy through interference of the protein binding site, ATP hydrolysis or alteration of cell membrane lipid integrity, improves the delivery of therapeutic agents and increase the intracellular concentrations of drugs (30). Due to high prevalence of side effects of commercially available synthetic P-gp inhibitors, plant based alternatives are sought for future drug candidates. Some active compounds of plants were shown to have inhibitory effect confirmed by *in vitro* and *in vivo* studies. Among these, flavonoids (3,7-dihydroxyflavone; 2',4'-dihydroxychalcone from *Zuccagnia punctata*, quercetin from *Ginkgo biloba*; rutin from *Ruta graveolens*; genistein from vegetables; kaempferol from *Kaempferia galanga* L. root; icaritin from *Herba epimedii*; baicalein from the roots of *Scutellaria*; biochanin A from the bark of *Aesculus hippocastanum* L., silymarin from the seeds of milk thistle, wogonin from the roots of *Scutellaria baicalensis* Georgi.), alkaloids (glaucine from the stems of *Corydalis yanhusuo*, cepharanthine from the roots of *Stephania cepharantha*, pyrrolidine from *Piper boehmeriifolium*, tetrandrine and fangchinoline from the root of *Stephania tetrandia*, indole-3-carbinol from Brassica, pervilleines B and C from *Erythroxylum pervillei*, stemocurtisine and oxystemokerrine from the roots of *Stemona aphylla* and *Stemona burkillii*), coumarins (cnidiadin from *Tordylium apulum*, clausarin from *Citrus sinensis*, galbanic acid from the roots of *Ferula szowitsiana*, farnesiferol A from the roots of *Ferula persica*, GUT-70 from stem bark of *Calophyllum brasiliense*), terpenoids ((R)-(+)-citronellal essential oil from *Zanthoxylum fructus*, abietic acid from pine and conifers, Glycyrrhetic acid from *Glycyrrhizae radix*, euphomelliferine and euphomelliferenes A from *Euphorbia mellifera*, Euphorbia factor L10 from *Euphorbia lathyris*, euphoportlandols A and B from *Euphorbia portlandica*) and steroids (Paris saponin VII from *Trillium tschonoskii*, ginsenoside Rg₃ and protopanaxatriol ginsenosides from *Panax ginseng*, gracillin and polyphyllin D from *Paris polyphylla*) were promising (31).

Meanwhile, genetically mediated P-gp deficiencies in dogs (several breeds including Longhaired whippet, Collie, Australian Shephard, Silken Woundhound are heterozygous for ABCB1-1 Δ) contribute increased brain penetration of P-gp substrates such as macrocyclic lactones, loperamide, acepromazine, butorphanol, vincristine leading neurotoxicity (32). The relation

between the P-gp inhibitors and genetic deficiencies should be as well considered. Such as, the potent inhibition of the drug transporter P-gp by the oral flea preventative spinosad was shown in canine lymphoid cell-line GL-1 and the P-gp overexpressing subline GL-40, where kinetics of ivermectin, cyclosporin, verapamil, loperamide and ketoconazole were altered (33). As currently available P-gp inhibitors can not discriminate between the expression of this protein in normal tissues and cancerous tissues, intrinsic toxicity (cytotoxicity) of the drugs are common which would eventually harm the patient. Therefore, monitoring systems are required for precautionary measures of such severe interactions (32). Contrary to dogs, few studies are available for the functional modeling of feline P-gp (use of feline lymphoma cells) for further plant-drug interactions (34).

Bioenhancing Through Chologogue/Choleretic Effect

Chologogues stimulate the release and secretion of bile from gallbladder, aiding in the digestion and absorption of lipids along with absorption from drugs from the gastrointestinal tract. Mainly, cholergics improve bile flow and chologogues stimulate gallbladder motility. They are mainly used in cholecystitis and cholelithiasis diseases along with cases where spasmolytic action is required in intestines. Drugs with low water solubility are well solubilized in bile salt-phospholipid micelles; where they are transported to the intestinal wall with increased bioavailability. Bile acids also serve as signaling molecules through binding the nuclear receptors for the control of hepatocyte metabolism; which would also have an effect on bioavailability (35). Medicinal plants with chologogic/choleretic properties include chamomile (*Chamomilla recutita*), elecampain (*Inula helenium*), dandelion (*Taraxacum officinalis*), St. John's wort (*Hypericum perforatum*), Artemisia sp, yarrow (*Achillea millefolium*), rosemary (*Rosmarinus officinalis*), chelidonium (*Chelidonium majus*). Essential oils of liquorice, coriander, turmeric, black pepper, red chili, cumin, onion, peppermint also have choleretic properties.

Bioenhancing Through Thermogenesis

Thermogenic agents increase the utilization of ATP or uncoupling oxidative phosphorylation of the reduced coenzymes. These compounds might mimic or antagonize hormones (activation of adrenergic, thyroid hormone or growth hormone receptors and the inhibition of glucocorticoid receptors), target miscellaneous intracellular mechanisms (modulation of transcriptional factors/enzymes to modulate mitochondrial biogenesis to promote fatty acid oxidation (36)). Besides its major role in weight loss, increased cellular energy levels utilize the nutrients through various mechanisms in digestion and gastrointestinal absorption. Natural compounds with thermogenic effects include berberine (AMPK activation), butein (Prdm4 induction), capsaicin (TrpV1 activation), 7,8-dihydroxyflavone (muscular TrkB activation), fucoxanthin (37).

SELECTED HERBAL BIOENHANCERS

Long Pepper (*Piper Longum*) and Black Pepper (*Piper Nigrum*)

Piperine, the major plant alkaloid present in *P. nigrum* Linn. (Black pepper) and *P. longum* Linn. (Long pepper), induce bioenhancing effects through inhibition of P-gp, drug metabolizing enzymes (arylhydrocarbon hydroxylase, uridine diphosphate, glucuronyl transferase, ethylmorphine-N-demethylase, 7-Ethoxycoumarin-O-deethylase, 3-Hydroxybenzo(a)pyrene glucuronidation, UDP-glucose dehydrogenase, 5-lipoxygenase, cyclooxygenase-1, cytochrome P450), increased blood supply to gastrointestinal system tract, decreased hydrochloric acid secretion and other proteins/enzymes involved in their transport leading increased bioavailability ranging 30–200%. Pyrazinamide, phytoin, propranolol, theophyllin, curcumin, rifampicin, amoxicillin, oxytetracycline, ciprofloxacin, and nevirapine are some examples that are bioenhanced by piperine and used in veterinary medicine (1, 38). For more, piperine decreases the cytotoxicity and genotoxicity of aflatoxin B1, through inhibition of metabolism pathways shown *in vitro* (39). In broiler chickens intoxicated by AFB1 (ingestion of 0.5 mg AFB1 kg⁻¹ bw); piperine (60 mg kg⁻¹) was able to reduce or even prevent the genotoxic and cytotoxic effects, presenting a safe option for the protection and supportive treatment of aflatoxicosis (40).

Turmeric (*Curcuma Longa*)

Curcumin, the natural phenolic coloring component of *Curcuma longa* suppresses drug metabolizing enzymes and P-gp to exert its bioenhancing properties; while it also influences multiple signaling pathways and antioxidant mechanisms for its other pharmacological effects (41). Curcumin were found to modulate (increase) the pharmacokinetics of drugs that are P-gp substrates such as oral administration of celiprolol, midazolam and paclitaxel in rats (42, 43), marbofloxacin in broiler chickens (44).

Ginger (*Zingiber officinale*)

The rhizome extract of *Zingiber officinale* contain gingerols to be further converted into shogaols, zingerone and paradol; which regulates the intestinal functions to facilitate absorption increasing the absorption of drugs along and have chologogous effects (45). It inhibits the human CYP2C9, CYP2C19, CYP2D6, and CYP3A4 metabolic related reactions (46, 47). As mentioned previously, in Ayurvedic medicine “Yogavahi,” the basis for modern bioenhancement theories, include “trikatu” preparation containing the mixture of *Piper longum* (long pepper), *Piper nigrum* (black pepper), and *Zingiber officinale* (ginger) (48). Through piperine combination, an increase of bioavailability is evident (49). Ginger significantly influenced the pharmacokinetic profile of pefloxacin when coadministered in rabbits, with an increase in maximal concentration, AUC and half-life (50). It was also shown to increase the bioavailability of methotrexate, 5-fluorouracil and acyclovir (49, 51).

Cumin (*Cuminum cyminum*)/Caraway (*Carum carvi*)

Novel flavonoid glycoside isolated from cumin (3',5-dihydroxyflavone 7-O- β -D-galacturonide-4'-O- β -D-glucopyranoside) were shown to enhance the peak concentration and AUC of rifampicin at coadministration (52). Caraway seed was also found to enhance the plasma levels of antitubercular drugs: rifampicin (RIF), pyrazinamide (PZA), and isoniazid (INH), when co-dosed in combination in Wistar rats (53). Bioenhancing effect of cumin/caraway was related to the permeation-enhancing property across the small intestinal absorptive surface. *Carum carvi* extracts were also found to inhibit the 2, 3, 7, 8-tetrachloro-dibenzo-p-dioxin-dependent gene expression of cytochrome P450 1A1 in the rat hepatoma cells (54), therefore it may affect the drugs metabolized by CYP1A1 such as chlorzoxazone, theophylline, bufuralol.

Black Cumin (*Nigella sativa*)

The methanolic extracts of *Nigella sativa* Linn. (Ranunculaceae), indigenous in Mediterranean region, was found to improve the intestinal permeability of amoxicillin in *in-vitro* experiments using excised rat intestinal segments in a dose-dependent manner (55).

Besides improving the intestinal permeability, the fatty acids of black cumin (especially eicosadeinoic acid) were found to inhibit the P-gp activity *in silico* against the primary amino acid sequence of P-gp from rats leading increased bioavailability of drugs (56). Contrary to *in silico* analysis, black cumin is associated with the activation of intestinal P-gp and/or CYP3A4, due to its ability to decrease the bioavailability of cyclosporine (cyclic polypeptide used as immunosuppressant in organ transplantation) in coadministration (57). Black cumin induced no significant effect on the theophylline pharmacokinetics in Beagle dogs indicating its lack of affinity to CYP1A2 activity; meanwhile fenugreek and garden cress decreased the bioavailability (58).

Morning Glory Plant (*Ipomoea* Spp.)

Lysergol is an alkaloid of the ergoline family isolated from the morning glory family and other higher plants. It was found to increase the bioavailability of curcumin. In order to evaluate the mechanism of this enhancing bioavailability related to curcumin, its effect on human P-gp and Breast Cancer Resistance Protein (BCRP) as major efflux transporters, were evaluated using *in situ* permeation and *in vitro* pharmacokinetic studies using specific substrates (digoxin for P-gp probe, sulfasalazine for BCRP probe) and inhibitors (verapamil for P-gp and pantoprazole for BCRP). The results indicate that the bioavailability enhancing potential of lysergol was attributed to BCRP efflux transport system (59). Lysergol also enhanced the oral bioavailability of berberine in rats; while mechanism of action of lysergol was not confirmed even though it was related to P-gp inhibition (60).

Garlic (*Allium sativum*)

Garlic (*Allium sativum*) has been used thousands of years mainly for the treatment of hypercholesterolaemia and prevention of arteriosclerosis (61). Allicin is an important allyl sulfur metabolite isolated from garlic and enhances the fungicidal activity of Amphotericin B against pathogenic fungi such as *Candida albicans*, *Aspergillus fumigatus* and yeast *Saccharomyces cerevisiae* (62–65) and antibacterial activity of β -lactams (cefazolin, oxacillin, and cefaperazone) tested at subinhibitory concentrations against *Staphylococcus* spp. and *Pseudomonas aeruginosa* (66). Also, garlic oils exhibited synergistic antifungal effects when combined with ketoconazole *in vitro* (67). It has been reported that garlic extracts inhibit some CYP enzymes (CYP2C9, CYP2C19, CYP3A4, and CYP3A5) *in vitro* but do not affect P-gp (68). Conversely, in a clinical study was demonstrated that garlic powder has no effect on CYP3A4 (69). Moreover, garlic oil can selectively inhibit CYP2E1 (70). In a later *in vivo* study, garlic extract was demonstrated to have stimulatory effects on both efflux and uptake transporters (71). These effects increase the risk of interactions with some drugs having narrow therapeutic index. For example, ajoene isolated from garlic is a weak inhibitor of platelet aggregation in baboons (72) and rats (73) when combined with antiplatelet dipyridamole. Careful addition of garlic homogenate in moderate doses (250 mg kg⁻¹) in propranolol treatment might result in beneficial effect during treatment of hypertension in animals with myocardial damage. Garlic induces a reduction in systolic blood pressure, cholesterol, triglycerides and glucose levels and an increase in the bioavailability and half-life along with decrease in the clearance and elimination rate constant of propranolol when ingested. Garlic also improved the survival and cardiac function in captopril or hydrochlorothiazide-treated rats with myocardial infarction (74–76). Overall, the bioenhancing effects of garlic are mainly attributed to its inhibitory effect of some CYP enzymes along with physiological changes in circulation leading a decrease in clearance and elimination of drugs.

Liquorice (*Glycyrrhiza glabra*)

In traditional medicine, *Glycyrrhiza glabra* or liquorice are used to treat peptic ulcer and cough (77). Glycyrrhizin is an active substance derived from liquorice and enhances the transport across the intestinal membrane of some antimicrobials (rifampicin, tetracycline, nalidixic acid, and ampicillin), vitamin B1, and vitamin B12 (6). Moreover, glycyrrhizin increases the Taxol effect by 5 times, inhibiting the division of the cell (MCF-7 cancer cell line) (78). Glycyrrhizin did not induce an effect on CYP3A4; meanwhile nine other compounds isolated from the extract of licorice including (3R)-vestitol, 4-hydroxyguaiaicol apiogluconide and liquiritigenin 7,4'-digluconide showed potent CYP3A4 activity (79). Another metabolite of liquorice, glycyrrhizic acid, does not inhibit the intestinal efflux transporter P-gp *in vitro* (80). However, a study suggested activator effects for both glycyrrhizin and glycyrrhetic acid on P-gp function *in vitro* (81). In a study reported that a metabolite of liquorice, glabridin, has inhibitory effects on CYP3A4, 2B6, and 2C9 (82). Other metabolite

of liquorice, glycyrrhetic acid exhibits inhibitory effects on CYP3A, 2C9, and 2C19 *in vitro* and *in vivo* (83) and induces UDP glucuronosyltransferases in rat liver *in vivo* (84). Glycyrrhizin and glycyrrhetic acid induced inhibitory effect on nucleoside transporters, thereby reduced bioavailability of ribavirin due to reduction in ribavirin transportation in intestinal tract (85).

Aloe (*Aloe vera*)

Aloe, a perennial and succulent xerophyte is widely been used in both human and veterinary medicine for its immunomodulatory, wound and burn healing, hypoglycemic, anticancer, gastro-protective, antifungal, and anti-inflammatory effects (86). The ethanolic extract of *Aloe vera* were found to augment the hypoglycemic effect of glipizide in streptozotocin induced diabetic rats (87). Due to its cytoprotective effects on gastric mucosa through induction of endogenous prostaglandin production, concomitant use of *Aloe vera* and pantoprazole for the gastroesophageal reflux symptoms in mustard gas victims were found to be improved compared to single treatments (88). Meanwhile, aloe ingestion were found to activate the functions of P-gp and CYP3A, decreasing the cyclosporine bioavailability in a rat model (89); therefore a decrease in the bioavailability of the related absorbed/metabolized drugs could be expected.

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CONCLUSION

Medicinal plants with bioenhancing potentials are not yet extensively explored especially in veterinary medicine. Bioenhancers are valuable tools to reduce the dose of the drugs and the duration of the treatment which is especially important for economic outcomes in livestock medicine along with their beneficial ecological implications. These compounds also reduce the drug resistance or related adverse reactions and toxicity which is especially important in anticancer drugs. Meanwhile drug-herb interactions are complex where species specific differences along with case specific differences play an important role. They are expected to produce least (or even no) pharmacological effects at the treatment concentrations; while they would increase the bioavailability and the efficacy of the target drug or nutraceutical (1, 6). Eventhough the major known example among herbal bioenhancers is piperine, various phytoactive compounds (capsaicin, quercetin, naringin) and plant extracts are yet to be exploited with their mechanism of action and complex drug interactions.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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