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AK RATHOD

ICAR-Indian Veterinary
Research Institute,
Department of Animal
Nutrition, Izatnagar, Bareilly,
U.P. India

AP DHOK

Maharashtra Animal and
Fishery Sciences University,
Nagpur Veterinary College,
Department of Animal
Nutrition, Nagpur,
Maharashtra India

Drug–nutrient–gut microbiota interactions in animals: An integrated veterinary review

AK RATHOD¹, AP DHOK²

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ABSTRACT

Drug response in animals depends on more than the dose of a medicine. Feed, nutritional status, gastrointestinal function and the gut microbiota can all influence how a drug is absorbed, metabolized and eliminated. In the opposite direction, drugs can change digestion, nutrient absorption and the composition of intestinal microorganisms. These interactions are especially important for orally administered drugs because the drug, feed and microbiota meet within the gastrointestinal tract. Mineral–drug interactions, changes in gastric acidity, microbial activation or inactivation of drugs, and antibiotic-associated dysbiosis are well-known examples. In veterinary medicine, understanding these relationships can help improve treatment response, nutritional management and antimicrobial use. This review explains the major drug–nutrient–gut microbiota interactions in a simple integrated manner, with emphasis on poultry, livestock and companion animals.

Keywords: Drug–nutrient interaction, Intestinal microbiota, Pharmacomicrobiomics, Nutrient absorption, Antibiotics, Poultry, Livestock

1 Introduction

Orally administered medicines enter a complex gastrointestinal environment. Feed composition, digestive secretions, intestinal motility, mucosal health and resident microorganisms can influence the amount of drug that is absorbed and the form in which it reaches the circulation. At the same time, a medicine may change these same factors and thereby affect nutrient utilization or intestinal health. (Carmody *et al.*, 2014; Koppel *et al.*, 2017; Sousa *et al.*, 2008) [1, 2, 3]

Drug–nutrient interactions can occur before absorption, during passage across the intestinal wall, after the drug enters the circulation, or during its metabolism and excretion. The result may be reduced drug availability, poor therapeutic response, increased toxicity or altered nutritional status. In many cases, the interaction can be managed by adjusting the timing of feed, supplements and medication rather than avoiding the treatment completely. (Carmody *et al.*, 2014; Sousa *et al.*, 2008) [1, 3]

The gut microbiota adds another important component. Intestinal microorganisms participate in digestion, fermentation, vitamin metabolism, mucosal defence and immune function. They can also chemically modify drugs. Because microbial populations differ among gastrointestinal regions and among individual animals, the microbiota may partly explain why animals respond differently to the same treatment. (Gong *et al.*, 2007; Shang *et al.*, 2018; Stanley *et al.*, 2014; Han *et al.*, 2016) [4, 5, 6, 7]

This review brings together drug–nutrient and drug–microbiota interactions and explains their importance for veterinary treatment, animal nutrition, antimicrobial stewardship and food-animal production.

2 Drug–nutrient interactions and gastrointestinal processes

2.1 Classification and sites of interaction

A drug–nutrient interaction occurs when feed, a nutrient, a supplement or the animal's nutritional status changes the action or disposition of a drug, or when a drug changes the digestion, absorption or use of nutrients. These interactions may be physical, chemical or physiological. Their importance depends on the drug, dose, duration of treatment, diet and health status of the animal. (Carmody *et al.*, 2014; Sousa *et al.*, 2008) [1, 3]

Corresponding Author:

AP DHOK

Maharashtra Animal and
Fishery Sciences
University, Nagpur
Veterinary College,
Department of Animal
Nutrition, Nagpur,
Maharashtra India

2.2 Nutrients as determinants of drug absorption

Feed can change drug absorption by altering gastric pH, digestive secretions, gastric emptying and intestinal transit. It can also bind directly to some drugs. Therefore, giving a medicine with feed is not always neutral; for some drugs it improves tolerance, whereas for others it can reduce absorption. (Carmody *et al.*, 2014; Sousa *et al.*, 2008) [1, 3]

Tetracyclines provide a clear example. Calcium, magnesium, iron and aluminium can bind to tetracycline molecules and form poorly soluble complexes. These complexes are absorbed less efficiently from the intestine, which may lower the effective drug concentration. When clinically relevant, tetracyclines and mineral supplements should therefore be given at different times. (Neuvonen, 1976) [8]

Drugs that reduce gastric acidity can also influence nutrient availability. Proton-pump inhibitors and histamine H₂-receptor antagonists increase gastric pH. During prolonged use, this change may affect the absorption of some minerals and vitamins. The practical importance depends on treatment duration, diet and the nutritional condition of the animal. (Imhann *et al.*, 2016) [9]

2.3 Drug-induced changes in digestion and nutrient absorption

Medicines can reduce nutrient availability by changing intestinal movement, damaging the mucosa, interfering with transport processes or altering the microbiota. Laxatives and osmotic agents can shorten the contact time between digesta and the absorptive surface. Drugs that injure the intestinal mucosa may reduce the efficiency of nutrient absorption. (Dalby *et al.*, 2006; Nagata *et al.*, 2019; Tropini *et al.*, 2018) [10, 11, 12]

Some medicines may also interfere with the use of specific vitamins. Drugs associated with impaired folate or vitamin B₁₂ status and agents that reduce the absorption of fat-soluble vitamins are most important when treatment is prolonged. Young, growing, geriatric or nutritionally compromised animals may be more sensitive to these effects.

2.4 Gastrointestinal adverse effects and nutritional consequences

The gastrointestinal tract is a common site of adverse drug effects. Non-steroidal anti-inflammatory drugs (NSAIDs) can weaken mucosal protection and contribute to gastric or intestinal injury. Experimental studies also indicate that the microbiota may participate in NSAID-associated intestinal damage, showing that drug toxicity can involve both host tissue and resident microorganisms. (Dalby *et al.*, 2006; Cheng *et al.*, 2018) [10, 13]

Antibiotic-associated diarrhoea develops through a different mechanism. Antimicrobials can suppress susceptible commensal bacteria and disturb normal colonization resistance. Other drugs may cause diarrhoea by increasing intestinal motility or changing water movement. In either situation, altered transit and microbial activity can influence both nutrient use and drug handling. (Buffie *et al.*, 2013) [14]

3 Intestinal microbiota in animals

3.1 Spatial distribution and microbial succession

The intestinal microbiota is not the same throughout the gastrointestinal tract. Each region provides a different environment because pH, oxygen availability, nutrient supply and host secretions vary. In chickens, *Lactobacillus* is common in the upper gastrointestinal tract, whereas the ceca contain a much denser and more diverse anaerobic community. These regional differences are important because microbial metabolism of nutrients and drugs also varies along the gut. (Gong *et al.*, 2007; Shang *et al.*, 2018; Han *et al.*, 2016) [4, 5, 7]

The microbiota develops rapidly after birth or hatching and continues to change with age. Diet, contact with adult animals, host genetics, disease, stress, housing and antimicrobial exposure can all influence its composition. Even animals kept under similar conditions may have

different microbial communities. (Stanley *et al.*, 2014; Zhao *et al.*, 2013; Kubasova *et al.*, 2019; Zhernakova *et al.*, 2016; Falony *et al.*, 2016) [6, 15, 16, 17, 18]

3.2 Functional significance of the microbiota

The function of the microbiota is more important than simply listing which bacteria are present. Different microbial communities contain different enzymes and produce different metabolites. As a result, they may differ in their ability to ferment nutrients, modify bile acids or transform drugs. This functional variation can contribute to differences in drug response between animals. (Carmody *et al.*, 2014; Koppel *et al.*, 2017; Zimmermann *et al.*, 2019) [1, 2, 19, 20]

4 Pharmacological effects of the intestinal microbiota

4.1 Microbial transformation of drugs

Pharmacomicrobiomics is the study of how the microbiome influences drug response. Gut microorganisms can chemically transform drugs by reactions such as reduction, hydrolysis, deconjugation, acetylation and deglycosylation. These reactions may activate a drug, inactivate it or produce a metabolite with a different biological effect. (Koppel *et al.*, 2017; Sousa *et al.*, 2008; Zimmermann *et al.*, 2019) [2, 3, 19, 20]

Several examples illustrate this principle. Sulfasalazine requires bacterial metabolism for release of its active component, whereas some intestinal bacteria can reduce the activity of digoxin. Irinotecan provides another important example: bacterial beta-glucuronidase can reactivate an intestinal metabolite and contribute to gastrointestinal toxicity. Thus, microbial metabolism can affect both efficacy and adverse effects. (Koppel *et al.*, 2017; Wallace *et al.*, 2010) [2, 21]

4.2 Drug sequestration and microbial metabolites

Microorganisms can influence drugs in ways other than chemical transformation. Some drugs may bind to bacterial cells, while microbial metabolites can interact with host metabolic pathways. Large screening studies have shown that many orally administered drugs can be modified by at least one gut bacterial strain. The gut microbiota should therefore be viewed as an active part of drug disposition rather than as a passive background population. (Maier *et al.*, 2018; Zimmermann *et al.*, 2019) [22, 19, 20]

5 Effects of drugs on the intestinal microbiota

5.1 Non-antibiotic drugs

The interaction between drugs and the microbiota works in both directions. Antibiotics have the most obvious effect, but many non-antibiotic medicines can also change microbial growth or alter the intestinal environment. Changes in gastric acidity, motility, mucosal integrity and nutrient supply can all shift microbial community structure. (Maier *et al.*, 2018; Vich Vila *et al.*, 2020) [22, 23]

5.1.1 Proton-pump inhibitors

Proton-pump inhibitors reduce gastric acidity. This allows more oral microorganisms to survive passage through the stomach and may change the intestinal microbial community. Studies in people have consistently reported microbiome changes during proton-pump inhibitor use. These findings are useful mechanistic examples, although the magnitude and clinical importance of the effect may differ among animal species. (Imhann *et al.*, 2016; Vich Vila *et al.*, 2020) [9, 23]

5.1.2 Metformin

Metformin is another example of a non-antibiotic drug that can influence the microbiota. Human studies have reported changes in several bacterial groups during treatment, and some of these changes may contribute to both therapeutic effects and gastrointestinal side effects. Metformin is not a routine veterinary drug, but it clearly demonstrates how a medicine can influence its host partly through microbial pathways. (Forslund *et al.*, 2015; Wu *et al.*, 2017) [24, 25]

5.1.3 NSAIDs and laxatives

NSAIDs may alter the microbiota directly or through intestinal mucosal injury. Laxatives can change transit time and stool consistency, which are closely related to microbial composition. Experimental osmotic diarrhoea can produce microbial changes that persist after bowel function returns toward normal. These observations show that a drug does not need to be an antibiotic to disturb the intestinal ecosystem. (Dalby *et al.*, 2006; Nagata *et al.*, 2019; Tropini *et al.*, 2018; Vandeputte *et al.*, 2016) [10, 11, 12, 26]

5.2 Antibiotics and the animal intestinal microbiome

Antibiotics are highly relevant to veterinary medicine because they can remove susceptible pathogens while also affecting beneficial or neutral commensal organisms. Studies in poultry have shown that different antibiotics produce different changes in cecal bacterial populations. The response depends on the antimicrobial used, dose, duration, age of the animal, diet and the microbial community present before treatment. (Crisol-Martinez *et al.*, 2017; Danzeisen *et al.*, 2011; Pedroso *et al.*, 2006; Xiong *et al.*, 2018) [27, 28, 29, 30]

Antimicrobial feed additives were historically associated with improved growth and feed efficiency in some production systems. Proposed explanations include reduced microbial competition for nutrients, changes in bile-acid metabolism and reduced intestinal tissue demands. These effects must now be considered together with the

risks of dysbiosis and selection for antimicrobial resistance. (Crisol-Martinez *et al.*, 2017; Lin, 2014; Yen *et al.*, 1985; Xiong *et al.*, 2018) [27, 31, 32, 30]

6 Recent veterinary evidence for drug–microbiota interactions

Recent veterinary studies increasingly examine drug concentrations and microbial changes in the same animals. This approach is important because it can show whether changes in the microbiota are associated with differences in pharmacokinetics, tissue residues or recovery after antimicrobial treatment. (Yoon, 2024; Kim *et al.*, 2025; Zhan *et al.*, 2025; Lee *et al.*, 2024; Yuan *et al.*, 2023) [33, 34, 35, 36, 37]

Evidence is also developing in companion animals. Reviews have highlighted possible effects of the microbiome on drug metabolism and treatment response, while experimental work in dogs suggests that probiotics may assist recovery of microbial diversity after antibiotic-associated dysbiosis. Such interventions should still be evaluated for the specific animal, antimicrobial and probiotic preparation used. (Yoon, 2024; Kim *et al.*, 2025) [33, 34]

In pigs, tylosin exposure has been studied together with gut microbiome changes and pharmacokinetic measurements. This work supports the view that infection status, antimicrobial exposure and microbial ecology should be considered together when interpreting variation in drug disposition. (Lee *et al.*, 2024) [36]

Table 1. Selected recent veterinary evidence on drug–microbiota interactions

Study	Animal/model	Main observation	Veterinary relevance
Yuan and Chen ⁴⁰	Silkie chickens	Ciprofloxacin residues and gut microbiota changed during treatment; selected taxa were associated with pharmacokinetic measures.	Links microbiome composition with antimicrobial disposition and residue elimination.
Lee <i>et al.</i> ³⁹	Pigs	Gut microbiome perturbation was examined together with tylosin pharmacokinetics in healthy and infected animals.	Supports integration of infection status, microbiome characteristics and pharmacokinetic variability.
Zhan <i>et al.</i> ³⁸	Chickens	Six antibiotics produced distinct, time-dependent changes in microbial diversity and community structure.	Demonstrates that microbiome disruption and recovery are antimicrobial-specific.
Kim <i>et al.</i> ³⁷	Dogs	Probiotic treatment supported recovery of antibiotic-associated dysbiosis.	Provides evidence for microbiome-directed recovery strategies in companion animals.

Chicken studies provide similar evidence. Different antibiotics can produce distinct and time-dependent changes in microbial diversity and community structure. In Silkie chickens, ciprofloxacin exposure has also been associated with changes in gut microbiota and with pharmacokinetic or tissue-residue measurements. These findings support further animal-specific research in veterinary pharmacomicrobiomics. (Zhan *et al.*, 2025; Yuan *et al.*, 2023; Mak *et al.*, 2025) [35, 37, 38]

7 Integration of drug, nutrient and microbiota interactions

Drug–nutrient and drug–microbiota interactions are closely connected. Diet determines which substrates reach the intestine and helps shape the microbial community. The microbiota then modifies nutrients and some drugs. A drug may also change intestinal pH, motility or microbial growth, which can alter nutrient utilization and possibly the handling of the same drug or another medicine. The final response is therefore the result of interaction among the animal, diet, microbiota and treatment. (Carmody *et al.*, 2014; Koppel *et al.*, 2017; Zimmermann *et al.*, 2019) [1, 2, 19, 20]

This integrated view is particularly useful when animals receive oral medicines together with mineral supplements, probiotics, formulated feeds or several drugs. Disease, dehydration, reduced feed intake and liver or kidney dysfunction can further change drug disposition and nutritional needs. These factors should be considered when treatment response is poorer or more variable than expected.

8 Implications for veterinary practice and animal production

8.1 Drug administration and nutritional management

In practice, the timing of medication in relation to feed and supplements should be considered whenever a known interaction exists. A simple example is separating susceptible tetracyclines from calcium-, magnesium-, iron- or aluminium-containing products. During long-term treatment, changes in appetite, body weight, faecal consistency and nutritional status may also provide useful clinical information. (Neuvonen, 1976) [8]

Nutrition can support intestinal health, but dietary or probiotic interventions should not be expected to correct every drug-induced microbiome change. Responses depend on the animal species, age, diet, disease condition and the microbial strain or product used. Nutritional management should therefore complement, not replace, appropriate veterinary treatment. (Kim *et al.*, 2025) [34]

8.2 Antimicrobial stewardship and One Health considerations

Antimicrobial use in food-producing animals can affect both the treated animal and the wider microbial ecosystem. Exposure may change intestinal bacteria and select for antimicrobial-resistance genes. Responsible antimicrobial use requires an accurate diagnosis, an appropriate drug and dose, a suitable treatment duration and observance of withdrawal periods. (Xiong *et al.*, 2018; Baur *et al.*, 2017) [30, 39]

These issues connect veterinary pharmacology, nutrition, microbiology and food safety. A One Health approach considers animal health together with antimicrobial resistance and the potential movement of resistant organisms or genes through animals, food and the environment. Better integration of treatment records, microbiome research and resistance surveillance can improve understanding of these links. (Xiong *et al.*, 2018; Baur *et al.*, 2017) [30, 39]

9 Research gaps and future directions

An important limitation of current knowledge is that much mechanistic evidence comes from human studies or laboratory models. Gut microbial communities differ among animal species, breeds, ages, production systems and intestinal regions. Findings from humans should therefore not be transferred directly to poultry, pigs, cattle or companion animals without species-specific evidence. (Gong *et al.*, 2007; Shang *et al.*, 2018; Zhao *et al.*, 2013) [4, 5, 15]

Future veterinary studies should measure more than microbial composition alone. Combining pharmacokinetics with feed composition, nutrient intake, disease status, metagenomics and metabolomics would help identify which microbial functions actually change drug response. Standardized sampling and clear reporting of diet and antimicrobial exposure would also make studies easier to compare. (Zimmermann *et al.*, 2019) [19, 20]

More research is needed to determine whether nutrition, probiotics or other microbiota-directed strategies can reduce unwanted drug-microbiota interactions without reducing treatment efficacy. Early-life antimicrobial exposure, recovery of the microbiota after treatment, and links between microbial change, nutrient utilization and disease resistance are especially important areas for veterinary research. (Kim *et al.*, 2025; Zhan *et al.*, 2025) [34, 35]

10 Conclusion

Drug response in animals is influenced by the combined effects of the host, diet and intestinal microbiota. Feed and nutrients can change drug absorption, while drugs can affect digestion, nutrient utilization and gastrointestinal health. Intestinal microorganisms can transform drugs, and drugs can in turn change the microbial community. These interactions help explain why the same treatment may not produce exactly the same response in every animal. (Carmody *et al.*, 2014; Koppel *et al.*, 2017; Sousa *et al.*, 2008) [1, 2, 3]

For veterinary practice, the main message is practical: consider feed, mineral supplements, gastrointestinal health, nutritional status and recent antimicrobial exposure when using medicines, especially during prolonged oral treatment. In food-producing animals, these considerations should be combined with antimicrobial stewardship and correct withdrawal practices. Better animal-specific research will help translate microbiome science into safer and more effective veterinary treatment. (Neuvonen, 1976; Xiong *et al.*, 2018; Baur *et al.*, 2017) [8, 30, 39]

Conflict of interest

The authors declare that there is no conflict of interest

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