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Mini-Review

Restoring healthy gut microbiome in poultry using alternative feed additives with particular attention to phytogenic substances: Challenges and prospects

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Abstract

The majority of pathologies in poultry are linked to intestinal chronic inflammation due to a disbalance of the gut microbiota. Thus, a healthy microbiota drives the gut integrity, and the gut's biological and metabolic functionalities, including efficacious use of nutrition, but also immunity, and neuroendocrine systems. However, many external factors are disturbing a stable, healthy gut microbiota. Heat stress, dysbiosis, leaky gut syndrome, and mycotoxins are the main "secret killers" in poultry that lead to chronic oxidative stress and inflammation, which in turn impact the health and animal performance. Additionally, chronic stress in poultry is linked with the emergence of antimicrobial resistance (AMR), which the WHO has recently identified to be among the most important problems threatening human health globally that increased the demand for safe antimicrobials to treat the collateral damages resulting from dysbiosis. Several alternative feed additives such as probiotics, prebiotics, fatty acids, and amino acids have been described to restore intestinal microbiota. Additionally, some phytogenic substances have anti-inflammatory and antioxidant activities. These natural products are also capable to modulate gut microbiota in a symbiotic equilibrium, thereby enabling the intestinal tract to withstand both infectious and non-infectious stressors. Nevertheless, several challenges, such as the bioavailability, rate of absorption, quality inconsistency, public acceptance, and cost-effective delivery methods, make the feasibility and application of phytogenic substances on a commercial scale complicated. In this review, the main drivers of chronic inflammation in poultry have been discussed. Additionally, the potential use of alternatives to antibiotics to restore the gastrointestinal microbiota in poultry and the possibilities for overcoming breakdowns in poultry farming were highlighted.

Keywords: Poultry, Oxidative stress, Inflammation, Phytotherapy, Antimicrobial resistance

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Introduction

Microorganisms constitute the largest fraction of biodiversity on Earth. Their functions are highly diverse, with fundamental roles to maintain chemical equilibria and cycles in their respective environments. It is, therefore, surprising that many humans consider all microorganisms as "dangerous", particularly when it comes to equating bacteria with pathogens (Musso et al., 2010; Bäckhed, 2011). As another aspect, the prokaryotic bacteria that have been there for billions of years have shaped the evolution of eukaryotic life (Kiers and West, 2016; Martin, 2017).

The nature of the early eukaryotes has been radically altered due to their affiliation with symbiotic prokaryotes, which has allowed for a beneficial co-evolution of the host and the microbe (Renoz et al., 2019). One clear example is the endosymbiotic theory established by Lynn Margulis. According to molecular and biochemical data, Proteobacteria and Cyanobacteria are thought to have evolved to become the mitochondria and the chloroplasts, respectively, in modern eukaryotic cells changing the evolution of life as we know it today (Gray, 2017; Lane, 2017; Lazcano and Peretó, 2021).

Next to this fundamental role of bacteria in evolution, diverse compartments of higher organisms such as the gut, skin, sexual organs, and even the lung and brain can be colonized by bacteria, most of them being highly beneficial. This especially holds for gut microbes (gut microbiota). On the other hand, any disturbance of this microbiota typically leads to disease. For example, 90% of pathologies are linked to chronic enteritis (Fasano, 2020). Disbalance of the gut microbiota has negative effects on the health and biology of metazoans because the gut integrity, biology, metabolism, nutrition, immunity, and neuroendocrine system are all dependent on a healthy microbiota (Maslowski and Mackay, 2011) which is in constant interaction in the microbiota-brain-gut axis (Sekirov et al., 2010; Liu and Wang, 2016). In the present review, we have discussed the drivers of chronic inflammation in poultry. Additionally, the potential use of alternative feed additives to ameliorate chronic stress in poultry and possibilities for overcoming breakdowns have been highlighted.

Chronic stress in poultry

Stress and inflammation are intrinsic responses in living organisms that involve hormones, immune cells, and molecular mediators (Diemer et al., 2003). They are critical mechanisms for the survival and healing of all forms of life, and a variety of stimuli trigger them. Especially the energy and vitality of healthy mitochondria are required for all of the systems to function properly during stress responses (Renoz et al., 2019). In chronic inflammation, an increase in the generation of reactive oxygen species causes peroxidation of lipids in cell membranes and mitochondrial membranes, finally leading to cell death (Bickler et al., 2020) (Figure 1).

Animal studies have long established that the interactions between diet ingredients, the gut microbiome, the nervous system, the immune system, and the endocrine system play critical roles in metabolic and gastrointestinal disorders, diabetes and cancers, autoimmune diseases, malnutrition and obesity, myopathies, cardiovascular and muscle function, and even neurological diseases (Gostner et al., 2013; Fasano, 2020). Interestingly, all of these metabolic diseases, as well as neurological pathologies in humans, such as autism, schizophrenia, bipolar disorder, dementia, Alzheimer's disease, Parkinson's disease, epilepsy, and stroke, are strongly associated with mitochondrial problems (Cryan and Dinan, 2012). As a result, we must recognize chronic oxidative stress and mitochondrial dysfunction as "the silent killers" of animals and humans (Stecher, 2015).

In animal farming, particular attention should be taken to chronic stress produced by heat stress, dysbiosis, leaky gut, mycotoxins, endotoxins, and oxidized diet that reduces the animal's performance and increases the animal's susceptibility to infections (Shehata et al., 2022). In poultry, heat stress can lead to disruption of gut tight junctions, reactive oxygen species (ROS) production that increases intestinal permeability, endotoxemia and systemic inflammation (Yu et al., 2006), hepatic inflammation (Liu et al., 2022), reduction of calcium absorption and decreasing the metabolism of vitamin D3 (cholecalciferol) to 1,25-dihydroxy vitamin D3 (1,25(OH)2D3) (Petruk and D. R. Korver, 2004) as well as growth retardation (Saracila et al., 2021). This also increases the need for antimicrobials in poultry due to, e.g., invasion of the intestinal epithelium by opportunistic bacteria.

Mycotoxins such as aflatoxin B1, deoxynivalenol, nivalenol, fumonisin B1, ochratoxin A, and zearalenone also induce oxidative stress and inflammation by down-regulation of intracellular antioxidants and up-regulation of pro-inflammatory cytokines that impact the membrane integrity (Longobardi et al., 2021), and may be accompanied by invasion of the intestinal epithelium by opportunistic microorganisms (Liu and Wang, 2016; Wang et al., 2017) due to leaky gut. This immediately highlights the need for antioxidants and anti-inflammatory substances in poultry subjected to mycotoxins.

Compared to saturated fats, polyunsaturated fatty acids (PUFA) oxidize more efficiently, which means they deteriorate more quickly (Alagawany et al., 2019). Because the double bonds are more reactive than CH2 groups in saturated fatty acids, molecular oxygen can attack those sites. The production of ROS-carrying free radicals, in turn, causes lipid autoxidation and the production of reactive substances that have the potential to be biologically harmful and give the product an unpleasant odor. Several factors can influence this process during feed pelleting and storage, including light, transition metals, and temperature. Moreover, lipid peroxidation generates many toxic metabolites, including peroxides, aldehydes, and molecules, which may multiply oxidative stress and persistent inflammation (Grigorakis et al., 2010; Goicoechea et al., 2011; Goicoechea and Guillén, 2014; Ben Hammouda et al., 2017).

Overall, these secret killers are predisposing factors for several pathological conditions that can lead to an increase in the use of antibiotics in the poultry industry, which pose a serious impact on human and animal public health (Benrabia et al., 2020). Indeed, the use of antibiotics is linked with AMR acquisition. This can be explained by the fact that both commensal and opportunistic bacteria are inhabitants of the gut microbiota. Commensal bacteria commonly carry genes for antibiotic resistance, which may contribute to the development of resistant clones of opportunistic pathogens (Ellabaan et al., 2021; Forster et al.,

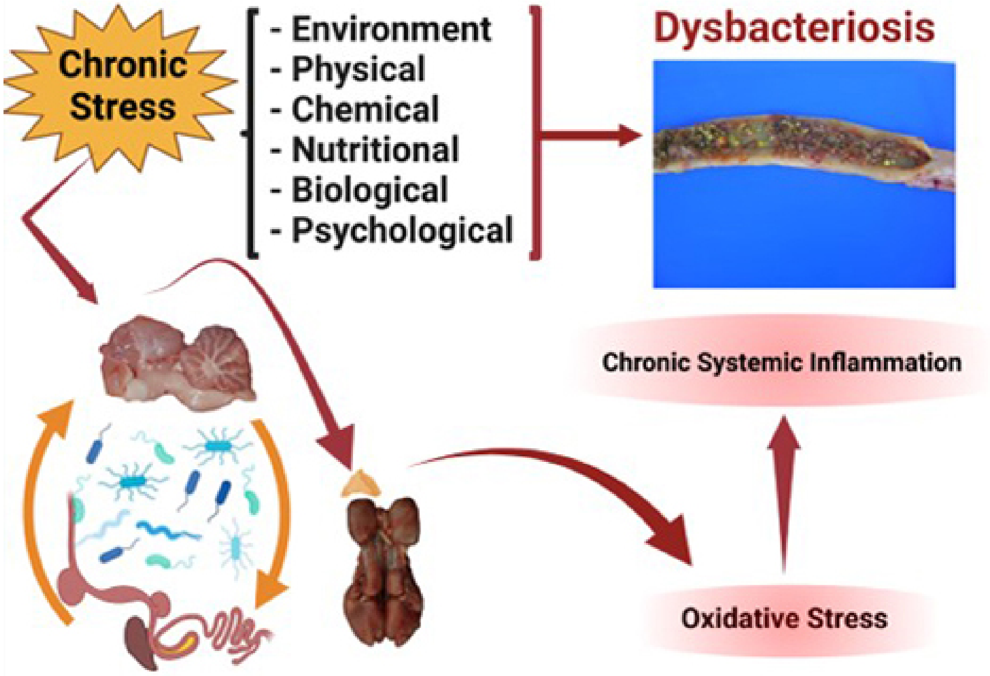

Figure 1: Inflammation is the result of stress, regardless of the source or nature of the stress (biological, environmental, nutritional, physical, chemical, or psychological). Stress and inflammation are intrinsic responses in living organisms that involve hormones, immune cells, and molecular mediators. Chronic stress induces chronic systemic inflammation and dysbacteriosis (created with BioRender.com).

2022). When antibiotics are used, susceptible bacteria are eliminated, but bacteria with inherent or acquired resistance persist. Due to vertical inheritance through cell division or horizontal gene transfer of mobile genetic components, can then result in further development of the resistant gene reservoir (Lamberte and van Schaik, 2022). Figure 2 illustrates the secret killers in poultry and the link with AMR acquisition.

Taken together, chronic stress is linked to dysbiosis, systemic inflammation due to cytokine release, and the so-called leaky gut syndrome, which is primarily caused by oxidative stress reactions impairing the barrier function of the cells lining the gut wall. Assessment of oxidative stress based on direct ROS and nitrogen oxygen species (RNS) measurement is difficult due to the short half-life of ROS (Poljsak et al., 2013). However, there are several indirect biomarkers (Dalle-Donne et al., 2003; Celi, 2011; Collins, 2014), that can be used for the assessment of intestinal health in poultry (Figure 3).

Restoring healthy gut microbiome

Natural alternatives to synthetic drugs, including antibiotic growth promoters (AGP), have been investigated to improve performance and gut health; however, there is no "magic bullet" for preventing chronic stress-related disorders (Tellez-Isaias and Latorre, 2022). It was implied that probiotics (Tellez-Isaias et al., 2021), prebiotics (Torres-Rodriguez et al., 2007), organic acids (Hernandez-Patlan et al., 2019), plant extracts (Leyva-Diaz et al., 2021), essential oils (Coles et al., 2021; Ruff et al., 2021), and trace minerals (Baxter et al., 2020) have promising potential to improve intestinal microbial balance, metabolism, and the integrity of the gut as alternative AGP in commercial poultry due to their anti-oxidant, anti-inflammatory, immune modulating, and bactericidal properties.

There have also been numerous studies conducted on phytogenics as feed additions for nutritional goals in animal production. The antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, immunomodulatory, and barrier integrity-enhancing qualities of phytogenics make them an important tool in preventing various diseases in production animals. Curcumin, the main curcuminoid found in turmeric (*Curcuma longa*), a member of the ginger family *Zingiberaceae*, has been demonstrated to lower the severity of necrotic enteritis (Hernandez-Patlan et al., 2019), salmonellosis (Hernandez-Patlan et al., 2018; Leyva-Diaz et al., 2021), aflatoxicosis (Solis-Cruz et al., 2019), and coccidiosis (Petrone-Garcia et al., 2021).

Improving disease resistance in antibiotic-free animals is beneficial not only to the animals' health, well-being, and production but also to be a crucial technique in enhancing the microbiological safety of animal products. Recent worldwide legislations and increasing consumer demands to phase out AGP and limit the therapeutic use of existing antimicrobials have prompted research and development of alternative feed additives. Table 1 shows an updated list of alternative feed additives to AGP to improve intestinal health in animals.

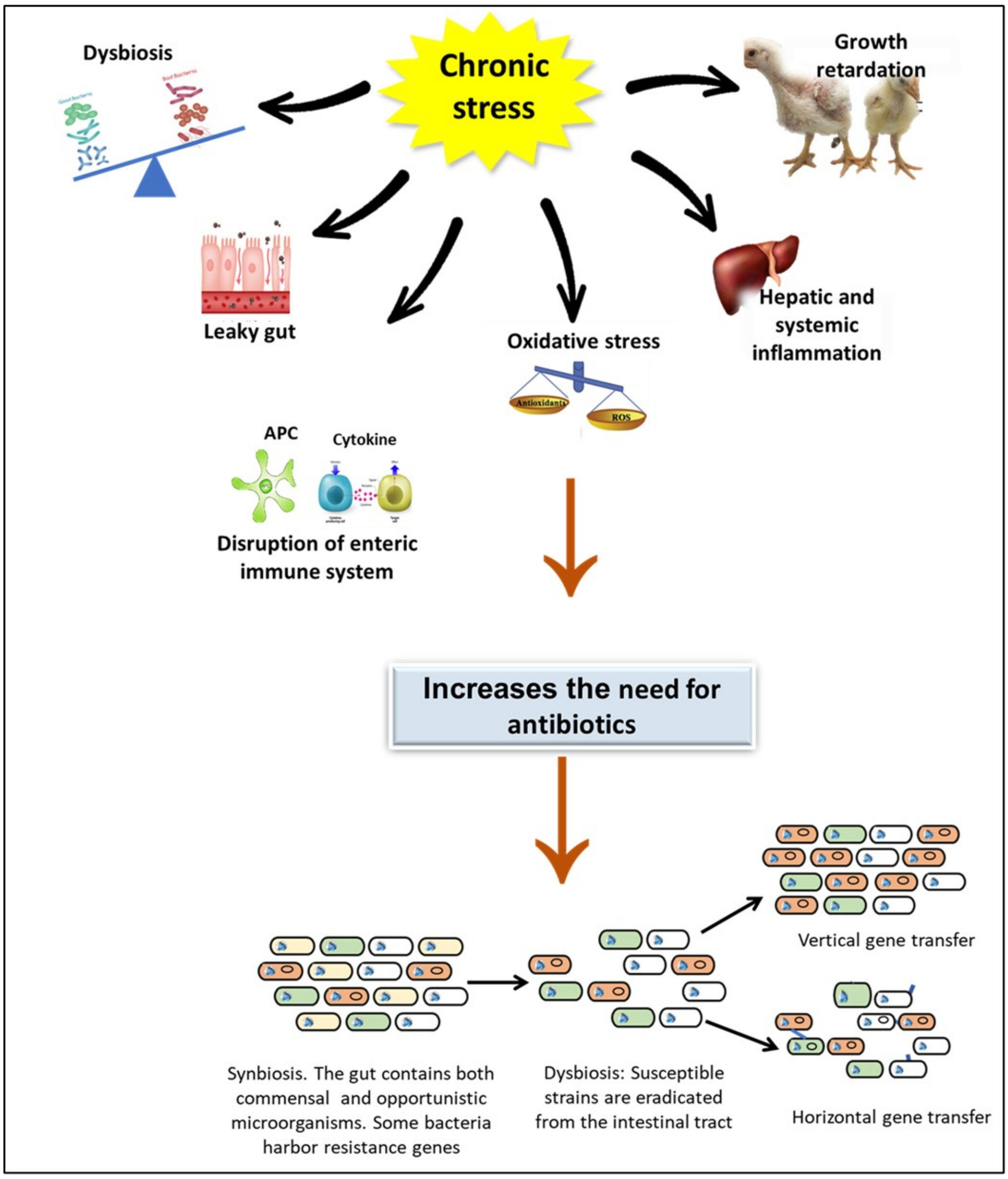

Figure 2: Secret killers (chronic stress) in poultry and the link with antimicrobial resistance acquisition. Upon antibiotic application, the resistant gene reservoir will be developed due to the eradication of susceptible strains from the gastrointestinal tract.

Challenges of phytogenic substances applications and possibilities for overcoming breakdowns

Several challenges have been associated with the use of phytogenic substances in the poultry industry, which can be categorized mainly into i) challenges related to bioavailability, ii) challenges related to the inconsistency of the effectiveness, iii) potential adulteration and presence of toxic compounds, iv) challenges related to the manufacturing, and v) public acceptance (Figure 4).

Bioavailability

It is challenging to determine the pharmacological properties of phytogenic substances, particularly their bioavailability (Atul Bhattaram et al., 2002). Some bioactive substances exhibit low efficacy *in-vivo* compared with *in-vitro* studies. It was reported that only 2–15% of some phytobiotic compounds can be absorbed in the small intestine (Kikusato, 2021), which might be a cause of the low effectiveness of some phytogenic compounds *in-vivo*. For example, the poor absorption and assimilation of polyphenols frequently lead to too low concentrations of the bioactive substances in the target tissues to be effective. The functional forms of phytogenic compounds may also be affected by the extensive bioconversion that takes place in the liver and intestine, which may have a negative impact on biological activities (Paszkiewicz et al., 2012). Additionally, bioactive substances might be metabolized and quickly removed from the bloodstream (Stevanović et al., 2018).

Indeed, studying the bioavailability of bioactive compounds becomes considerably more challenging when synergistic effects between the active constituents are unknown. Therefore, additional means are required

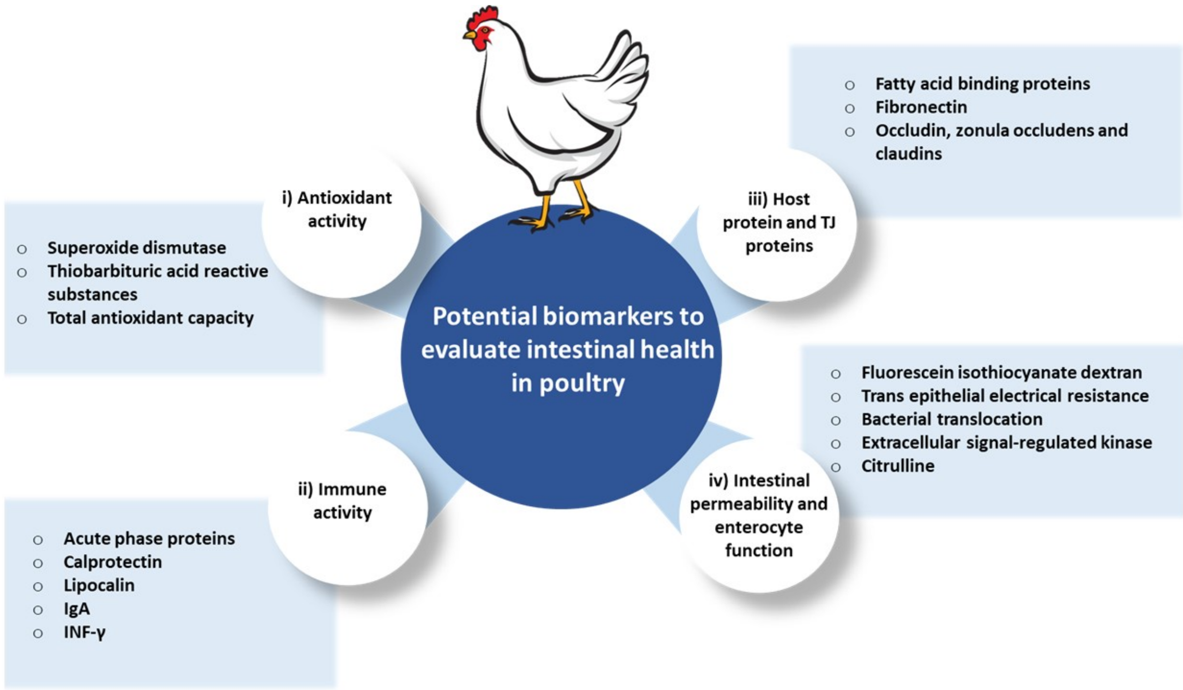

Figure 3: Assessment of oxidative stress in poultry. i) biomarkers for antioxidant activity, ii) biomarkers for immune activity, iii) biomarkers for gene expression of protein biomarkers and tight junctions, and iv) biomarkers of intestinal permeability and enterocyte function.

Table 1: Alternative feed additives to antibiotic growth promoters as means to improve intestinal health in animals.

Nutraceutical	Mode of action	Reference
Probiotics	Performance, gut integrity, immune/microbiota modulation, and enteropathogens control	Tarabees et al. (2020, 2021); Elsayed et al. (2021)
Prebiotics	Improve gut integrity, adsorbent capacity against aflatoxin B1, carcass yield, and performance, reduce systemic inflammation	Mullenix et al. (2021)
Enzymes	Improve digestibility and reduce necrotic enteritis	Nusairat and Wang (2021)
Short and medium-chain fatty acids	Reduce necrotic enteritis and improve gut health	Gomez-Osorio et al. (2021)
Phytochemicals	Reduce enteropathogens and inflammation, improve performance, antioxidant activity, and gut integrity	Anderson et al. (2021); Park et al. (2021)
Vitamins	Improve antioxidant and anti-inflammatory action, improve gut integrity	Ma et al. (2021)
Functional amino acids	Improve gut health, anti-viral activity	Chalvon-Demersay et al. (2021); Takano et al. (2021)
Vaccines and immunoglobulins	Control enteropathogens	Jabif et al. (2021); Juárez-Estrada et al. (2021)
Bile acids	Control enteropathogens	Asakura et al. (2021)
Changes in dietary energy levels	Improve performance	Zhang et al. (2021)

to increase the bioavailability and uptake of phytogenic compounds. Additionally, the quality and origin of the plant, and the extraction methods, should be strictly controlled as they can impact the stoichiometry and stability of phytogenic substances (Říha et al., 2014).

The stability of phytogenic compounds during storage is also a critical challenge. Several phytogenic substances, such as polyphenols and phenolics, are sensitive to light, heat, and oxygen, affecting their stability during storage (Thakur et al., 2011; Trucillo et al., 2018; Tolve et al., 2021) and causing the conversion of functional components into inactive metabolites, or

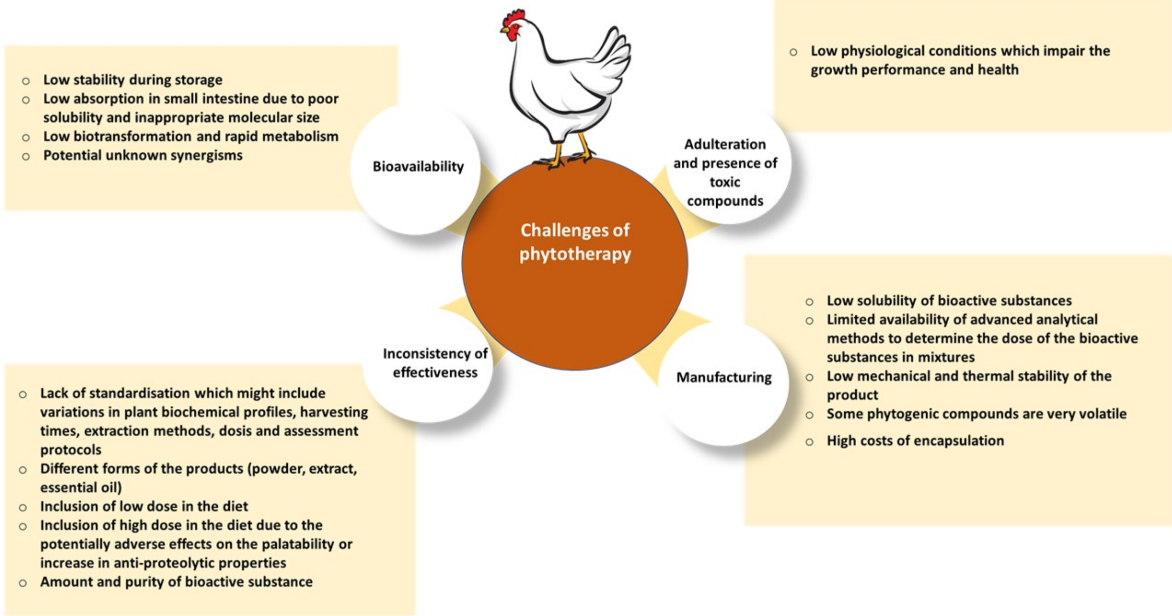

Figure 4: Challenges related to the application of phytogenic substances in poultry.

even toxic products. These processes might also be the reason for the limited bioavailability and effectiveness of phytogenic compounds in poultry (Suganya and Anuradha, 2017; Tolve et al., 2021).

Inconsistency

More attention and efforts should also be put into the inconsistent biological activities of bioactive substances in a specific product. This may be related to variations in plant biochemical profiles, harvesting times, locations, extraction methods, form of the extracts (powder, extract, essential oil), and inappropriate assessment protocols (Shehata et al., 2022). Indeed, the lack of standardization explains these variations resulting in inconsistent effectiveness (Vlaicu et al., 2021; Sugiharto and Ayasan, 2022).

Some phytogenic substances might reduce the feed intake due to their palatability resulting in low performance of chickens (Demir et al., 2003; Sugiharto, 2021; Vlaicu et al., 2021). The hardly controllable dose of phytogenic substances could also explain the inconsistency of their effectiveness in poultry. Low doses could not be sufficient to induce significant biological activity. Additionally, high doses do not necessarily result in an improvement in the effectiveness of phytogenic substances in poultry (Hafeez et al., 2020). For example, increasing the dose of an herbal formulation containing ajwain, fenugreek, and black cumin did not show an increase in the performance of broilers (Saleh et al., 2018). The efficacy of phytogenic substances depends on the hygienic status of poultry farms. For example, chickens kept under good hygienic conditions without health problems might not show significant effectiveness of phytogenic substances as growth promoters, antioxidants, or antimicrobial agents (Sarica et al., 2007). It should be kept in mind that the evaluation of bioactive substances in poultry requires animals under a level of stress (Sugiharto and Ayasan, 2022).

Adulteration and contamination with toxic substances

Some traditional herbal products have been demonstrated to exhibit potentially harmful action, and some have mutagenic and carcinogenic properties (Fennell et al., 2004). Examples of these toxic actions include the hepatotoxic effects of polygermander (Savvidou et al., 2007; Khaligh et al., 2011; Al-Mufarrej et al., 2019) and impairment of the intestinal epithelium and gut motility by eugenol (Al-Mufarrej et al., 2019). However, the assessment of toxicity in phytogenic products always has to consider the purity of the bioactive fraction, the potential contamination with hazardous compounds, their bioavailability and reported side effects, as well as synergistic effects between compounds in mixtures.

Prospective and recommendation to improve the use of phytotherapy in poultry

Based on the challenging aspects for efficient usage of phytogenic compounds in poultry, it is immediately obvious that further improvements must be envisaged for safe and efficient usage. One of these improvements implies encapsulation, i.e., entrapping the bioactive compounds into a particle's core. Encapsulation of phytogenic compounds has the following advantages: i) protect the active principle in the gastrointestinal tract, particularly in the stomach and small intestine, to increase the bioavailability, ii) improves the palatability by masking the potentially unpleasant smell and taste of the active compound, iii) provide the bioactive substances from the environmental stressors and thus to enhance the shelf life, iv) reduce the toxicity and costs by reducing the required dose (Stevanović et al., 2018;

Ghorani et al., 2019; Timilsena et al., 2020; Sugiharto and Ayasan, 2022).

Several materials for encapsulation are certified as "generally recognized as safe" (GRAS) and include lipids (waxes, glycerides, phospholipids, etc.), proteins (corn gluten, caseins, gelatin, etc.), or carbohydrate polymers (Arabic gum, cellulose, starch, alginate, etc.) (Timilsena et al., 2020). In the meantime, several studies demonstrated the use of encapsulated phytogenic substances in poultry, such as nano-encapsulated garlic essential oil (Amiri et al., 2021), soy-protein and polysaccharide encapsulated cinnamaldehyde (Yang et al., 2021), thymol- and carvacrol-based essential oils (Lee et al., 2020), chitosan encapsulated mint, thyme, and cinnamon (Nouri, 2019), and nano-encapsulated aloe vera, dill, and nettle root extract (Meimandipour et al., 2017). In the future, optimizing the method of encapsulation but also understanding the impacts of microbial fermentation on the rate of degradation and kinetics of phytogenic compounds are also required.

It is also time to expand methods for safe and reproducible media culture, i.e., controlled cultivation of medicinal plants on a scientific basis to emphasize the genetic stability and uniformity of plant population. Conventional plant breeding methods can improve agronomic, medicinal traits, and molecular markers coupled with assisted selection will be used increasingly in the future (Ahmar et al., 2020).

There is a huge demand for raw plant materials due to the widespread and increasing use of herbal medicine. Therefore, domestic cultivation under controlled conditions should be encouraged. Domestic cultivation also offers the opportunity to overcome some inherent problems in herbal medicine/extracts: misidentification, genetic and phenotypic variability, extract variability and instability, toxic components, and contaminants.

Manufacturing of phytogenic products is important to ensure: i) the quality of raw materials and their freedom from contamination, ii) maintenance of adequate quality control measures, iii) safety and quality measures in the transport and storage conditions, as well as processing and packaging. Additionally, new molecular techniques allow an accurate assessment of the flora composition resulting in improved strategies for elucidating mechanisms. Given the recent international legislation and domestic consumer pressures to withdraw growth-promoting antibiotics and reduce the use of antibiotics to treat mild bacterial infections, probiotics, postbiotics, and phytogenic substances can offer alternative options with increasing market values.

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