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Review Article
Carotenoids Blood Level as Biomarker for Intestinal Functionality in Broiler Chicken Trials: A Review

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Abstract

Searching for new additives and nutritional strategies to improve broiler gastrointestinal functionality and consequently, animal performance, is an objective of many research centers and industries in the past decades. This search prompted new studies to identify biomarkers and develop new tools to evaluate the benefits of dietary additives and nutritional solutions strategies. An efficient biomarker must be strongly correlated to improvements in gastrointestinal functionality. Additionally, the biomarker should be stable, fast and easy to measure, preferably non-invasive and cost-effective. This review aims to show that the measurement of blood carotenoid level is a potential biomarker for broiler's experimental trials, to evaluate nutritional additives as enhancers of gastrointestinal functionality and has a consistent correlation with animal performance and digestive efficiency. There are several factors that interfere with the bioavailability of carotenoids, then to use this biomarker it is necessary to isolate some factors such as diet and genetics, for example, to make it possible to consider changes in blood levels as an indirect measure of intestinal functionality. On the other hand, to extrapolate this measurement of blood carotenoid level to uncontrolled field situations, a wider range of variables should be evaluated so that it is possible to reach a similar conclusion regarding the health of the animals.

Key words: Biomarker, carotenoids, functionality, gut, performance, broilers

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The search for additives and nutritional strategies that improve broiler gastrointestinal functionality and, consequently, improve performance is increasing in research centers and animal nutrition technology companies. As a result, many reports of studies and development of methodologies that attempt to identify the strategies and their degree of success are found in recent literature. Improvements in gastrointestinal functionality are mainly related to better use of the diet, through the maintenance of the integrity and function of the intestinal mucosa, modulation of the gastrointestinal microbiota, better capacity of digestion and absorption of nutrients and modulation of the immune system[1]. The balance between the intestinal barrier function, inflammation and microbiota homeostasis is essential for optimal feed efficiency and animal performance[2].

The first interaction between the external environment and the animal occurs at the inner surface of the gastrointestinal tract, so the mucosa has a fundamental role in physiological functions involving digestion, absorption and metabolism. This barrier allows the passage and absorption of nutrients and, simultaneously, has the function of regulating the contact between the antigens and the immune system[3-5].

Several approaches can be used to characterize the integrity and functionality of the intestinal tract and its interactions with the components present in intestinal contents. In recent years, more complex methodologies such as metagenomics, metatranscriptomics, metaproteomics and metabolomics, in addition to studies on immune response and complete microbiome have been current. However traditional and simpler methodologies such as histological analyses of villus height and crypt depth are still widely used.

Recent reviews report that in both human and animal medicine researchers around the world are putting effort into identifying biomarkers that are strongly correlated with improvements in gastrointestinal functionality that are stable, easy, fast to measure and preferably non-invasive. However, they also state that a combination of multiple biomarkers will likely be needed to reach a more complete and assertive diagnosis[4,5].

Based on studies evaluating the impact of coccidiosis in chickens, it was observed that the blood level of carotenoids can be a simple and non-invasive biomarker for assessing the impacts on intestinal functionality. These studies show that lesions caused by *Eimerias* are related to reduced carotenoid absorption and reduced animal performance[6-13].

The purpose of this paper was to review the scientific literature evaluating the suitability of measurement of blood levels of carotenoids as a potential biomarker of the effects of nutritional additives or strategies in maintaining or improving gastrointestinal functionality in experiments with broiler chickens. It is important to emphasize that the investigation of a potential biomarker must go through a series of planned or controlled studies and a challenging step of field validation, in the present case, the complexity of gastrointestinal functionality must be recognized[5]. It should also be recognized that markers of intestinal inflammation or microbiota composition are factors that play an essential role in homeostasis and it is essential that they are added to the analysis when the studies are further evaluated[4].

CHALLENGE BY *EIMERIA* AND CAROTENOID ABSORPTION

Most of the studies available in the literature that negatively correlate carotenoid blood levels with intestinal integrity, which means, that higher lesion scores of intestinal epithelium represent lower carotenoid blood levels, use the *Eimeria* challenge as an experimental model.

The impacts caused by *Eimeria* infection on the absorption capacity of carotenoids are related to the impairment of lipid absorption capacity, by the reduction in the formation of micelles[8] and with the increase in oxidative stress caused by the infection, which increases the oxidation of carotenoids. A similar response was also observed in the reduction of plasma α-tocopherol levels[10]. Rochell *et al.*[13] in a more recent study with *Eimeria acervulina* challenge, observed impacts on plasma carotenoid levels, which was associated with reduced broiler performance and ileal digestibility of amino acids.

A variety of biomarkers have been studied to estimate the severity of coccidiosis lesions. Three decades ago, Conway *et al.*[7] considered the determination of plasma levels of carotenoids as one of the best indicators to measure the impacts on intestinal integrity. These impacts, observed even in infections with low levels of oocysts and with minimal reduction in animal performance described by these authors, were corroborated in studies that followed[11-14].

An immediate consequence of the reduction in plasma carotenoids level is the decrease in the efficiency of skin pigmentation of chickens, an important parameter for the markets of some Latin American countries. A study conducted in Mexico[4] relates broiler skin pigmentation with health, showing that the deposition of xanthophylls on the skin is influenced by the negative impacts on digestion and absorption caused by coccidiosis lesions. In the same study, it was also observed a reduction of blood carotenoid levels and

worse performance parameters. Uniform pigmentation usually indicates the health status and quality of poultry products[15].

Blood carotenoid level and body weight gain have a negative correlation with the level of *Eimeria* contamination and oocyst count in a litter, some authors consider blood carotenoid level as an excellent indicator of intestinal integrity[7,9,13].

MECHANISMS OF ABSORPTION AND BIOAVAILABILITY OF CAROTENOIDS

Animals are not able to synthesize carotenoids, so these compounds come from the diet. The efficiency of assimilation via diet is dependent on several factors and absorption occurs preferentially in the intestine[16].

The carotenoid absorption mechanism is closely related to lipid metabolism. First occurs the enzymatic digestion, followed by emulsification and micelles formation, then absorption through the cells of the intestinal mucosa and distribution through the plasma via the lymphatic system in mammals, very similar to what occurs with vitamin E. In birds, that do not have a well-developed lymphatic system, carotenoids are distributed directly to the liver and other tissues by lipoproteins released from intestinal cells to the hepatic portal vein[16].

The main site of lipid absorption is the jejunum, with less intensity in the ileum. The absorption occurs by passive diffusion, at the brush edge of the intestinal villi[17,18].

Some factors influence the bioavailability of carotenoids, Castenmiller and West[19] summarize nine main points: Type of carotenoid, molecular bonding, carotenoid diet concentration, matrix in which the carotenoid is incorporated, factors that affect the absorption and conversion, nutritional condition of the animal, genetic factors, factors related to animals and nutritional interactions. Nutritional factors such as dietary fat and protein levels, amount of soluble fiber, mycotoxins, vitamin A, iron and zinc status and high carotenoid levels affect carotenoid absorption[19-22].

BIOMARKER OF DIGESTIVE EFFICIENCY

Beauclercq *et al.*[23] show a relationship between digestive efficiency and serological composition in broilers. Comparing two strains of chickens of high and low digestive efficiency, they observed differences in the color of serum lipophilic portion, which was confirmed by spectrophotometry. Spectra between 430 and 516 nm have been reported, which corresponds to the absorption zone of the carotenoid lutein and zeaxanthin. Birds with low digestive capacity presented 31% lower serum coloration compared to birds with high digestive capacity, thus indicating that the colorimetric approach can be a quick and easy possibility of determining digestive efficiency.

In a follow-up study by the same group Mignon-Grasteau *et al.*[24] the authors considered serum staining at absorbance 492 nm a potential biomarker for chicken genetic selection for greater digestive efficiency, as an alternative to metabolic assays for calculating metabolizable energy. As advantages, they report the evaluation in a larger number of animals on the floor and reduction of tests in cages, adding, however, that further studies would be needed to be carried out on different diets and genetics.

INTEGRITY, PERMEABILITY AND INFLAMMATION OF INTESTINAL MUCOSA

Maintenance of a barrier function is the main role of the intestinal epithelium, controlling the entry of pathogens and toxins and at the same time allowing the selective permeability of nutrients[4]. Therefore it is responsible for maintaining homeostasis and regulating the passage of pro-inflammatory molecules, microorganisms, toxins and antigens[3]. Factors that cause the loss of intestinal integrity, that is, disruption of the enterocyte's tight junctions, result not only in an increase in permeability to luminal antigens and translocation of bacteria but also in a decrease in the capacity of nutrient absorption and consequent loss of animal productivity[25].

Impaired integrity of the intestinal mucosa caused by enteric pathogens is related to increased local inflammation and malabsorption[25]. The consequence is reduced growth. The mechanisms involved include: (a) Decreased efficiency in protein synthesis and degradation, (b) Decreased nutrient absorption because of increased damage of enterocytes, (c) Use of nutrients by pathogenic microorganisms, (d) Increase of the maintenance requirements for immune system demands and (e) Decreased active and synthesis of digestive enzymes and consequently decrease digestibility of dietary nutrients.

Lower carotenoid absorption could be related to oxidative stress caused by local inflammation, which consumes carotenoids[10], associated with the reduced capacity of the enterocyte to absorb nutrients[25].

It's important to study further how broilers absorb carotenoids to better understand the factors that affect this process. This could involve controlled experiments focusing

on specific parts of their diet and genetic factors. It's also crucial to conduct field studies with a large and diverse group of broilers to see if measuring blood carotenoid levels reliably reflects their performance. Additionally, other ways to assess broilers' digestive systems for a more complete understanding must be explored. Lastly, there is a need to check if using blood carotenoid levels is practical and financially viable for broiler production, taking into account the cost, ease of measurement and whether it can be widely adopted by the industry.

CONCLUSION

This review emphasizes the potential of blood carotenoid levels as a valuable biomarker for assessing the effectiveness of dietary additives and nutritional strategies in enhancing broiler gastrointestinal functionality. While controlled experiments have isolated influential factors like diet and genetics, allowing changes in blood levels to serve as an indirect measure of intestinal functionality, applying this biomarker in uncontrolled field situations necessitates a broader evaluation of variables. This comprehensive approach is crucial for drawing meaningful conclusions about the overall health and performance of the animals in field evaluations.

SIGNIFICANCE STATEMENT

The purpose of this article is to review the evidence that carotenoid blood level may be a potential biomarker of the effects of nutritional additives or strategies in maintaining or improving gastrointestinal functionality in experiments with broiler chickens. Evaluation of published research allows us to indicate blood carotenoids as an excellent biomarker not only for intestinal integrity but also for a broader characterization of intestinal functionality.

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