The broiler industry has experienced a significant improvement in production efficiency over the past decade, and with the annual production of 100 million tons of meat, it is the fastest growing animal sub-sector while its growth is expected to continue worldwide. However, a negative consequence of such intensive rearing conditions is the compromised resistance of birds to a variety of environmental challenges, which manifests as increased health abnormalities and gut-associated issues and impaired metabolic features of carcass meat. Consequently, enteric disease in broiler chickens results in an economic loss of more than $2 billion through worsened performance indices and high morbidity and mortality. Moreover, chicken meat continues to be recognized as a source of human gastroenteritis, and it has an increasing contribution to antimicrobial resistance due to the misuse of drugs and lack of a preventive strategy.

However, research has indicated that the process of inflammation resulting from specific challenging conditions can be controlled via preventive veterinary treatment using bioactive feed components as alternatives to drugs. Because optimal gut functionality in coordination with the intestinal microbiota represents the first line of antigen contact and a key component of the innate immune response determining the performance of fast-growing chickens, it is a potential target for avian immune robustness and represents an intervention priority. Cannabinoids from hemp (*Cannabis sativa*) and selenium (Se) are potential mediators with biological activities in mechanical, humoral, neurological and immunological elements of the gut-associated environment (including the microbiome). Although the mechanisms underlying the actions of cannabinoids and Se have not yet been fully elucidated, reports have indicated that bioactive agents mediating both gut functionality and integrity, including host mechanisms involved in infection resistance, may have considerable potential for reducing susceptibility to infectious diseases. However, this reduced susceptibility might only be achieved once the mechanisms determining the interactions of bioactive nutrients with the host gut have been elucidated.

We hypothesize that the addition of cannabidiol (CBD), a novel extract from hemp, and nanosized selenium (nano-Se) to the diet of broilers challenged with necrotic enteritis (NE; *C. perfringens*) will have a direct regulatory action on gut integrity and functionality and improve the host protective response. The investigated bioactive components will indirectly prevent structured biofilm formation by necrotic bacteria in the distal region of the gut. The application of additives to the broiler diet will regulate the nutritional cost of the immune response during challenging conditions and will therefore maintain the performance of the birds and affect the metabolic processes that contribute to meat quality traits.

The proposed study will be implemented in three sequential stages: In the **First stage** (two experiments performed on broiler chickens), the optimal doses of CBD (experiment 1) and nano-Se (experiment 2) for modulation of the gut response to the NE model will be determined. In the **Second stage** (one experiment conducted on broiler chickens), the interactive actions of CBD and nano-Se will be examined. Herein, the optimal doses of both agents (verified in the previous stage) will be added to the experimental diets to investigate their simultaneous actions on gut functionality and barrier functions in NE model birds according to the following parameters: (i) immune-, metabolic-, and junction-related gene expression, (ii) the mucosal antioxidant defense system, (iii) morphological indices of the intestinal mucosa, (iv) intestinal microbiota composition and activity, and (v) structured biofilm formation by necrotic bacteria. In the **Third stage** (one experiment each conducted on chickens and rats), the rates of CBD and nano-Se deposition in carcass tissues will be determined, and whether CBD and nano-Se affect metabolic processes determining meat quality traits will be assessed. For this stage, the broilers will be fed the same dietary treatments as described previously, and then they will be subjected to the NE challenge model. At 35 days of age, breast muscles will be collected, and physio-chemical indices will be evaluated. The carcasses of the remaining birds will be boiled, deboned, lyophilized and pooled by group. The obtained materials will be included in the diets fed to 10-week-old Wistar rats (proxy for a human model at a young age) for at least 8 weeks to assess their potential influences on parameters related to rat health.

With the continued threat caused by the misuse of pharmacological treatments in broiler production, promoting GIT functionality to reduce infections based on the use of dietary bioactive feed components instead of drugs is now justified and urgently required. Therefore, the proposed study is expected to provide valuable insights into the mechanisms underlying the influences of bioactive molecules on the GIT response and provide a missing element to accelerate the identification of new pathways for investigating these interactions. Such a proposal is justified, as it may provide the poultry industry with more effective and safe options for promoting efficient productivity while maintaining avian welfare and consumer safety. We hypothesize that the proposed research will likely contribute to a better understanding of the unique functional mechanism of avian GIT, provide new tools for the development of effective control strategies using bioactive agents, and facilitate their application through dietary intervention. Even if these outcomes do not occur immediately, they will certainly be observed in the future.