

## Gut inflammation in monogastric animals: do phytogetic feed additives help? - A review

Ofongo, Ruth T. S.

Department of Animal Science, Faculty of Agriculture, Niger Delta University, Wilberforce Island,  
Bayelsa State, Nigeria.



Corresponding author's Email address: [ruthofongo@ndu.edu.ng](mailto:ruthofongo@ndu.edu.ng) ; [ruthofongo@gmail.com](mailto:ruthofongo@gmail.com)

### Abstract

Modern day livestock production is plagued with many challenges, from feed, health of livestock to appropriate production systems that will yield good quality livestock products for human consumption. Amongst these several challenges, health of animals is very vital with regards to meat, eggs and milk for human consumption without compromising the health of consumers of these products. The gut is a major immune regulatory organ in monogastric animals, of which the gut associated lymphoid tissues (GALT) play a major role in its immune modulatory function. The gut portents launch of both innate and acquired immune response as a means of ensuring organ integrity and body defense. Whichever factors either of internal or external sources such as toxic insult or feed related factors that disturbs gut homeostatic balance, triggers gut inflammatory responses which may ultimately affect productivity of animals. Any product or strategy to maintain gut homeostasis is a step in the right direction of ensuring animal productivity and sustainable livestock production for health. Phytogetic feed additives (PFA) are the latest additions to livestock production, however, the role they play in animal health and maintenance of gut homeostasis in the presence and absence of a disease challenge in monogastric animals is gradually being elucidated. The PFA have been reported to modulate gut inflammation and consequently gut health by diverse means. Some PFA targets metabolic and immune pathways of the host, which ultimately affects disease causing pathogens. Immune modulatory effects of PFA have been adduced to their unique structures and possibly strong antioxidant properties or perhaps via metabolic responses initiated by metabolites present in individual PFA. This review was aimed at highlighting the anti-inflammatory and immune response modulatory effect of a few phytogetic feed additives fed to monogastric animals.

**Keywords:** Gut inflammation, immune response, phytogetics, pig, poultry

**Running title:** Significance of phytogetic feed additives on gut inflammation in monogastric animals – A Review

**Inflammation intestinale chez les animaux monogastriques : les additifs alimentaires phytogéniques sont-ils bénéfiques ? - Une revue**

### Résumé

La production animale moderne est confrontée à de nombreux défis, allant de l'alimentation et la santé du bétail à la mise en place de systèmes de production appropriés pour obtenir des produits de qualité destinés à la consommation humaine. Parmi ces défis, la santé animale est essentielle pour garantir la qualité de la viande, des œufs et du lait consommé par l'homme, sans compromettre la santé des consommateurs. L'intestin est un organe clé de régulation immunitaire chez les animaux monogastriques, où les tissus lymphoïdes associés à l'intestin (GALT) jouent un rôle majeur dans sa fonction immunomodulatrice. L'intestin déclenche des réponses immunitaires innées et acquises afin de préserver son intégrité et d'assurer la défense de l'organisme. Tout facteur interne ou externe, comme une intoxication ou des problèmes liés à l'alimentation, perturbant l'homéostasie intestinale, peut déclencher une réaction inflammatoire susceptible d'affecter la productivité animale. Tout produit ou stratégie permettant de maintenir cette homéostasie constitue une avancée vers une production animale durable et une meilleure santé des animaux. Les additifs alimentaires phytogéniques (PFA) sont des solutions récemment introduites en production animale. Leur rôle dans la santé animale et le maintien de l'homéostasie intestinale, en présence ou en l'absence de défis pathogènes chez les animaux monogastriques, est progressivement élucidé. Les PFA modèleraient l'inflammation intestinale et amélioreraient ainsi la santé digestive par

*divers mécanismes. Certains PFA ciblent les voies métaboliques et immunitaires de l'hôte, affectant finalement les agents pathogènes. Leurs effets immunomodulateurs pourraient être liés à leurs structures uniques, à leurs propriétés antioxydantes puissantes ou encore aux réponses métaboliques induites par leurs métabolites. Cette revue vise à mettre en lumière les effets anti-inflammatoires et immunomodulateurs de certains additifs phytogéniques utilisés dans l'alimentation des animaux monogastriques.*

---

**Mots-clés :** Inflammation intestinale, réponse immunitaire, phytogéniques, porc, volaille

## **Introduction**

The gut of monogastric animal takes part in the critical functions involved in nutrient digestion, absorption and overall growth performance. Besides this functions, it is involved in other functions which ultimately result in appropriate immune responses. Yang *et al.* (2015) reported that epithelial cells of the gut can function as “watch dogs” for the immune system. When it comes to gut health, the role of diet interaction with gut microbiota and the gastrointestinal tract (GIT) cannot be underestimated. This interaction ultimately affects the overall performance of animals. The gut is the largest immune system which expresses its functionality in diverse ways and processes. Some of these functions are, secretion of water and electrolytes in addition to secretion of mucin, immunoglobulins as well as acting as a selective barrier for protection against harmful pathogens and antigens (Lallès *et al.*, 2004). As a means of ensuring organ integrity and body defense; the gut portends the launch of both innate and acquired immune response (Eckmann *et al.*, 1995; Pitman and Blumberg, 2000). The obvious difference between the GIT immune-system and the systemic immune system is the point of maintaining equilibrium between two fundamental opposing processes. Firstly, it mounts immune feedback to the host regarding pathogens and secondly upholds tolerance to antigens from both commensal bacteria and consumed feed (Pitman and Blumberg, 2000). As earlier reported, any imbalance in these two opposing functions results in gut malfunction which can be evidenced in intolerance to feed, inflammation and ultimately in gut-related diseases. Gut inflammation negatively impacts on growth of the gut itself not to mention the adverse effect it has on efficient nutrient utilization. This fact has been reported in different studies demonstrating a link between GIT inflammations, chronic inflammatory diseases with GIT morphological changes, mucosa

damage, better mucosa absorbency, poor gut maturity and lessened nutrient absorption capability (Waters *et al.*, 1999; Nagura *et al.*, 2001; Strober *et al.*, 2002; Podolsky, 2002). Various factors, besides disease causing pathogens, can trigger gut inflammation in monogastric animals (Teirlynck *et al.*, 2009; Teirlynck *et al.*, 2011; Kogut *et al.*, 2018). In poultry birds for instance, diet related factors have been reported to cause inflammatory response in the GIT (Dal Pont *et al.*, 2020). Factors such as non–starch polysaccharides, oxidized oils, proteins and mycotoxins are feed components that elicit negative impact on gut homeostasis (Dal Pont *et al.* 2020).

Three already identified types of gut inflammation includes inflammation associated with infection, diet hypersensitivity–linked and weaning –linked (pigs). The GIT inflammation can lead to severe reduction of animal performance causing economic losses to the farmer (Yang *et al.*, 2015). In the light of the impact of gut inflammation on the performance of animals, various diet-targeted strategies to inhibit gut inflammatory processes that affect growth are an immense study focal point. Phytogenic feed additives (PFA) are no longer new to the livestock industry. They have been successfully added to the diet of both monogastric and ruminant animals. This is especially noteworthy in poultry nutrition where various phytogenic feed additives have been supplemented to poultry diets and reported to elicit various effects of which anti-inflammatory effect is one (Salman, 2019; Lee *et al.*, 2021). Although the antioxidant capacity of polyphenolic compounds has been investigated in the food industry and medicine owing to their prospects to ward off oxidative stress related diseases (Huang *et al.*, 2018; Mahfuz *et al.*, 2021). However, antioxidant effectiveness of polyphenolic compounds for monogastric diets is yet imprecise even though, they may act together

with other antioxidant compounds substantially utilized in animal feed (Bottegal *et al.*, 2024).

This review seeks to present the anti-inflammatory and immune response modulatory effect of a few phytogetic feed additives that have been highlighted in literature.

#### ***Uniqueness of gut immune response***

One notable attributes of the GIT immune system which differentiates it from the systemic immune system is the way the gut prompts inflammation. The gut brings about inflammation by means of cytokines which play a strategic role in the recruitment and activation of neutrophils, macrophages, T and B cells as well as dendritic cells (Eckmann *et al.*, 1995; Pitman and Blumberg, 2000). Furthermore, taking the case of poultry for example; feed constituents such as anti-nutritional compounds, oxidized lipids, mycotoxins, surplus soluble fibre or protein may bring about low-grade inflammatory reactions (Dal Pont *et al.*, 2020), or a toxic insult which can altogether bring about a surge of inflammatory response inducing events (Broom and Kogut 2017; Kogut, 2017; Kogut *et al.*, 2018; Broom, 2019). Unlike as stated earlier, the innate immune system primarily functions to recover and repair tissues that have been infected and or damaged (Broom and Kogut, 2017). However, maintenance of intestinal homeostasis in the GIT is very vital because of the constant contact with outwardly derived triggers – pathogenic microbes, food antigens and inflammation generating toxins (Kogut, 2013). According to Dal Pont *et al.* (2020); during homeostasis in the chicken GIT, intestinal immune tissue continues to take on gut microbiota and nutritional antigens which is not the case during infection or dysbiosis. Earlier literature published by various authors (Broom and Kogut 2017; Kogut, 2017; Kogut *et al.*, 2018; Broom, 2019) gave detailed description of the unique role and processes of inflammatory reaction in poultry. It was also revealed that innate immune cells, which include intestinal epithelial cells express pattern recognition receptors (PRRs) or their downstream portending molecules (Furness *et al.*, 2013). Other innate immune cells (macrophages, granulocytes, dendritic cells) also prompt PRRs together with intestinal epithelial cells which identify and act in response to infectious microbial constituents as microbe-

associated molecular patterns (MAMPs) (Keestra *et al.*, 2013; Smith *et al.*, 2014; Wu and Chen, 2014). These authors further stated that, PRRs also recognize and respond to endogenous host molecules secreted during cell death or stress. Earlier research findings asserted that, it is by means of PRRs, inflammatory response is induced in poultry during toxic insult (Broom and Kogut 2017; Kogut, 2017; Kogut *et al.*, 2018; Broom, 2019). It is in the light of these mechanisms this review seeks to look at immune and inflammatory responses triggered by few phytogetic feed additives. Do they really help?

#### ***Immune modulatory action and gut anti-inflammatory effect of some phytoetics Tannins***

Although tannins are attributed to the bitter taste of feed, resulting in depressing feed intake due to diminished palatability (Pizzi, 2019); however, recent information assert that low concentrations of several tannin sources can enhance the nutrition and health standing of monogastric animals (Huang *et al.*, 2018). Tannins exist as secondary plant metabolites with potent antioxidants, described to decrease oxidative and inflammatory stress in macrophages (Kaur *et al.*, 2008). A recent study by Tonda *et al.* (2018) illustrated that Tris-Acetate-EDTA (TAE) and Tris-Acetate (TA) minimized intestinal lesions triggered by *Eimeria* by means of downgrading oxidative stress and/or inflammation inside the intestine, thereby bringing about a more undamaged intestinal barrier. According to Redondo *et al.* (2014), tannins may be embroiled in modification of the interaction between gut microbiota and the GIT by eliciting anti-inflammatory and anti-parasitic functions. It is noteworthy to state that the ultimate effect of *Eimeria* parasites inside the birds' intestinal epithelial cells is gross intestinal lesions, resulting from reproduction of the parasite, thereby diminishing intestinal barrier integrity, absorptive capability finally creating elevated heights of oxidative and inflammatory stress inside the intestine (Tonda *et al.* 2018). As such, the anti-parasitic and anti-inflammatory properties of tannins make it proper to reduce parasite number on one hand while reducing oxidative and inflammatory stress response in the gut of infected birds. Different plants have tannins as secondary metabolites of which

chestnut is one. The study by Lee *et al.* (2021) further explained the immune-regulatory and host-targeted therapy choice of chestnut tannin for poultry disease. According to the authors, phytobiotic may be directed at metabolic and immunologic pathways of the host which may perhaps ultimately impinge on disease pathogen. Tannins possess added relevance as favorable bioactive ingredients to aid the challenges of antimicrobial growth promoters (AGP) removal in poultry production as a result of their antimicrobial, antioxidant and anti-inflammatory properties (Choi and Kim, 2020). The poultry industry, though plagued with many problems, heat stress is among the few key problems in the industry. It detrimentally influences growth performance, gut health, meat quality, and welfare of chickens (Attia *et al.*, 2017; Quinteiro-Filho *et al.*, 2010). Excessive production of reactive oxygen species (ROS) by means of augmented metabolic responses due to mitochondrial respiration is a conceivable cause for negative effects of heat stress in chickens (Lin *et al.*, 2006; Choi *et al.*, 2020). Under conventional circumstances, enzymatic along with non-enzymatic antioxidants know how to defuse ROS thereby maintaining equilibrium between oxidants and antioxidants (Lauridsen 2019). In otherwise conditions, such as disproportion involving oxidants and antioxidants in chickens, copious production of ROS can impair GIT health thereby inducing inflammation, resulting in reduced growth performance (Nawab *et al.*, 2018).

Plant extracts (Jiang *et al.*, 2019; Yang *et al.*, 2019), are among several antioxidants (Sahin *et al.*, 2003; Yun *et al.*, 2012; Kumbhar *et al.*, 2018; Shakeri *et al.*, 2019; Terruzi *et al.*, 2019) experimented to lessen heat and oxidative stress. In animals, tannins are thought to mitigate effects of oxidative stress, by foraging ROS thereby regulating enzymatic antioxidants in animals (Yang *et al.*, 2019). According to Ramnath and Rekha (2009); adding *Brahma rasayana* comprising diverse kinds of tannins improved activities of enzymatic antioxidants plus superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and decreased glutathione (GSH) in plasma of chickens reared under temperate conditions. Another study with grape (*Vitis vinifera*) pomace,

loaded with condensed tannins (CT), improved antioxidant enzyme activities (GPx and SOD); intestinal morphology, and upgraded relative weight of bursa of Fabricius and thymus in heat-stressed broiler chickens (Hosseini-Vashan *et al.*, 2020). Thus, augmenting suitable concentrations of tannins in practice may be an effective approach to mitigate oxidative stress in heat-stressed birds (Choi and Kim 2020). It is noteworthy to state here that the bursa of Fabricius is part of the GALT which plays a significant role in immune responses in poultry birds.

Furthermore, adding tannins at suitable quantities can enrich the immune system, gut ecosystem and gut microbiota of chickens reared in conventional surroundings (Choi and Kim 2020). Tannins are valuable in maintaining factors of mucosal immunity in chickens by up-regulation of IgA and mucin 2 (Karaffová *et al.*, 2019). Erlejman *et al.* (2008) similarly established that CT can merge with tumor necrosis factor- $\alpha$  (pro-inflammatory cytokines) receptors in the bid to slow down inflammatory reactions. This implies a direct modification of the immune system by tannins without provoking or prompting antimicrobial and antioxidant activities (Choi and Kim 2020). Furthermore, Diaz Carrasco *et al.* (2018) described a mixture of chestnut (hydrolysable tannins - HT) and quebracho tannins (CT) to modulate multiplicity in cecal microbiome in chickens. The resultant effect was a decline in the genus *Bacteroides* genus with specific members of the order *Clostridiales*; - mostly the *Ruminococcaceae* and *Lachnospiraceae* families' increasing. According to Shang *et al.* (2018); a meticulous connection exists between the chicken's microbiota and the GIT ecosystem, consequently, the microbiome – modifying effects of tannins may help to explain its gut health-improving outcomes in chickens. Furthermore, *in-vitro* trial by Brus *et al.* (2018) revealed that chestnut tannins improved the anti-oxidative qualities of chicken small intestine epithelial cells and furthered the growth of enterocytes.

In an experiment with pigs fed oxidized oil, Koo and Nyachoti (2019) showed how tannic acid effectively altered microbial metabolites. Tannin's selective antimicrobial properties would amend the animals gut microbiome (Pacheco-

Ordazet *et al.*, 2018). Viveros *et al.* (2011) similarly mentioned that tannins most likely have prebiotic effects by invigorating large numbers of beneficial bacteria. Bilic'-Šobot *et al.* (2016) verified HT to decrease causing cell debris inside large intestine of pigs, leading to dwindled production of skatole, a member of the indole family. It has been suggested that carob's flavonoids and tannins yield anti-diarrheal aftereffect in piglets by means of up surged reabsorption of water and electrolytes within the colon (Špoljaric *et al.*, 2019).

Nuamah *et al.* (2024) asserted in their meta-analysis report of studies with tannins in pigs that tannins promoted amounts of glutathione peroxidase, superoxide dismutase, along with total antioxidant volume in the serum. Generally, this approach may also be a consistent feed-based method to mitigate oxidative stress. Furthermore, their meta-analysis similarly indicated tannin-associated upturn of immunoglobulin G and M. Appending tannins to weaned piglets' diet, specifically chestnut and grape seed proanthocyanidins, may well serve as good feed-based means to enhance then support healthy GIT, thereby ultimately alleviating diarrhea incidences (Nuamah *et al.*, 2024). A possible explanation for this phenomenon could be the capability of polyphenols, comprising tannins, to reduce the activity of inflammatory mediators NF- $\kappa$ B and Nrf2 by means of inhibiting NF- $\kappa$ B/P38 signaling pathways (Huang *et al.*, 2019; Capelli *et al.*, 2021), thereby reducing the risk of intestinal diseases (Gessner *et al.*, 2013). The global immunomodulation effects of supplementing diets with tannins in Nuamah *et al.* (2024) meta-analysis suggest tannins as possible nutritional additive to abate inflammatory mediators. Granting the precise metabolic mechanisms of polyphenols, plus tannins, is yet to be completely explained in pigs (Lipin'ski 2017). Nonetheless, the results observed in Nuamah *et al.* (2024) meta-analysis denotes that digestion and uptake of ingested tannins in GIT of weaned piglets are afterwards transported to the bloodstream thereby function as exogenous antioxidants.

The amount of glutathione peroxidase, superoxide dismutase, and total antioxidant capacity ( $P < 0.01$ ) were raised in the serum of weaned pigs in response to tannin

supplementation (Nuamah *et al.*, 2024) whereas malon-dialdehydes concentration was decreased ( $P < 0.01$ ). Likewise, improved immunoglobulin M and G levels ( $P < 0.01$ ) were noticed as reported by Nuamah *et al.* (2024). Lastly, including tannins in diets of weaned piglets' specifically chestnut and grape seed proanthocyanidins, increased yield of weaned piglets. Simultaneously, it is a promising dietary method for mitigating oxidative stress thereby stimulating GIT health.

### **Quercetin**

Quercetin is a component of various foods, especially vegetables, green tea, fruits, wine apples, onions and tomatoes. Quercetin has been reported to exert positive effect on poultry production and health (Saeed *et al.*, 2017). The properties it exerts when included in poultry diet includes not just growth promoting but anti-inflammatory, anti-lipolytic, antioxidant, immune boosting effect and enhancing gut health (Parmar *et al.*, 2019). The pivotal C-ring of quercetin coupled alongside its numerous hydroxyl groups coupled with conjugated 'p' orbitals as its structural components has been attributed to observed strong antioxidant properties of quercetin (Saeed *et al.*, 2017). Possibly this plant metabolite is one of the unique phyto-biotic exhibiting multidimensional properties when consumed by poultry (Parmar *et al.*, 2019). Results of several broiler studies have pointed to this fact with regards to its immunomodulator potential (Manach *et al.*, 2004; Huang *et al.*, 2010; Surai and Fisinin, 2016; Kamboh. *et al.*, 2018; Rehman *et al.*, 2018a; Rehman *et al.*, 2018b). In the same line, Kamboh and Zhu, (2014) suggested that flavonoids like genistein and hesperidin stimulated intestinal morphology along with absorptive functions in growing broilers. This gut modifying action is not precisely established for quercetin nevertheless it could be owing to its poly-phenolic configuration and robust antioxidant prospective (Parmar *et al.*, 2019).

Enhanced type 1 interferon-regulated genes (IRGs) and type 1 and 2 interferon (IFN) was demonstrated by quercetin *ex vivo* showcasing significant decrease in pro- and anti-inflammatory cytokine characteristics in highly pathogenic porcine reproductive and respiratory syndrome virus (HP-PRRSV) -inoculated

monocyte-derived macrophages (Ruansit and Charerntantanakul, 2020). *In-vivo* porcine study by the authors further evaluated the immunomodulatory effect of oral administration of quercetin by improving cross defense of porcine reproductive as well as respiratory syndrome virus-1 (PRRSV-1) modified-live virus (MLV) vaccine against highly pathogenic (HP)-PRRSV-2 challenge. Immune modulatory parameters monitored in pigs administered quercetin demonstrated significant increase of IFN regulatory factor 3, stimulate IFN genes, IFN $\alpha$ , and drastically diminished transforming growth factor beta (TGF $\beta$ ) mRNA expressions. Furthermore, quercetin up-regulated IRGs, IFN $\alpha$ , and down-regulated TGF $\beta$  mRNA expressions which can participate towards additional reduced extent of viremic pigs and HP-PRRSV viremia given by PRRSV-1 MLV vaccine. According to their report (Ruansit and Charerntantanakul, 2020) quercetin possibly will serve as a valuable oral immunomodulator for enhancing cell-mediated immune protection to HP-PRRSV.

Other researchers also had earlier stated few probable means of action triggering the advantageous outcomes of quercetin on inflammation and immunity. According to Penissi *et al.*, (2003), quercetin has mast cell maintenance and gastrointestinal cytoprotective action, while Chirumbolo (2010) stated it can also play a modulating, biphasic and regulatory action on inflammation and immunity. Zou *et al.* (2016a) reported the protective effect of quercetin on pig intestinal integrity after transport stress to be associated with regulation of oxidative status and inflammation.

Further to this, quercetin was reported to have an immunosuppressive effect on dendritic cells function (Huang *et al.*, 2010). The results obtained from an earlier study (Nair *et al.*, 2002) suggested that the helpful immuno-stimulatory effects of quercetin may be mediated by setting off Th-1 derived cytokine, IFN- $\gamma$ , and inhibition of Th-2 derived cytokine, IL-4. Li *et al.* (2016); further stated that more studies are required to describe well the processes of action that lie behind the advantageous outcomes ensuing quercetin addition on inflammation besides immunity.

### **Thymol**

Thymol is also one of the secondary metabolites found in *Ocimum gratissimum* with antioxidant, free radical scavenging, anti-inflammatory, analgesic, antispasmodic, antibacterial, antifungal, antiseptic and antitumor activities (Nagoor Meeran *et al.*, 2017). Thymol (2-isopropyl-5-methylphenol) is a colorless crystalline monoterpene phenol. It can be found in some other plants besides *O. gratissimum* (Pandey *et al.*, 2014; Ofongo, 2022 – unpublished data). These are *Thymus vulgaris* (Amiri, 2012) and *Thymbra capitata* (Miguel *et al.*, 2015) just to mention a few. Thymol has been catalogued by the United States Food and Drug Administration as GRAS (Generally Recognized as Safe) for use as a food additive, with negligible toxicity (Nagoor Meeran *et al.*, 2017). Several poultry studies with thymol have reported its immune regulatory activity. Hashemipour *et al.* (2013) asserted that thymol can heighten immune response in broiler chickens by increasing immunoglobulin G (IgG) and tolerance to hypersensitivity. Further studies with the essential oil of *Zataria multiflora* (containing thymol) supplementation of chickens' diet was reported to promote humoral immune reactions by means of improving antibody titres (Mosleh *et al.*, 2013).

Results obtained from pig studies have also elucidated the anti-inflammatory and immune regulatory activities of thymol. According to Trevisi *et al.* (2010); supplementing 1% thymol in weaning pigs' diet improved amounts of immunoglobulin A (IgA) and immunoglobulin M (IgM) within sera of *Salmonella typhimurium* challenged pigs. This finding may have been further confirmed by the report of Li *et al.* (2012) which stated that thymol increased levels of IgA and IgM in the GIT of pigs thereby improving the immune system. Taranu *et al.*, (2012) further explained the immune regulatory effect of thymol in handling low-weight growing-finishing pigs. According to the authors, utilization of thymol increased the CD4C, CD8C, plus MHC-II percentage within peripheral 4CC blood. It was observed that thymol was able to down regulate tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) expression in GIT of post-weaned pigs (Taranu *et al.*, 2012). Amirghofran *et al.* (2016) in their study established that 10mg/mL of thymol attenuated maturation of dendritic cells, constrained

mitogenic plus allogenic T cell reactions besides secretion of (interferon) IFN- and (interleukin) IL-g4 cytokines. While Chauhan *et al.* (2014) had earlier stated that the potent immuno-stimulatory effect of thymol was by augmenting phagocytosis.

#### ***Immune regulatory effect of other phytoGENICS***

Several other phytogetic feed additives have been supplemented in diets of monogastric animals having potent immune regulatory properties. According to Dhama *et al.* (2015); immune activation via herbal extracts can possibly lessen an animal's vulnerability to infectious diseases. In the light of immunodeficiency which could occur by several factors such as misuse of antimicrobials, vaccination lapses or immune-suppressive infective ailment (Gholami-Ahangaran *et al.*, 2013); boosting immunity becomes a key objective to avert virulent infections (Gholami-Ahangaran *et al.*, 2014). From the perspective of how vital the health of animals is to livestock producers; it is pertinent to mention that the potent immune regulatory properties of phytogetic feed additives need to be better understood for application purposes Gholami-Ahangaran *et al.* (2022).

This section attempts to cite a few studies reporting such data either in poultry or pigs. Several research reports have revealed phytogetic compounds such as purple sweet potato anthocyanin (Hwang *et al.*, 2011) and epicatechin (Bahia *et al.*, 2008) to modify Nrf2 and Nf-B pathways. The implication of such modification is protection against oxidative stress and reducing inflammation which eventually culminates in improved animal health and growth performance (Yang *et al.*, 2015). An earlier report stated a down-regulation of numerous pro-inflammatory genes in the mucosa within different sections of the GIT may possibly play a part to increased feed efficiency observed in pigs fed polyphenol-rich plant products (Fiesel *et al.* 2014). Dietary supplementation with cinnamon oil also indicated its potential to alleviate LPS-induced injury by repressing inflammation (Wang *et al.*, 2015). The presence of the alkaloid sanguinarine in feed of weaner pigs demonstrated its beneficial outcomes on growth performance and furthered anti-inflammatory activity (Kantas *et al.*, 2015).

#### ***Oregano***

Oregano is another phytogetic product used in livestock feed. Results obtained in a study in which Oregano essential oil (OEO) was administered to pigs, made known that OEO improved the integrity of intestinal barrier (Zou *et al.*, 2016b). Significantly ( $P < 0.05$ ) lower population of *Escherichia coli* in the jejunum, ileum and colon was observed in OEO – treated pigs which was in accordance with greater inactivation ( $P < 0.05$ ) of inflammation reflected by mitogen-activated protein kinase (MAPK), protein kinase B (PKB or Akt), and nuclear factor  $\kappa$  B (NF- $\kappa$  B) signaling pathways culminating in expression of inflammatory cytokines in the jejunum (Zou *et al.*, 2016b). The results provide illustration of intestinal barrier integrity promoting effect of OEO possibly by means of modulating intestinal bacteria and immune status in pigs.

Studies with poultry have also reported the Immune regulatory effect of other phytoGENICS with or without disease challenge. Administration of small amounts of carvacrol, cinnamaldehyde and capsicum was reported to show immune-boosting qualities to shield broiler chickens from live coccidiosis challenge (Lillehoj *et al.*, 2011). However, not all studies with carvacrol showed improved response (Botsoglou *et al.* 2002) as envisaged due to declared antioxidant, antibacterial and antiviral actions of carvacrol. It was asserted by Perez-Roses *et al.* (2015); that the phagocyte system, humoral and cellular immune reactions may possibly be increased by consuming essential oils. According to the author this intensifies the capacity of the defense system towards managing infectious organisms besides the immuno-stimulating action of polyphenol fractions of thymol and carvacrol.

Unpublished *in - vitro* assays reported by Lillhoj *et al.* (2018) revealed spearmint and peppermint essential oils possess cellular antioxidant activities involved in intensifying intracellular glutathione amount in H<sub>2</sub>O<sub>2</sub>-stimulated gut epithelial cells. In addition, Vaccinated chickens fed diets supplemented with carvacrol/cinnamaldehyde/capsicum presented heightened intestinal numbers of macrophages, while addition of *Capsicum/Curcuma/oleoresin* alone resulted in augmented intestinal T cell numbers in contrast to untreated chickens (Kim *et*

*al.*, 2010). Although many studies have reported disease prevention or immune-enhancement properties of phytochemicals, however, limited research has examined the mechanisms involved in observed results (Kim and Lillhoj 2019).

Going further, (Pirgoliev *et al.*, 2019); reported that feeding phytochemical additive to broiler birds significantly down regulated the expression of CD40LG, interferon G (IFNG) and interleukin 6 (IL6). The *CD40LG* gene is a gene that provides instructions for making a protein called *CD40 ligand*, which is found on the surface of immune system cells known as T cells. According to the authors, dietary inclusion of phytochemical additives improved overall performance variable and intestinal cytokines expression in broiler chickens. In another broiler study, aqueous extracts of *Azadirachta indica* and *Vernonia amygdalina* were reported to elicit positive impact on humoral immune response (Ahmed *et al.*, 2018). Nameghi *et al.* (2019) in their work stated improved humoral immunity when a blend of thyme, peppermint and eucalyptus essential oils was administered to broiler chickens. According to Acamovic and Brooker (2005) herbs abundant in flavonoids - thymol, carvacrol - may possibly upgrade immune functions by functioning as antioxidants as a result increasing Vitamin C activity.

The aqueous extract of *V. amygdalina* has been shown to have positive effect on peripheral lymphoid tissues (spleen and proventriculus) (Young-Man *et al.*, 2021a, Young-Man *et al.*, 2021b). It can be said or postulated that phytochemical feed additives modulate immune response via distinct pathways which ultimately boost animal health. Adams *et al.* (2023); asserted that modification of avian innate immune system using immuno-stimulatory composites offers a favorable way out for augmenting poultry immune reactions to an extensive bacterial infection devoid of the possibility of engendering antibiotic resistance.

### Conclusion

Plant derived products in different PFA modulate gut inflammation cum gut health by diverse means. Primary data from pig and poultry experiments cited here make evident how phytochemical feed additives help with gut inflammation in both pigs and poultry. It is

obvious from earlier works in literature cited that some phytochemical feed additives cum secondary plant metabolites do help with gut inflammation in pigs and especially poultry birds. In addition, phytochemicals or phytobiotics can target metabolic and immunologic pathways of the host which may ultimately affect disease pathogen. Plant extracts can improve the immunity of monogastric animals thereby decreasing their susceptibility to infectious disease by acting as immune stimulators when consumed. It can be said that PFA are potential diet targeted strategy to inhibit gut inflammation processes which can impact performance of monogastric animals. Stimulation of intestinal morphology including absorptive functions in broiler chickens or gut regulating action of PFA is another positive effect of PFA supplementation to broiler diet. Certain PFA such as quercetin may perhaps help as a valuable oral immunomodulator for better cell-mediated protection against HP-PRRSV in pigs. Thymol stimulates humoral immune response by increasing antibody titres in chickens. In the case of pigs, thereby increasing levels of IgA and IgM in the GIT thereby improving the immune system. Immune modification by means of PFA can possibly lessen vulnerability of farmed animals to infectious diseases. Immunomodulatory effects of PFA may be added to their unique structure and possibly strong antioxidant properties. Discriminatory antimicrobial mode of action of tannins would help alter the microbiome of poultry birds and pigs. Immune and inflammatory responses triggered by few phytochemical feed additives show they really help in one way or another however the implications of these findings on current research thrust is vital. Current research thrust on impacts of livestock gut microbiome in livestock production implies understanding the effect of different feed additives including PFA on the gut microbiome of monogastric animals. Although microbiome studies are not inexpensive, they shed light on specific microbiome function in modulating growth and health in animals regardless of the type of feed additive utilized.

### References

- Acamovic, T., and Brooker, J. D. 2005: Biochemistry of plant secondary metabolites and their effects in animals. *Proceedings of*

- the Nutrition Society*, 64 (3), 403 – 412.  
<https://doi.org/10.1079/pns2005449>.
- Adams, J.R.G.; Mehat, J.; La Ragione, R. and Behboudi, S. 2023:** Preventing bacterial disease in poultry in the post-antibiotic era: a case for innate immunity modulation as an alternative to antibiotic use. *Front. Immunol.* 14:1205869. doi: 10.3389/fimmu.2023.1205869
- Ahmed, A. S.; Tarck, A. E. and Alaeldein, M. A. 2018:** Effect of dietary phytochemicals (Herbal Mixtures) supplementation on growth performance, nutrient utilization, anti-oxidative properties and immune response in broilers. *Environment Science Poultry Research.* 25(15): 14606 – 14613.
- Amirghofran, Z.; Ahmadi, H.; Karimi, M. H.; Kalantar, F.; Gholijani, N. and Malek-Hosseini, Z. 2016:** *In vitro* inhibitory effects of thymol and carvacrol on dendritic cell activation and function. *Pharm. Biol.* 54, 125 – 132. doi: 10.3109/13880209.2015.1055579.
- Amiri, H. 2012:** Essential oils composition and antioxidant properties of three *Thymus* species. *Evid. Based Complement. Alternat. Med.* 2012:728065. doi: 0.1155/2012/728065
- Attia, Y.A.; Al-Harathi, M.A.; El-Shafey, A.S.; Rehab, Y.A. and Kim, W.K. 2017:** Enhancing tolerance of broiler chickens to heat stress by supplementation with vitamin E, vitamin C and/or probiotics. *Ann. Anim. Sci.* 17: 1155 – 1169.
- Bahia, P.K.; Rattray, M. and Williams, R.J. 2008:** Dietary flavonoid (2) epicatechin stimulates phosphatidylinositol 3-kinase-dependent antioxidant response element activity and up-regulates glutathione in cortical astrocytes. *J. Neurochem.* 106: 2194 – 2204.
- Bilic-Šobot, D.; Kubale, V.; Škrlep, M.; Candek-Potokar, M.; Prevolnik Povše, M.; Fazarinc, G. and Škorjanc, D. 2016:** Effect of hydrolysable tannins on intestinal morphology, proliferation and apoptosis in entire male pigs. *Arch. Anim. Nutr.* 70: 378 – 388.
- Botsoglou, N. A., Florou-Paneri, P., Christaki, E., Fletouris, D. J., and Spais, A. B. 2002.** Effect of dietary oregano essential oil on performance of chickens and on iron-induced lipid oxidation of breast, thigh and abdominal fat tissues. *British Poultry Science.* 43 (2): 223 – 230.  
<https://doi.org/10.1080/00071660120121436>
- Bottegai, D.N.; Latorre, M.Á.; Lobón, S.; Verdú, M.; Álvarez-Rodríguez, J. 2024:** Fattening Pigs with Tannin-Rich Source (*Ceratonia siliqua* L.) and High Doses of Vitamin E: Effects on Growth Performance, Economics, Digestibility, Physiology, and Behavior. *Animals* 14(13): 1855.  
<https://doi.org/10.3390/ani14131855>.
- Broom, L.J. and Kogut, M.H. 2017:** Inflammation: friend or foe for animal production? *Poult. Sci.* 97: 510 – 514.
- Broom, L.J. 2019:** Host-microbe interactions and gut health in poultry — focus on innate responses. *Microorganisms* 7(5): 139. doi: 10.3390/microorganisms7050139.
- Brus, M.; Gradišnik, L.; Trapecar, M.; Škorjanc, D. and Frangež, R. 2018:** Beneficial effects of water-soluble chestnut (*Castanea sativa* Mill.) tannin extract on chicken small intestinal epithelial cell culture. *Poult. Sci.* 97: 1271 – 1282.
- Cappelli, K.; Sabino, M.; Trabalza-Marinucci, M.; Acuti, G.; Capomaccio, S.; Menghini, L.; Verini-Supplizi, A. 2021:** Differential effects of dietary oregano essential oil on the inflammation related gene expression in peripheral blood mononuclear cells from outdoor and indoor reared pigs. *Front. Vet. Sci.* 8: 602811.
- Chauhan, A. K.; Jakhar, R.; Paul, S. and Kang, S. C. 2014:** Potentiation of macrophage activity by thymol through augmenting phagocytosis. *Int. Immunopharmacol.* 18: 340 – 346. doi: 10.1016/j.intimp.2013.11.025.
- Chirumbolo, S. 2010:** The role of quercetin, flavonols and flavones in modulating inflammatory cell function. *Inflamm. Allergy Drug Targets.* 9: 263 – 285.
- Choi, J. and Kim, W. K. 2020:** Dietary Application of Tannins as a Potential Mitigation Strategy for Current Challenges in Poultry Production: A Review. *Animals* 10 (12): 2389; doi: 10.3390/ani10122389.
- Choi, J.; Li, W.; Schindell, B.; Ni, L.; Liu, S.; Zhao, X.; Gong, J.; Nyachoti, M. and**

- Yang, C. 2020: Molecular cloning, tissue distribution and the expression of cysteine /glutamate exchanger (xCT, SLC7A11) in different tissues during development in broiler chickens. *Anim. Nutr.* 6: 107 – 114.
- Dal Pont, G. C.; Farnell, M.; Farnell, Y. and Kogut, M. H. 2020: Dietary Factors as Triggers of Low-Grade Chronic Intestinal Inflammation in Poultry. *Microorganisms* 8: 139 – 148; doi: 10.3390/microorganisms8010139.
- Dhama, K., Latheef, S. K., Mani, S., Samad, H. A., Karthik, K., Tiwari, R., Khan, R. U., Alagawany, M., Farag, M. R., Alam, G. M., Laudadio, V. and Tufarelli, V. 2015: Multiple beneficial applications and modes of action of herbs in poultry health and production-a review. *International Journal of Pharmacology*, 11 (3), 152 – 176. <https://doi.org/10.3923/ijp.2015.152.176>.
- Diaz Carrasco, J.M.; Redondo, E.A.; Pin Viso, N.D.; Redondo, L.M.; Farber, M.D. and Fernandez Miyakawa, M.E. 2018: Tannins and bacitracin differentially modulate gut microbiota of broiler chickens. *Biomed. Res. Int.* 21; 2018:1879168. doi: 10.1155/2018/1879168.
- Eckmann, L.; Kagnoff, M.F. and Fierer, J. 1995: Intestinal epithelial cells as watchdogs for the natural immune system. *Trends Microbiol.* 3: 118 – 120.
- Erlejan, A.G.; Jagers, G.; Fraga, C.G. and Oteiza, P.I. 2008: TNF $\alpha$ -induced NF- $\kappa$ B activation and cell oxidant production are modulated by hexameric procyanidins in Caco-2 cells. *Arch. Biochem. Biophys.* 476: 186 – 195.
- Fiesel, A.; Gessner, D. K.; Most, E. and Eder, K. 2014: Effect of dietary polyphenol-rich plant products from grape or hop on pro-inflammatory gene expression in the intestine, nutrient digestibility and faecal microbiota of weaned pigs. *BMC Vet. Res.* 10: 96. <https://doi.org/10.1186/s12917-014-0196-5>
- Furness, J. B., Rivera, L. R., Cho, H. -J., Bravo, D. M., and Callaghan, B. 2013: The gut as a sensory organ. *Nature Reviews Gastroenterology and Hepatology*, 10 (12): 729 – 740. <https://doi.org/10.1038/nrgastro.2013.180>.
- Gessner, D.K.; Fiesel, A.; Most, E.; Dinges, J.; Wen, G.; Ringseis, R.; Eder, K. 2013: Supplementation of a grape seed and grape marc meal extract decreases activities of the oxidative stress-responsive transcription factors NF- $\kappa$ B and Nrf2 in the duodenal mucosa of pigs. *Acta Vet. Scand.* 55: 18.
- Gholami-Ahangaran, M., Fathi-Hafshejani, E., and Seyed-Hosseini, R. 2013: Seromolecular study of chicken infectious anemia in chickens, ostriches, and turkeys in Iran. *Journal of Applied Poultry Research.* 22 (3): 404 – 409. <https://doi.org/10.3382/japr.2012-00567>.
- Gholami-Ahangaran, M., Zia-Jahromi, N., and Namjoo, A. 2014: Molecular detection of avian pox virus from nodular skin and mucosal fibrino necrotic lesions of Iranian backyard poultry. *Tropical Animal Health and Production.* 46 (2): 349 – 353. doi: 10.1007/s11250-013-0495-z.
- Gholami-Ahangaran, M.; Ahmadi-Dastgerdi, A.; Azizi, S.; Basiratpour, A.; Zokaei M. and Derakhshan M. 2022: Thymol and carvacrol supplementation in poultry health and performance. *Veterinary Medicine and Science Vet. Med Sci.* 8(1): 267 – 288. DOI: 10.1002/vms3.663.
- Hashempour, H.; Kermanshahi, H.; Golian, A. and Veldkamp, T. 2013: Effect of thymol and carvacrol feed supplementation on performance, antioxidant enzyme activities, fatty acid composition, digestive enzyme activities, and immune response in broiler chickens. *Poult. Sci.* 92: 2059 – 2069. doi: 10.3382/ps.2012-02685.
- Hosseini-Vashan, S.J.; Safdari-Rostamabad, M.; Piray, A.H.; and Sarir, H. 2020: The growth performance, plasma biochemistry indices, immune system, antioxidant status, and intestinal morphology of heat-stressed broiler chickens fed grape (*Vitis vinifera*) pomace. *Anim. Feed Sci. Technol.* 259: 114343. <https://doi.org/10.3390/antiox8090336>
- Huang, C.; Wang, Y.; He, X.; Jiao, N.; Zhang, X.; Qiu, K.; Piao, X.; Yin, J. 2019: The involvement of NF- $\kappa$ B/P38 pathways in *Scutellaria baicalensis* extracts attenuating of *Escherichia coli* K88-induced acute

- intestinal injury in weaned piglets. *Br. J. Nutr.* 122: 152 – 161.
- Huang, Q.; Liu, X.; Zhao, G.; Hu, T.; Wang, Y. 2018:** Potential and Challenges of Tannins as an Alternative to In-Feed Antibiotics for Farm Animal Production. *Anim. Nutr.* 4: 137–150.
- Haung, R.Y.; Yu, Y.L.; Cheng, W.C.; Yang, C.N.O.; Fu, E.; Chu, C.L. et al. 2010:** Immunosuppressive effect of quercetin on dendritic cell activation and function. *The Journal of Immunology.* 184: 6815 – 6821.
- Hwang, Y.P.; Choi, J.H.; Yun, H.J.; Han, E.H.; Kim, H.G.; Kim, J.Y.; Park, B.H.; Khanal, T.; Choi, J.M.; Chung, Y.C.; and Jeong, H.G. 2011:** Anthocyanin from purple sweet potato attenuate dimethyl nitrosamine-induced liver injury in rats by inducing Nrf2-mediated antioxidant enzymes and reducing COX-2 and iNOS expression. *Food Chem. Toxicol.* 49: 93 – 99.
- Jiang, Q.; Zhang, H.; Yang, R.; Hui, Q.; Chen, Y.; Mats, L.; Tsao, R. and Yang, C. 2019:** Red-Osier Dogwood Extracts Prevent Inflammatory Responses in Caco-2 Cells and a Caco-2 BBe1/EA. hy926 Cell Co-Culture Model. *Antioxidants* 8(10): 428. doi: 10.3390/antiox8100428.
- Kamboh, A.A. and Zhu, W.Y. 2014:** Individual and combined effects of genistein and hesperidin on immunity and intestinal morphometry in lipopolysaccharide-challenged broiler chickens. *Poultry Science.* 93 (9): 2175-83. doi: 10.3382/ps.2014-03971.
- Kamboh, A. A. Khan, M. A.; Kaka, U.; Awad, E. A.; Memon, A.M. and Saeed, M. Korejo, N. A.; Bakhetgul, M. and Kumar, C. 2018:** Effect of dietary supplementation of phytochemicals on immunity and hematology of growing broiler chickens. *Italian Journal of Animal Science.* 17:4. 10381043. DOI: 10.1080/1828051X.2018.1438854
- Kantas, D.; Papatsiros, V.G.; Tassis, P.D.; Athanasiou, L.V. and Tzika, E.D. 2015:** The effect of a natural feed additive (*Macleaya cordata*), containing sanguinarine, on the performance and health status of weaning pigs. *Anim. Sci. J.* 86: 92 – 98.
- Karaffová, V.; Bobíková, K.; Levkut, M.; Revajová, V.; Ševčíková, Z. and Levkut, M. 2019:** The influence of Farmatan® and Flimabend® on the mucosal immunity of broiler chicken. *Poult. Sci.* 98, 1161 – 1166.
- Kaur, G.; Athar, M. and Sarwar Alam, M. 2008:** *Quercus infectoriac* galls possess antioxidant activity and abrogates oxidative stress induced functional alterations in murine macrophages. *Chem. Biol. Interact.* 171:272 – 282.
- Keestra, A. M.; de Zoete, M.R.; Bouwman, L.I.; Vaezirad, M.M. and van Putten, J.P. 2013:** Unique features of chicken tolllike receptors. *Dev. Comp. Immunol.* 14(3): 316 – 323. doi: 10.1016/j.dci.2013.04.009.
- Kim, D. K., Lillehoj, H. S.; Lee, S. H.; Jang, S. I. and D. Bravo. 2010:** High-throughput gene expression analysis of intestinal intraepithelial lymphocytes after oral feeding of *carvacrol*, *cinnamaldehyde*, or *Capsicum oleoresin*. *Poult. Sci.* 89(1): 68 – 81. doi: 10.3382/ps.2009-00275.
- Kim, W. H. and Lillehoj, H. S. 2019:** Immunity, immunomodulation, and antibiotic alternatives to maximize the genetic potential of poultry for growth and disease response. *Animal Feed Science and Technology* 250 (2019) 41–50.
- Kogut, M.H. 2013:** The gut microbiota and host innate immunity: Regulators of host metabolism and metabolic diseases in poultry? *J. Appl. Poult. Res.* 22: 637 – 646.
- Kogut, M.H. 2017:** Issues and consequences of using nutrition to modulate the avian immune response. *J. Appl. Poult. Res.* 26: 605 – 612.
- Kogut, M.H.; Genovese, K.J.; Swaggerty, C.L.; He, H. and Broom, L. 2018:** Inflammatory phenotypes in the intestine of poultry: not all inflammation is created equal. *Poult. Sci.* 97: 2339 – 2346.
- Koo, B. and Nyachoti, C.M. 2019:** Effects of thermally oxidized canola oil and tannic acid supplementation on nutrient digestibility and microbial metabolites in finishing pigs. *J. Anim. Sci.* 97: 2468 – 2478.
- Kumbhar, S.; Khan, A.Z.; Parveen, F.; Nizamani, Z.A.; Siyal, F.A.; Abd El-Hack, M.E.; Gan, F.; Liu, Y.; Hamid, M. and Nido, S.A. 2018:** Impacts of selenium and vitamin E supplementation on mRNA of heat

- shock proteins, seleno-proteins and antioxidants in broilers exposed to high temperature. *Amb Express* 8: 1 – 10.
- Lallès, J.P.; Boudry, G.; Favier, C.; le Floch, N.; Luron, I.; Montagne, L.; Oswald, I.P.; Pié, S.; Piel, C. and Sève, B. 2004.** Gut function and dysfunction in young pigs: *Physiol. Anim. Res.* 53: 301 – 306.
- Lauridsen, C. 2019:** From oxidative stress to inflammation: Redox balance and immune system. *Poult. Sci.* 98: 4240 – 4246.
- Lee, A.; Dal Pont, G. C.; Farnell, M. B.; Jarvis, S.; Battaglia, M.; Arsenaault R. J.; and Kogut M. H. 2021:** Supplementing chestnut tannins in the broiler diet mediates a metabolic phenotype of the ceca. *Poultry Science* 100: 47 – 54 <https://doi.org/10.1016/j.psj.2020.09.085>.
- Li, S.Y.; Ru, Y.; Liu, M.; Xu, B.; Péron, A. and Shi, X. G. 2012:** The effect of essential oils on performance, immunity and gut microbial population in weaner pigs. *Livest. Sci.* 145: 119 – 123. 10.1016/j.livsci.2012.01.005
- Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M. T.; Wang, S.; Liu, H. and Yin, Y. 2016:** Review: Quercetin, Inflammation and Immunity. *Nutrients.* 8(3):167. doi: 10.3390/nu8030167.
- Lillehoj, H.S.; Kim, D.K.; Bravo, D.M. and Lee, S.H. 2011:** Effects of dietary plant-derived phyto nutrients on the genome-wide profiles and coccidiosis resistance in the broiler chickens. *BMC Proc.* 5 Suppl 4(Suppl 4): S34. doi: 10.1186/1753-6561-5-S4-S34.
- Lillehoj H.; Liu, Y.; Calsamiglia, S.; Fernandez-Miyakawa, M.E.; Chi, F.; Cravens, R.L.; Oh, S. and Gay, C.G. 2018:** Phytochemicals as antibiotic alternatives to promote growth and enhance host health. *Vet Res.* 2018 Jul 31; 49(1):76. doi: 10.1186/s13567-018-0562-6.
- Lin, H.; Decuypere, E. and Buyse, J. 2006:** Acute heat stress induces oxidative stress in broiler chickens. *Comp. Biochem. Physiol. Part A Mol. Integr. Physiol.* 144: 11 – 17.
- Lipin'ski, K.; Mazur, M.; Antoszkiewicz, Z.; Purwin, C. 2017:** Polyphenols in monogastric nutrition—a review. *Ann. Anim. Sci.* 17: 41 – 58.
- Mahfuz, S.; Shang, Q. and Piao, X. 2021:** Phenolic Compounds as Natural Feed Additives in Poultry and Swine Diets: A Review. *J. Anim. Sci. Biotechnol.* 12(1):48. doi: 10.1186/s40104-021-00565-3.
- Manach, C.; Scalbert, A.; Morand, C.; Remesy, C. and Jimenez, L. 2004:** Polyphenols: Food sources and bioavailability. *American Journal of Clinical Nutrition.* 79:727 - 747.
- Miguel, M. G.; Gago, C.; Antunes, M. D.; Megias, C.; Cortes-Giraldo, I.; Vioque, J.; Lima A.S.; Figueiredo, A.C. 2015:** Antioxidant and anti-proliferative activities of the essential oils from *Thymbra capitata* and thymus species grown in Portugal. Evidence Based Complement. *Alternat. Med.* 2015:851721. doi: 10.1155/2015/851721.
- Mosleh, N., Shomali, T., and Kazemi, A. 2013:** Effect of *Zataria multiflora* essential oil on immune responses and faecal virus shedding period in broilers immunized with live Newcastle disease vaccines. *Iranian Journal of Veterinary Research,* 14 (3): 220 – 225.
- Nagoor Meeran, M. F.; Javed, H.; Al Taei, H.; Azimullah, S. and Ojha, S. 2017:** Pharmacological Properties and Molecular Mechanisms of Thymol: Prospects for Its Therapeutic Potential and Pharmaceutical Development. *Front. Pharmacol.* 2017 Jun 26; 8:380. doi: 10.3389/fphar.2017.00380.
- Nagura, H.; Ohtani, H.; Sasano, H. and Matsumoto, T. 2001:** The immuno-inflammatory mechanism for tissue injury in inflammatory bowel disease and *Helicobacter pylori*-infected chronic active gastritis. Roles of the mucosal immune system. *Digestion* 63 (suppl 1):12 – 21.
- Nair, M.P.; Kandaswami, C.; Mahajan, S.; Chadha, K.C.; Chawda, R.; Nair, H.; Kumar, N.; Nair, R.E. and Schwartz, S. A. 2002:** The flavonoid, quercetin, differentially regulates Th-1 (IFN gamma) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. *Biochim Biophys Acta.* 2002 Dec 16; 1593(1): 29-36. doi: 10.1016/s0167-4889(02)00328-2.
- Nameghi, H.A.; Edalatian, O. and Bakhshalinejad, R. 2019:** Effects of a blend of thyme, peppermint and eucalyptus essential oils on growth performance, serum lipid and hepatic enzyme indices, immune response and ileal morphology and microflora in broilers. *J Anim Physiol Anim*

- Nutr* (Berl). 2019 Sep; 103(5):1388-1398. doi: 10.1111/jpn.13122.
- Nawab, A.; Ibtisham, F.; Li, G.; Kieser, B.; Wu, J.; Liu, W.; Zhao, Y.; Nawab, Y.; Li, K. and Xiao, M. 2018:** Heat stress in poultry production: Mitigation strategies to overcome the future challenges facing the global poultry industry. *J. Therm. Biol.* 78: 131 – 139.
- Nuamah, E.; Poaty Ditengou, J.I.C.; Hirwa, F.; Cheon, I.; Chae, B.; Choi, N.-J. 2024:** Dietary Supplementation of Tannins: Effect on Growth Performance, Serum Antioxidant Capacity, and Immunoglobins of Weaned Piglets—A Systematic Review with Meta-Analysis. *Antioxidants* 13: 236. <https://doi.org/10.3390/antiox13020236>.
- Ofongo, R.T.S. 2022:** Detection of metabolites present in methanol extract and essential oil of *Ocimum gratissimum* (lyn) using Gas Chromatography – Mass Spectroscopy (GC/MS) – unpublished data
- Pacheco-Ordaz, R.; Wall-Medrano, A.; Goñi, M.G.; Ramos-Clamont-Montfort, G.; Ayala-Zavala, J.F. and González-Aguilar, G. 2018:** Effect of phenolic compounds on the growth of selected probiotic and pathogenic bacteria. *Lett. Appl. Microbiol.* 66: 25 – 31.
- Pandey, A. K.; Singh, P., and Tripathi, N. N. 2014:** Chemistry and bioactivities of essential oils of some *Ocimum* species: an overview. *Asian Pac. J. Trop. Biomed.* 4: 682 – 694. doi: 10.12980/APJTB.4.2014C77.
- Parmar, A.; Patel, V.; Patel, J.; Usadadia, S.; Rathwa, S.; Prajapati D. and Rathva, A. 2019:** Quercetin, a health promising phyto-additive for poultry production: Trends and advances. *The Pharma Innovation Journal* 8(9): 68 - 74.
- Penissi, A.B.; Rudolph, M.I. and Piezzi, R.S. 2003:** Role of mast cells in gastrointestinal mucosal defense. *Biocell.* 27: 163 – 172.
- Perez-Roses, R., Risco, E., Vila, R., Penalver, P., and Canigueral, S. 2015:** Effect of some essential oils on phagocytosis and complement system activity. *Journal of Agricultural and Food Chemistry*, 63 (5): 1496 – 1504. <https://doi.org/10.1021/jf504761m>
- Pirgozliev, V.; Mansbridge, S.C.; Rose, S.P.; Lillehoj, H.S. and Bravo, D. 2019:** Immune modulation, growth performance, and nutrient retention in broiler chickens fed a blend of phytogetic feed additives. *Poultry Science.* 98: 3443 – 3449.
- Pitman, R.S.; Blumberg, R.S. 2000:** First line of defense: The role of the intestinal epithelium as an active component of the mucosal immune system. *J. Gastroenterol.* 35:805 – 814.
- Pizzi, A. 2019:** Tannins: Prospectives and Actual Industrial Applications. *Biomolecules* 9 (8): 344. <https://doi.org/10.3390/biom9080344>
- Podolsky, D.K. 2002:** Inflammatory Bowel Disease. *N. Engl. J. Med.* 347: 417 – 429.
- Quinteiro-Filho, W.; Ribeiro, A.; Ferraz-de-Paula, V.; Pinheiro, M.; Sakai, M.; Sá, L.; Ferreira, A. and Palermo-Neto, J. 2010:** Heat stress impairs performance parameters, induces intestinal injury, and decreases macrophage activity in broiler chickens. *Poult. Sci.* 89: 1905 – 1914.
- Ramnath, V. and Rekha, P. 2009:** *Brahma Rasayana* enhances in vivo antioxidant status in cold-stressed chickens (*Gallus gallus domesticus*). *Indian J. Pharmacol* 41(3): 115 - 9. doi: 10.4103/0253-7613.55209.
- Redondo, L. M.; Chacana, P. A.; Dominguez, J. E. and Fernandez Miyakawa M. E. 2014:** Perspectives in the use of tannins as alternative to antimicrobial growth promoter factors in poultry. *Front. Microbiol.* 5: article 118: 1 – 7.
- Rehman, Z.U.; Che, L. and Ren, S. 2018a:** Supplementation of vitamin E protects chickens from Newcastle disease virus mediated exacerbation of intestinal oxidative stress and tissue damage. *Cellular Physiology and Biochemistry.* 47(4): 1655 – 1666.
- Rehman, Z.U.; Meng, C.; Sun, Y.; Safdar, A.; Pasha, R.H.; Munir, M. and Ding, C. 2018b:** Oxidative Stress in Poultry: Lessons from the Viral Infections. *Hindawi Oxidative Medicine and Cellular Longevity.* Volume 2018, Article ID 5123147, 14 pages. doi: 10.1155/2018/5123147
- Ruansit, W. and Charerntantanakul, W. 2020:** Oral supplementation of quercetin in PRRSV-1 modified-live virus vaccinated

- pigs in response to HP-PRRSV-2 challenge. *Vaccine*, 38 (19): 3570 – 3581 <https://doi.org/10.1016/j.vaccine.2020.03.019>.
- Saeed, M.; Naveed, M.; Arain, M.; Arif, M.; Abd El-Hack, M.E.; Alagawany, M.; Siyal, F.A.; Soomro, R.N and Sun, C. 2017:** Quercetin: Nutritional and beneficial effects in poultry. *World's Poultry Science Journal*. 70: 23 – 28.
- Sahin, K.; Sahin, N. and Kucuk, O. 2003:** Effects of chromium, and ascorbic acid supplementation on growth, carcass traits, serum metabolites, and antioxidant status of broiler chickens reared at a high ambient temperature (32°). *Nutr. Res.* 23: 225 – 238.
- Salman, K.A.A. 2019:** Medicinal plants and its effect on some physiological traits in birds: A Review. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. RJPBCS 10 (1): 1194 – 1198.
- Shakeri, M.; Cottrell, J.J.; Wilkinson, S.; Le, H.H.; Suleria, H.A.; Warner, R.D. and Dunshea, F.R. 2019:** Growth performance and characterization of meat quality of broiler chickens supplemented with betaine and antioxidants under cyclic heat stress. *Antioxidants* 8 (9): 336.
- Shang, Y.; Kumar, S.; Oakley, B. and Kim, W.K. 2018:** Chicken gut microbiota: Importance and detection technology. *Front. Vet. Sci.* 5: 254. doi: 10.3389/fvets.2018.00254
- Smith, A.L.; Powers, C. and Beal, R.K. 2014:** The avian enteric immune system in health and disease. In *Avian Immunology*, 2nd ed.; Shat, K.A., Kaspers, B., Kaiser, P., Eds.; Academic Press: London, UK, 2014; pp. 227 – 250.
- Špoljaric´, D.; Marenc´ic´, D.; Benkovic´, M.; Špoljaric´, B.; Cvitanovic´, A.B.; Mršic´, G.; Vlahovic´, K.; Popovic´, M.; Srečec, S.; Stolic´, I.; et al. 2019:** Effect of Dietary Carob Whole meal on Blood Parameters in Weaned Pigs. *Vet. Arh.* 89: 351 – 366.
- Strober, W.; Fuss, I. J. and Blumberg, R. S. 2002:** The immunology of mucosal models of inflammation. *Ann. Rev. Immunol.* 20: 495 – 549.
- Surai, P.F. and Fisinin, V.I. 2016:** Vitagenes in poultry production: Part 3. Vitagene concept development. *World's Poultry Science Journal*. 72: 793 – 804.
- Taranu, I.; Marin, D. E.; Untea, A.; Janczyk, P.; Motiu, M.; Criste, R. D. and Souffrant, W.B. 2012:** Effect of dietary natural supplements on immune response and mineral bioavailability in piglets after weaning. *Czech. J. Anim. Sci.* 57 (7): 332 – 343. DOI: 10.17221/6008-CJAS
- Terruzzi, I.; Montesano, A.; Senesi, P.; Villa, I.; Ferraretto, A.; Bottani, M.; Vacante, F.; Spinello, A.; Bolamperti, S.; Luzi, L. and Rubinacci, A. 2019:** L-Carnitine reduces oxidative stress and promotes cells differentiation and bone matrix proteins expression in human osteoblast-like cells. *Biomed Res. Int.* Volume 2019, Article ID 5678548, 13 pages <https://doi.org/10.1155/2019/5678548>
- Teirlynck, E.; Bjerrum, L.; Eeckhaut, V.; Huygebaert, G.; Pasmans, F.; Haesebrouck, F.; Dewulf, J.; Ducatelle, R.; Van Immerseel, F. 2009.** The cereal type in feed influences gut wall morphology and intestinal immune cell infiltration in broiler chickens. *Br. J. Nutr.* 102, 1453 – 1461.
- Teirlynck, E.; Gussem, M.D.E.; Dewulf, J.; Haesebrouck, F.; Ducatelle, R.; Van Immerseel, F. 2011:** Morphometric evaluation of “dysbacteriosis” in broilers. *Avian Pathol.* 40, 139 – 144.
- Tonda, R. M.; Rubach, J. K.; Lumpkins, B. S.; Mathis, G. F. and Poss, M. J. 2018:** Effects of tannic acid extract on performance and intestinal health of broiler chickens following coccidiosis vaccination and/or a mixed-species *Eimeria* challenge. *Poultry Science* 97:3031 – 3042. <http://dx.doi.org/10.3382/ps/pey158>.
- Trevisi, P.; Merialdi, G.; Mazzoni, M.; Casini, L.; Tittarelli, C.; De Filippi, S.; Minieri, L.; Lalatta-Costerbosa, G. and Bosi, P. 2007:** Effect of dietary addition of thymol on growth, salivary and gastric function immune response, and excretion of *Salmonella enterica* serovar *Typhimurium*, in weaning pigs challenged with this microbe strain. *Ital. J. Anim. Sci.* 6 (sup 1): 374 – 376. doi: 10.4081/ijas.2007.1s.374.
- Viveros, A.; Chamorro, S.; Pizarro, M.; Arija, I.; Centeno, C. and Brenes, A. 2011:** Effects

- of dietary polyphenol-rich grape products on intestinal microflora and gut morphology in broiler chicks. *Poult. Sci.* 90: 566 – 578.
- Wang, L.; Hou, Y.; Yi, D.; Ding, B.; Zhao, D.; Wang, Z.; Zhu, H.; Liu, Y.; Gong, J.; Assaad, H. and Wu, G. 2015:** Beneficial roles of dietary oleum cinnamon in alleviating intestinal injury. *Front. Biosci.* 20: 814 – 828.
- Waters, W.R.; Sacco, R.E.; Dorn, A.D.; Hontecillas, R.; Zuckermann, F.A. and Wannemuehler, M.J. 1999:** Systemic and mucosal immune responses of pigs to parenteral immunization with a pepsin-digested *Serpulina hyodysenteriae* bacterin. *Vet. Immunol. Immunopathol.* 69:75 – 87.
- Wu, J. and Chen, Z.J. 2014:** Innate immune sensing and signaling of cytosolic nucleic acids. *Annu. Rev. Immunol.* 32: 461 – 488.
- Yang, C.; Kabir Chowdhury M. A.; Hou, Y. and Gong, J. 2015.** Phytogetic Compounds as Alternatives to In-Feed Antibiotics: Potentials and Challenges in Application. *Pathogens.* 4: 137 – 156. Doi: 10.3390/pathogens4010137.
- Yang, R.; Hui, Q.; Jiang, Q.; Liu, S.; Zhang, H.; Wu, J.; Lin, F. and Yang, C. 2019:** Effect of Manitoba-grown red-osier dogwood extracts on recovering Caco-2 cells from H<sub>2</sub>O<sub>2</sub>-induced oxidative damage. *Antioxidants* 8(8): 250; <https://doi.org/10.3390/antiox8080250>
- Young-Man, T.S.; Jarikre, T.A.; Ockiya, M. and Ofongo, R.T. S. 2021a:** Challenge of change - effect of *Vernonia amygdalina* as alternative to antibiotics on lymphoid cells in broiler chicken. British Society of Animal Science, virtual conference. April 12th – 15th 2021.
- Young-Man, T.S.; Jarikre, T.A.; and Ofongo, R.T.S. 2021b:** Comparative histopathology and immune cell Response of some lymphoid tissues in broilers administered *Vernonia amygdalina* and antibiotics. *J. Anim. Prod. Res.* 33 (1): 14 – 22.
- Yun, S.-H.; Moon, Y.-S.; Sohn, S.-H. and Jang, I.-S. 2012:** Effects of cyclic heat stress or vitamin C supplementation during cyclic heat stress on HSP70, inflammatory cytokines, and the antioxidant defense system in Sprague Dawley rats. *Exp. Anim.* 61: 543 – 553.
- Zou, Y.; Wei, H.K.; Xiang, Q.H.; Wang, J.; Zhou, Y.F. and Peng, J. 2016a:** Protective effect of quercetin on pig intestinal integrity after transport stress is associated with regulation oxidative status and inflammation. *Journal of Veterinary Medical Science.* 78 (9):1487 – 1494. doi: 10.1292/jvms.16-0090.
- Zou, Y.; Xiang, Q.; Wang, J.; Peng, J. and Wei, H. 2016b:** Oregano Essential Oil Improves Intestinal Morphology and Expression of Tight Junction Proteins Associated with Modulation of Selected Intestinal Bacteria and Immune Status in a Pig Model. *BioMed Research International* volume 2016 Article ID 5436738, 11 pages. <http://dx.doi.org/10.1155/2016/5436738>

**Date received: 26<sup>th</sup> March, 2025**

**Date accepted: 9<sup>th</sup> May, 2024**