19

Pathogenesis of Gizzard Erosion and Ulcerations and Comprehensive Control Strategy in Poultry

AUTHORS DETAIL

Md Atiqul Haque[1], Zonghui Zuo[2] and Cheng He[1]

[1]Key Lab of Animal Epidemiology and Zoonoses of Ministry of Agriculture and Rural Affairs, College of Veterinary Medicine, China Agricultural University, Beijing, 100193, China
[2]Tianjin Key Laboratory of Agricultural Animal Breeding and Healthy Husbandry, College of Animal Science and Veterinary Medicine, Tianjin Agricultural University, Tianjin 300384, China.
*Corresponding author: hecheng@cau.edu.cn

Received: Oct 05, 2022 Accepted: Dec 19, 2022

INTRODUCTION

Ulceration in stomach has constantly been reported in poultry and livestock. It usually causes persistent diarrhea and poor absorption in animals, which leads to economic loss (Li et al. 2020, Wang et al 2021). Gizzard erosion and ulceration syndrome (GEU) was firstly reported in chicken in 1930s. It was described and termed as 'ventriculitis', 'black vomit', 'vomito negro' and 'Muskelmagenerosionen' in different published articles. GEU is characterized by erosive lesions in the koilin layer of gizzard, and macroscopic defects in mucosa (Gjevre et al. 2013). *Bacillus* species, particularly *Bacillus cereus* (*B. cereus*) group, is being widely applied as probiotics in plant pesticides, animal feed or human food chains. However, some pathogenic *B. cereus* isolates have been recently proved to be responsible for GEU in birds and have potential hazards to cause vomiting, diarrhea or ulceration in birds, pigs and human as well (Li et al., 2020; Zuo et al. 2020, Haque et al 2021a). In another study, a pathogenic isolate of *B. cereus* was obtained from a diseased hen with hemorrhaged pneumonia and its feed. Subsequently, typical diarrhea and GEU were determined after post oral administrations in chickens. Moreover, its genome contained virulence genes which mediated intestinal cell death and host immune system dysfunction (Zhang et al., 2019). When *B. cereus* along with some other pathogens co-infected the chicken and ducks, it caused GEU, and sometimes lead to respiratory infection with immunosuppression, promoted severe diarrhea and malnutrition (Zuo et al 2020, Haque et al 2021b, Haque et al 2022).

Epidemiology of GEU in Poultry Worldwide

GEU has been reported in many countries across the world. It affects various domestic birds with a prevalence of 1-50 % depending on species, region and etiological factors. The distribution of GEU is well summarized in Table 1. It is worth noting that in American and Asian countries, 20-30% commercial broilers have been identified to develop mild to moderate gizzard erosions (GE) (Contreras 2016). In China, GE is commonly found in fast growing broilers, yellow-feather broilers, and ducklings. It resulted in acute diarrhea and malabsorption within the first with an average 15% mortality (Wang et al. 2021). In Bangladesh, the prevalence of GE in broilers has reached 70.6-87.2% (Moula et al. 2020). In regions of Southeast Asia and South America, gizzard ulceration (GU) is emerging in the field again, which highlights the global threat to poultry industry (Kichou et al. 2020).

Etiology of GEU in Poultry

There are multiple factors playing a role in the development of GEU, including congenital factors, starvation, malnutrition, feed material, toxicants (copper sulphate, biogenic amines, gizzerosine and mycotoxin, such as T-2 toxin, MAS, DAS, DON) and viral/bacterial infection (Fig. 1). Microbial invasion accounts for a large proportion of GEU epidemics. In previous studies, fowl adenovirus (FAdV-1, FAdV-4, FAdV-A) has been linked to GEU in broilers and layers in Japan, South Korea, Germany, Poland, Italy, Sweden and China (Ono et al. 2001; Lim et al. 2012; Schade et al. 2013; Zhang et al. 2017; Domanska-Blicharz and Bartczak 2019; Wang et al. 2021; Lindgren et al. 2022). The opportunistic bacteria *Clostridium perfringens* was also identified in commercial hens with gizzard ulcerations (Wang et al. 2021). In another study, *B. cereus*, co-infection with avian influenza virus H9N2 or *Chlamydia psittaci* induced GEU, respiratory distress and pneumonia in SPF chickens (Zhang et al. 2019; Zuo et al. 2020). Gastric ulcers are initiated and exacerbated by increased acid secretion and a weakened mucosal barrier (Al-garni et al. 2021). Feed microbial contamination will generate the majority of biogenic amines (histamine) which catalyzes the secretion of gastric acid. Histamine is also a potential toxic chemical to livestock and poultry as well. Besides this, gizzerosine produced in poor grade fish meal is even a more effective stimulator of gastric acid secretion in poultry (Smith et al. 2000). Malnutrition status like deficiency of vitamin B6, vitamin E and decreased sulphur-containing amino acids are

Citation: Haque MA, Zuo Z and He C, 2023. Pathogenesis of Gizzard Erosion and Ulcerations and Comprehensive Control Strategy in Poultry. In: Abbas RZ, Saeed NM, Younus M, Aguilar-Marcelino L and Khan A (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 2, pp: 129-137. https://doi.org/10.47278/book.oht/2023.52

Table 1: Prevalence of GEU in different countries during last two decades

Year	Country /region	Affected animal type	Age of bird	Prevalence	Mortality	Clinical signs (CS)	Postmortem lesions	Causal agent	Reference
1998	Japan	Broiler	51 days	9-11%	2%	No apparent CS	Ulcerated gizzard	FAdV-1	Ono et al. 2001
1999	Japan	Broiler	55 days	4-50%	3%	No apparent CS	GE	FAdV-1	Ono et al. 2001
1995-2006	Italy	Broiler	42-63 days	n.a.	n.a.	No apparent CS	Variable size of GE with brown or black discoloration	FAdV-1	Manarolla et al. 2009
2007-2008	Nepal	Pullets and broiler	2-10 weeks	n.a.	1-10%	n.a.	Hemorrhagic proliferative proventriculitis and GE	*Penicillium* spp. *Candida* spp. *Salmonella* spp. *E. coli* and *Staphylococcus* spp.	Karki et al 2009
2010	Bulgaria	Broiler	38 days	n.a.	7%	n.a.	Typical necrotic pseudomembranous inflammation of the gizzard mucosa	*Clostridium perfringens*	Dinev 2010
2010	Korea	Layer	150 days	1-2%	0.2%	Dullness, anorexia and emaciation	Dilated proventriculus and gizzard with bloody fluids, GEU	FAdV-1, K181 strain	Lim et al. 2012
2011	Germany	Broiler	27-32 weeks	5-10%	2.2-9%	n.a.	Variable areas of GEU with brown or black discoloration in the koilin layer	FAdV-1	Grafl et al. 2012
2011	Germany	Broiler	15-36 days	n.a.	3.6-8%	A reduced daily growth	Detached koilin layer with multifocal ulcerations and bloody exudates	FAdV-1	Schade et al. 2013
2013	USA	Broiler	3-6 days	n.a.	20-24%	Lethargic, moribund, lying down, with greenish loose droppings	Multifocal erosions in the koilin and proventricular-ventricular junction	Tribasic Copper Chloride	Malinak et al. 2014
2013-2014	India	Layer	12 weeks	n.a.	10-30%	Dullness, uneven growth, decreased appetite	Detach koilin layer and blackish discoloration of gizzard contents, GE	FAdV-1	Bulbule et al. 2016
2012-2015	Poland	Layer	19-73 weeks	n.a.	0.05-0.4%	n.a.	Haemorrhagic changes in provetriculus and destruction of the koilin layer	FAdV-A	Domanska-Blicharz and Bartczak 2019
2015	USA	Quail	2-3 weeks	n.a.	n.a.	Loose droppings, depression	Irregular dark brown fissures within the koilin layer	FAdV-1	Kumar et al. 2021
2009-2016	Great Britain	Pullets and layer	6 weeks, 21-23 weeks	n.a.	0.12–0.3%	No apparent CS	Different of GEU with discoloration of the koilin layer	FAdV-1	Grafl et al. 2018
2016	Poland	Turkey	2 days	n.a.	7.3%	n.a.	GEU with dark green color of the koilin lining and congestion of the gizzard	Copper sulphate	Giergiel et al. 2019
2016	Sweden	Broiler	9-10 days	n.a.	n.a.	Decreased growth and uneven growth	Detached koilin layers, discoloration, bleeding, GE	FAdV-1	Lindgren et al. 2022
2016-2018	India	Layer	9-13 weeks	n.a.	0.3-7.7%	Dullness, reduced appetite and growth	Mild to severe GE with blackish discoloration of gizzard contents	FAdV-2 and 3	Chitradevi et al. 2020
2008-2019	Diverse region	Broiler and layer	23-189 days	11%	n.a	n.a	Characteristic GEU	FAdV-A	Kiss et al. 2021
2019	Iran	Broiler	16 days	5–10%	6%	Decreased growth	Severe GE with multiple black-brown areas of variable size in the koilin layer and mucosal inflammation	FAdV-1	Mirzazadeh et al. 2021

GE=Gizzard erosions, GEU=Gizzard erosions and ulcerations, n.a.=Not available

associated with gizzard ulceration as well (Dinev 2010). Furthermore, mycotoxins will exacerbate hatching chickens and survival of offspring. In recent report, FB1 or FB1+DON induced poor hatchability, an increasing mortality of chicks, GEU and hemorrhagic pneumonia (Wang et al. 2021). Nevertheless, the etiology of GEU is still not well-known, various studies of GEU are summarized in Table 2.

Pathogenesis of GEU in Poultry

Due to the complexity of GEU etiology, its pathogenesis varies from case to case. Digestive disorders in poultry mostly involve the changes of gastric secretions, either hyper- or hypo-secretion affects the internal milieu of gastrointestinal tract (Hoerr 1998). A hypothetical mechanism of GEU caused by *B. cereus* in poultry is illustrated in Fig. 2.

Table 2: Studies in the research of GEU etiology

Year	Animal model	Age of bird	Exposure period	TCID50 or CFU/ml or mg/kg or diet and route	Main findings	Pathogen/ Causal agent	Reference
2002	Broiler chicken	7 days	5 days	0.65-1.15 ppm, orally	Pervasive alterations in the gizzard and proventiculus with acute cuticle erosions and lamina propria swelling	Gizzerosine	Tisljar et al. 2002
2005	Layer chicken	28 weeks	3 weeks	2.5-10 mg/kg b.w. daily, orally	Discolorations and GEU of gizzerosine-treated bird compared to control group	Gizzerosine	Artuković et al. 2005
2006	Broiler chicken	day 1	35 days	n.a.	Bacterial number rose considerably with the severity of mucosal gizzard injuries	*Clostridium perfringens*	Novoa-Garrido et al. 2006
2010	SPF chicken	7 days	21 days	106, orally	Chicks had focal gizzard ulcers including a course or hazy koilin layer	FAdV-1	Lim et al. 2012
2013	Broiler chicken	day 1	17 days	107.8, Orally	Gross and histopathological alterations may be associated with an increased viral load in gizzards	FAdV-1	Grafl et al. 2013
2014	Layer chicken	4 weeks	21 days	107.2, IP	GEs are linked with adenovirus in commercial layer chickens	FAdV-C, D and E	Bulbule et al. 2016
2016	Pullets	21 days	14 days	107, Orally	FAdV-1 infected birds exhibited distinctive pathomorphological alterations in gizzard	FAdV-1	Grafl et al. 2018
2017	Chicken embryo	11 days	20 days	FB1=6-24 µg/egg FB1+DON=0.1+(3-12) µg/egg	FB1 and FB1+ DON contamination are linked to reduced hatchability and GUs in chicks	Mycotoxin FB1 and DON	Wang et al. 2021
2019	SPF chicken	Day old	21 days	1x108, IG	Feed-borne *B. cereus* exposure could worsen GU and promote H9N2-induced pneumonia	*Bacillus cereus*	Zhang et al. 2019
2019	Layer chicken	20 weeks	14 days	108, Orally	The major pathogens and the cause of AGE in layers are FAdV-1 strains	FAdV-1	Grafl et al. 2020
2019	Pullets	Day old	14 days	107, Orally	Infected birds Characteristic lesions and histopathological changes of AGE, as well as reduced growth	FAdV-1	Mirzazadeh et al. 2021
2020	SPF chicken	1 week	42 days	1x108, orally	*B. cereus* produced a significant GEU as well as promotes prolonged chlamydial infection and aggravates immunological reactions	*Bacillus cereus*	Zuo et al. 2020

TCID50=Tissue culture infective dose, IP= Intraperitoneal, IG=Intragastrically, n.a.=Not available, GE=Gizzard erosion, GU=Gizzard ulcer, GEU=Gizzard erosion and ulceration, AGE=Adenoviral gizzard erosion.

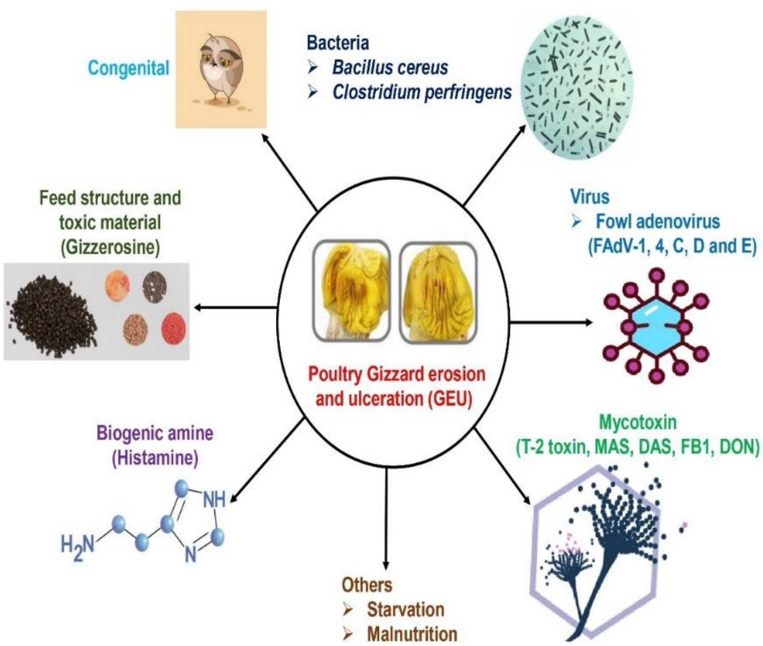

Fig. 1: Etiology and predisposing factors of GEU in poultry (Smith et al. 2000; Tisljar et al. 2002; Ono et al. 2003; Dinev 2010; Gjevre et al. 2013; Schade et al. 2013; Contreras 2016; Zhang et al. 2019; Li et al. 2020; Zuo et al. 2020; Haque et al. 2022)

Pathogenic *B. cereus* isolates harbor a set of virulence factors, including emetic/diarrheal toxins (Table 3) and tissue-destructive enzymes (PI-PLC, PC-PLC, SMase, β-lactamase, InhA1, NprA). However, the specific molecular mechanisms of most toxins remain unclear (Haque et al 2021a). *In vivo* data demonstrated that the emetic toxin, cereulide, interacted with serotonin 5-HT3 receptor to facilitate proapoptotic or necrotic factors, thereby inhibiting ATP formation,

Table 3: Toxins of *B. cereus* (Ehling-Schulz et al. 2006; Fagerlund et al. 2010; Haque et al. 2021a; Haque et al. 2021b)

Toxins		Properties	Toxicity	Encoded genes	Prevalence (%)
Emetic toxin	Ces	K+ ionophore, heat-stable, highly lipophilic cyclopeptide (1.2 kDa)	Hepatic and immune dysfuntion, cerebral effects, respiratory distress, bioaccumulation in vital organs and tissues, cytotoxic and mitochondriotoxic to various mammalian primary cells and cell lines, and necrotic cell death	*cesA, cesB*	1.5-32.8
Enterotoxin	HBL	Heat-labile, three component proteins, B (35 kDa), L1 (36 kDa) and L2 (45 kDa)	Intestinal fluid secretion, disrupting osmotic equilibrium, pore formation, hemolysis, cytotoxicity, dermonecrotic and vascular permeability activities	*hblA, hblB, hblC, hblD*	29–92
	NHE	Heat-labile, three component proteins NheA (39 kDa), NheB (45 kDa) and NheC (105 kDa)	Intestinal fluid secretion, transmembrane pore formation, osmotic and Vero cell lysis and cell death	*nheA, nheB, nheC*	84− 100
	CytK	Heat-labile, single-cell protein (34 kDa)	Pore formation, hemolysis, cytotoxicity (Caco 2 and Vero cells) and necrosis	*cytK1, cytk2*	37–89
	Ent-FM/ CwpFM	Single-cell protein (45 kDa)	Hemolysis, capillary permeability and cytotoxicity (Vero cells)	*entFM*	84− 100
	ENT	Single- cell protein (40/41 kDa)	Cytotoxicity, capillary permeability and diarrheal toxigenicity	*bceT*	12–75
Hemolysins	HlyI/ CLO	Heat-labile, cholesterol-binding hemolysin (52 kDa)	Pore formation, cell lysis and necrosis	*clo*	-
	HlyII	Heat-labile, β-barrel channel-forming toxin	Pore formation, cytotoxicity and apoptosis in macrophages (pathways)	*hlyII*	19–56
	HlyIII	Oligomeric pore-forming hemolysin (24 kDa)	Hemolysis and pore formation	*hly-III*	-

Ces = Cereulide; HBL = Hemolysin BL; NHE = Nonhemolytic enterotoxin; CytK = Cytotoxin K; Ent-FM = Enterotoxin FM; CwpFM = cell wall peptidases FM; ENT = Enterotoxin T; HlyI = Hemolysin I; CLO = Cereolysin O; HlyII = Hemolysin II; HlyIII = Hemolysin III.

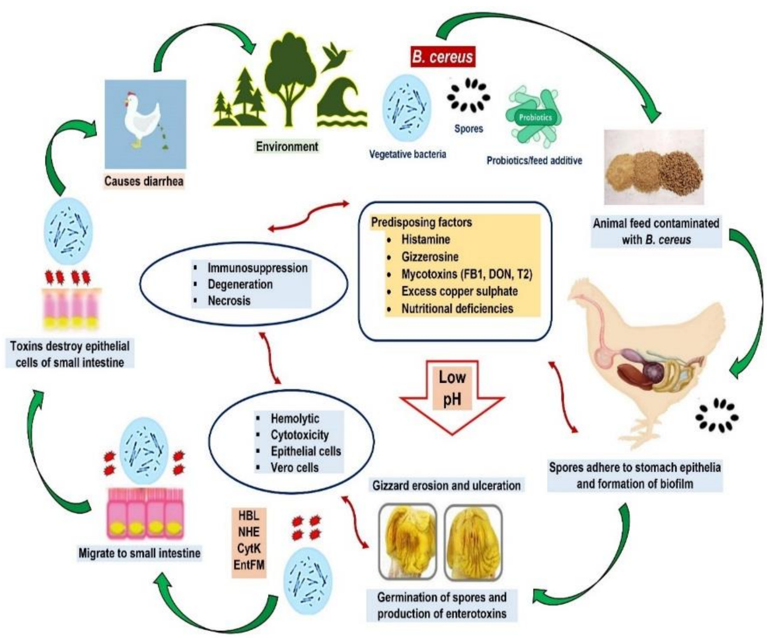

Fig. 2: Possible pathogenesis of GEU and diarrhea in poultry due to *B. cereus* infection (Zhang et al. 2019; Zuo et al. 2020; Haque et al. 2021a; Haque et al. 2021b; Haque et al. 2022)

downregulating mitochondrial function and interfering respiratory activity and lipid oxidation, leading to liver failure during its from the stomach to small intestine (Haque et al 2021a; Haque et al 2021b). *B. cereus* can tolerate a very low pH by forming spores which attach to the hydrophobic layer of gastric epithelium (Tsilia et al. 2016). The koilin layer of gizzard contains high quantities of leucine proteins and arginine which accounts for about 80% of it and may assist *B. cereus* to form biofilms, leading to stomach acid tolerance and metabolism (Majed et al. 2016; Zuo et al 2020; Haque et al 2021a). Notably, *Hbl* and *Cytk* genes are enterotoxins produced by *B. cereus* which belongs to the group of β-barrel pore-forming toxin family. These can cause dermonecrotic, cytotoxic and hemolytic effects (Ehling-Schulz et al. 2006). *B. cereus* toxins reach to the highest level during the late phase of growth and have the potential to directly destruct

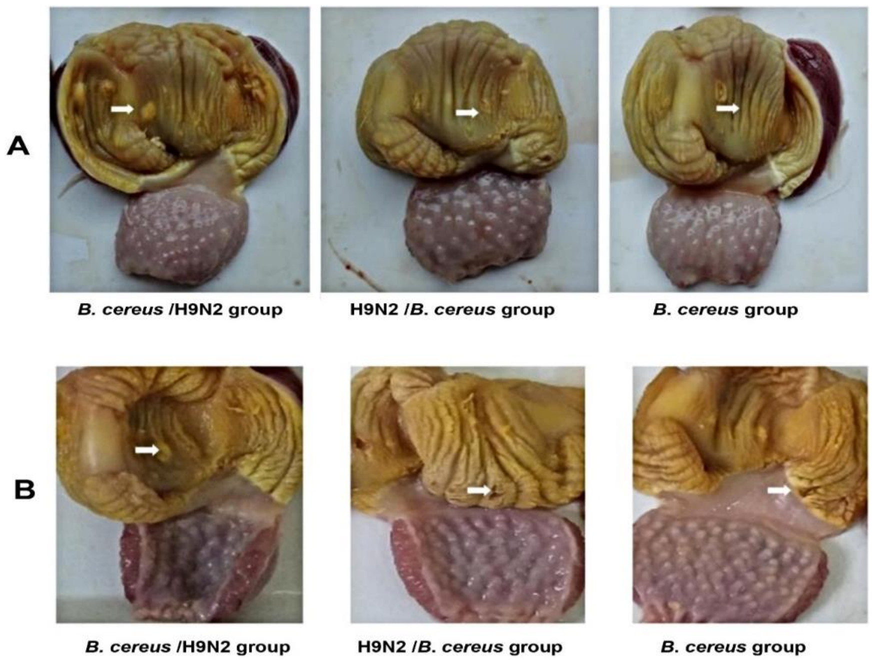

Fig. 3: The effect of *B. cereus*/H9N2 co-infection on GE by day 7 post infection. *B. cereus* or *B. cereus*/H9N2 displayed severe GEU syndrome while medium GEU was observed in the H9N2/*B. cereus* group (white arrows). B) The effect of *B. cereus*/H9N2 co-infection on GE by day 14 PI. *B. cereus*/H9N2 or H9N2/*B. cereus* displayed typical GEU and GEU recovery was observed in the *B. cereus* group (white arrows) (Zhang et al., 2019).

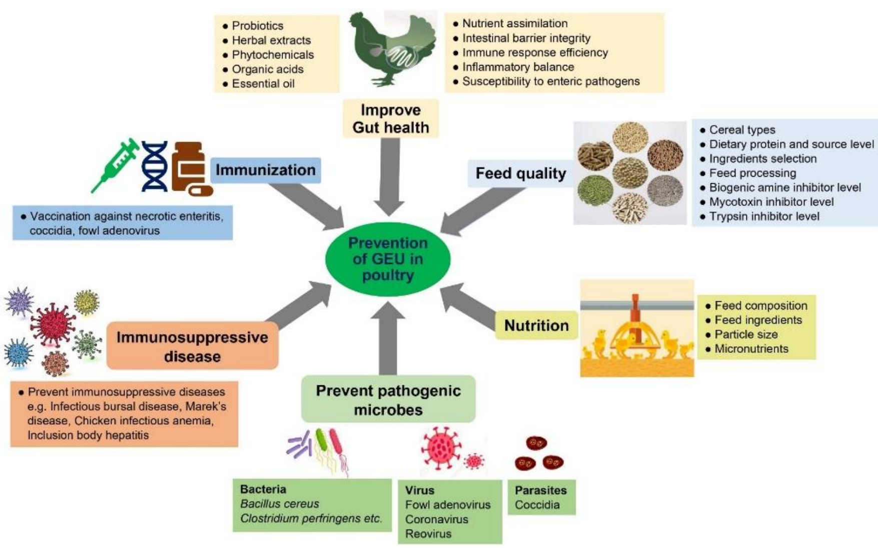

Fig. 4: Comprehensive strategies against poultry gastric erosions and ulcerations (GEU)

the koilin layer and mucosa of gizzard which alter the permeability of blood vessels and therefore resulted in gastric internal tract damage, long-term ulceration and diarrhea (Fagerlund et al. 2010; Zuo et al 2020; Haque et al 2021a). A study reported that feed-borne *B.* cereus co-infected with avian influenza virus (H9N2) or *Chlamydia psittaci* lead to serious GEU in all tested chickens (Fig. 3 A-B), which implies that the damage of the integrity of gizzard surface allows susceptible pathogens to thrive (Zhang et al. 2019; Zuo et al 2020).

Prevention and Control Strategies against GEU

Comprehensive measures are urgently needed against GEU and a series of measures are highlighted in Fig. 4. To ensure the sustaining poultry industry and food safety, microbial control is critical to GEU prevalence. Thus, antibiotic-free, alternative approaches are on highly demand for poultry industry. Probiotics, herbal medicine, plant extract and phytochemicals are documented to show some promising effects in multiple studies (Table 4).

Healthy birds with a good capability of digestion, absorption and immunity are the cornerstone to combat GEU. Therefore, good environment and proper managements are essential for GEU control. Feed industry should process animal feed in an economical and quality control ways (Smith et al. 2000). The material and size of feed needs to be carefully adjusted. Highly oat hulls in daily diet alleviates GEU effectively in broilers (Kaldhusdal et al. 2012; Moula et al. 2020), because of coarse-grained material containing non - soluble fibers,

Table 4: Probiotics/phytochemicals/herbal extract used to control gastric ulcerations

Herbal extract / probiotics / phytochemicals	Concentration in diet/Doses	Model	Group/ active ingredients	Mechanism of Gastroprotection	Percentage of GU inhibition	Reference
Stevia rebaudiana extract	Diet containing 0.2% Stevia extract (on dry matter basis)	Histamine induced GEU in broiler	Glycosides	Antioxidant activity, blocking of H2-histamine receptor, inhibition of H^+/K^+ -ATPase	-	Takahashi et al. 2001
Lactobacillus rhamnosus	10^8- 10^9 CFU /day	Acetic acid induced gastric ulcer in rats	-	Cell apoptosis to cell proliferation ratio ↓, angiogenesis ↑, ODC ↑, Bcl-2 ↑, VEGF ↑, EGF ↑	-	Lam et al. 2007
Epicatechin	25, 50 and 75 mg/kg	Ethanol/indomethacin induced GU in rats	Flavonoids	GMS ↑, H^+ secretion ↓, HSP-70 ↑, SOD ↑, NO ↑	67.8%, 57.9%, 43.8%	Rozza et al. 2012
Bifidobacterium bifidum	7.5 × 10^{10} CFU /mL	HCL/Ethanol induced GU in rats	-	Mucin production ↑, mucin 5ac gene expression ↑	51.1%	Gomi et al. 2013
Moringa oleifera leaf meal	Dietary inclusion of *M. oleifera* leaf meal @ 1- 25 g per kg of feed	Broiler	Polyphenols, lipids, amino acids	Antimicrobial and antioxidant activity, FCR ↑	-	Nkukwana et al. 2014
Astaxanthin (ASX)	Basal diet containing 100 ppm ASX	Histamine induced GEU in broiler	Carotenoid	Antioxidant activity, SOD ↑, MDA ↓	-	Ohh et al. 2016
Rhus tripartita stem (RSE)	200, 400 and 800 mg/kg	Ethanol induced GU in rats	Gallic acid, catechin, proanthocyanidin	pH ↑, GJV ↓, GMS ↑, MDA ↓, CAT ↑, SOD ↑, GSH ↑	82.4%, 87.5%, 95.11%	Barka et al. 2017
Lactobacillus reuteri	1 × 10^{10} CFU/ml	Ethanol induced GU in rats	-	GMS ↑, MPO ↓, MDA ↓, GSH ↑, NO ↑, NF-κB ↓, TNF-α ↓, IL-1β ↓, COX-2 ↓	90%	Sun et al. 2018
Pulicaria undulata subsp. *undulata* plant extract	500 mg/kg	Ethanol induced GU in rats	Polyunsaturated fatty acids, sterols, minerals, polysaccharides, terpenoids, proteins, and halogenated compounds	GJV↓, SOD ↑, GSH ↑, MDA ↓, LDH ↓, SDH ↓, AP ↓, G-6-Pase ↓, 5´NT ↓, ICAM-1 ↓, TNF-α ↓, IL-10 ↑, Protein content ↑	71.42%	Fahmi et al. 2019
Myristica fragrans seeds	200mg/kg	Ethanol induced GU in rats	Flavonoids, tannins, terpenoids, alkaloids, saponins, steroids, glycosides, diterpenes and phenols	pH ↑, GJV ↓	60.41%	Sattar et al. 2019
Juglans regia L. (Walnut)	220, 440, and 880 mg/kg	Ethanol induced GU in rats	Oligopeptides	pH ↑, GJV ↑, IL-1β ↓, IL-6 ↓, IL-10 ↑, TNF-α ↓, PGE2 ↑, NO ↑, Bcl-2 ↑, IκBα ↑, Bax ↓, Caspase-3 ↓, NF-κB p65 ↓, AST ↓, ALT ↓, MDA ↓, CAT ↑, SOD ↑, GSH ↑	-	Liu et al. 2020
Ficus thonningii aqueous extract (Fruits)	125, 250 and 500 mg/kg	HCL/Ethanol induced GU in rats	Flavonoids, tannins, gallic acids, saponins, mucilage, betacyanins	Antioxidant activity, Anti-inflammatory activity, GJV ↓, GMS ↑	70.7%, 71.8%, 95.9%	Uku et al. 2020
Euphorbia hirta crude extract + Honey	*E. hitra* @ 200, 400, and 800 mg/kg bodyweight + Honey @ 1 ml	HCL induced GU in rats	Alkaloids, triterpenoids, phytosterols, tannins, polyphenols, and flavonoids	GMS ↑, GJV ↓	94.7%, 87.9%, 87.97%	Onyeka et al. 2020
Gallic acid	10, 30 and 50 mg/kg	Ethanol induced GU in rats	Phenolic compound	pH ↑, GMS ↑, IL-1β ↓, IL-6 ↓, TNF-α ↓, PGE2 ↑, NO ↑, Bcl-2 ↑, Nrf2 ↑, HO-1 ↑, Bax ↓, Caspase-3 ↓, TBARS ↓, CAT ↑, SOD ↑, GSH ↑	17.5%, 50.2%, 57.5%	Zhou et al. 2020
Polygonum cuspidatum Root	100 and 300 mg/kg	HCL/Ethanol induced GU in rats	Anthraquinones and stilbenes	SOD ↑, GSH ↑, PGE2 ↑	82.8%, 97.9%	Kim et al. 2020a
Inula britannica L. flower	100 and 300 mg/kg	HCL/Ethanol induced GU in rats	Flavonoids and sesquiterpene lactones	GMS ↑, SOD ↑, CAT ↑, GSH ↑, MDA ↓, PGE2 ↑	94.5%, 98.7%	Kim et al. 2020b
Lactobacillus acidophilus	0.5 mg/ml (100 million CFU /ml)	Aspirin induced GU in rats	-	IL-6 ↑, IL-10 ↑, TNF-α ↓, PGE2 ↑, GSH ↑, MDA ↓, CAT ↑, SOD ↑	-	Al-garni et al. 2021
Pachira glabra L. extract	100, 1000, and 400 mg/kg	Ethanol induced GU in rats	Ferulic acid, coumaric acid, gallic acid, quercetin glycosides, maltol, methyl coumarate	NF-κB p65 ↓, COX-2 ↓, Bcl-2 ↑, Bax ↓, Caspase-3 ↓	-	El-Din et al. 2021

Brassica oleracea var. *capitata* L. extract (Cabbage)	25, 50 and 100 mg/kg	HCL/Ethanol induced GU in rats	Polyphenols, glucosinolates, vitamins and minerals	Inhibition of H^+/K^+ -ATPase, Histamine ↓, mRNA expression ↓, MDA ↓, CAT ↑, SOD ↑, NF-κB ↓, IL-1β ↓, IL-6 ↓, IL-18 ↓, TNF-α ↓, COX-2 ↓, iNOS ↓	-	Kim et al. 2021
Lactobacillus plantarum	1.0×10^9 CFU/kg	Alcohol induced GU in rats	-	SOD ↑, GSH ↑, MDA ↓, PGE2 ↑, SS ↑, GSH-Px ↑, TNF-α ↓, IL-1β ↓, IL-6 ↓, IL-10 ↑, Nrf2 ↑, SOD ↑, CAT ↑, GSH1 ↑	83.61%	Wu et al. 2021
Alcea kurdica extract	100mg/L	Quails	Gallic acid, quercetin, mucilage, vitamin C	HDL ↑, LDL ↓, VLDL ↓, TCHO↓	-	Jabbar 2022

ALT=Alanine aminotransferase; AP=Acid phosphatase; AST=Aspartate aminotransferase; Bcl-2=B-cell lymphoma 2; CAT=Catalase; COX-2=Cyclooxygenase-2; EGF=Epidermal growth factor; FCR=Feed conversion ratio; GEU=Gastric erosion and ulceration; GJV=Gastric juice volume; GMS=Gastric mucus secretion; GSH=Glutathione; GSH-Px=Glutathione peroxidase; GSH1= Gamma-glutamylcysteine synthetase; G-6-Pase=Gluose-6-phosphatase; GU=Gastic ulcer; HDL=High density lipoprotein, HO-1=Heme oxygenase-1; HSP-70=Heat-shock protein 70; ICAM-1=Intracellular adhesion molecule-1; IκBα=Inhibitor kappa Bα; IL-1/6/18=Interleukin-1/6/18; iNOS=Inducible nitric oxide synthase; LDH=Lactate dehydrogenase; LDL=Low density lipoprotein, MDA=Malondialdehyde; MPO=Myeloperoxidase; NF-κB p65 =Nuclear factor kappa B p65; NO=Nitric oxide; Nrf2=Nuclear factor erythroid 2–related factor 2; 5´NT=5´-Nucleotidase; ODC=Ornithine decarboxylase; PGE2=Prostaglandin E2; SDH=Succinate dehydrogenase; SOD=Superoxide dismutase; SS=Somatostatin; TBARS=Thiobarbituric acid reactive substances; TCHO=Total cholesterol; TNF-α=tumor necrosis factor alpha; VLDL=Very low density lipoprotein, VEGF=Vascular endothelial growth factor

which helps the digestion of gizzard. Moreover, hygiene surveillance should be included to check microbial contaminations in feed and raw stuff and human food chains transmitted from animal feed. Once toxic biogenic amines (histamine, gizzerosine) residual in the feed, these are unable to remove by heating approaches. Although astaxanthin, a natural antioxidant, has potential to improve gastric-intestinal tract during GEU and stress (Ohh et al. 2016), it also keeps feed and raw material in hygienic condition during the period of processing or storage (Feddern et al. 2019).

Probiotics compete with pathogens for niches in gastric internal tracts, thus these are able to interfere infections and alter host's metabolism. *B. cereus* has widely contaminated in animal diets, however, the limited knowledge and improper isolation and identification of different strains, may let virulent toxins be overlooked and promote the potential transfer of antibiotic resistant genes among microbes. Therefore, virulence analysis on gene level and generally recorded as safe (GRAS) regulation should be combined together to decide whether *B. cereus* probiotic can be used as feed additive or being eliminated from animal diets (Haque et al 2021b). Moreover, feed fermentations are abused for growth promotion using too many probiotics. The process without inspection and supervision may facilitate *B. cereus* to synthesize toxins. For this reason, protocols for processing and fermentation of raw material need to be standardized and assessed by animal nutritionists and veterinary experts. Moreover, some material with antimicrobial activities such as asteraceae, roselle, rosemary, clove and thyme can be used to control pathogenic *B. cereus* in poultry (Haque et al. 2021a). Acidifiers (organic acids and their derivate) have been utilized to regulate gut microflora, enhance immunity, improve feed conversion ratio (FCR) and body weight. Synergistic organic acid and compounds like phytochemicals or permeabilizers are regarded as the novel measures to control infections (Pearlin et al. 2020; Haque et al. 2021b).

Herbal medicines are regarded as for GEU and resources of new drugs against digestive disorders. Herbal medicines are widely practiced, accessible, effective and safe in routine administration (Onyeka et al. 2020). Many studies have demonstrated that herbal plants, such as *Carica papaya*, *Zingiber officinale* Roscoe, *Musa paradisiaca*, *Allium sativum*, *Moringa oleifera*, *Rhus tripartita* *Pulicaria undulata* subsp. *undulata*, *Myristica fragrans*, *Brassica oleracea* var. *capitata*, *Pachira glabra*, *Polygonum cuspidatum*, *Inula britannica*, *Juglans regia*, *Stevia rebaudiana* and *Alcea kurdica* are capable of reducing ulcerations and gastric syndrome (Takahashi et al. 2001; Nkukwana et al. 2014; Barka et al. 2017; Fahmi et al. 2019; Kayode et al. 2019; Sattar et al. 2019; Liu et al. 2020; Kim et al. 2020a; Kim et al. 2020b; El-Din et al. 2021; Kim et al. 2021; Jabbar 2022). Feed-borne mycotoxins (FB1, DON, AFB1, OTA) negatively impact on the integrity of intestinal epithelium and cause necrotic enteritis as well as GEU in broiler chicks. A study reported severely impaired feed intake and growth of chickens and decrease in feed consumption and average body weight gain up to 12% and 14%, respectively during GEU development (Wang et al 2021). In a recent report, protocatechuic acid (PCA), a naturally occurring phenolic compound, increased the hatchability and decreased GEU of chicks caused by FB1-contaminated corn and feed (Wang et al. 2022). Furthermore, PCA exhibited significant antimicrobials against gram-positive and gram-negative bacteria, and fungi. It also improves humoral and cellular immune responses, suggesting a prospective usage in poultry industry (Guo et al 2018; Wang et al 2022).

Conclusion

The epidemic GEU in poultry across the world indicates the transmissible factors playing a key role in feed or food chain.

Considering the immense threat posed by GEU, the overwhelming majority of contaminations are microbial and toxin contaminations in animal feed. GEU impairs the digestion and immune responses in animal industry, and also exacerbates secondary infections and poisonings, which endangers food safety and public health. In order to prevent and control GEU in poultry, long-term monitoring and surveillance are necessary along with adopting a set of measures.

REFERENCES

Al-garni AA et al., 2021. Comparative study of the efficacy of prebiotics and probiotics as dietary supplements in rats with gastric ulcer. Journal of Pharmaceutical Research International 33: 137–145.

Artuković B et al., 2005. Gizzerosine induced histopathological changes in laying hens. Veterinarski Arhiv 75: 1-13.

Barka ZB et al., 2017. Protective effects of edible *Rhus tripartita* (Ucria) stem extract against ethanol-induced gastric ulcer in rats. Journal of Functional Foods 30: 260–269.

Bulbule NR et al., 2016. Pathogenicity and genotyping of fowl adenoviruses with gizzard erosion in commercial layer grower chicken in India. Indian Journal of Comparative Microbiology, Immunology and Infectious Diseases 37: 84-91.

Chitradevi S et al., 2020. Molecular typing of fowl adenovirus associated with gizzard erosion in commercial layer grower chicken in Tamil Nadu. Indian Journal of Animal Sciences 90: 977–981.

Contreras M, 2016. Gizzard erosion in broilers and the impact of avian adenoviruses. International Meat Topics 7: 27-28.

Dinev I, 2010. Enzootic outbreak of necrotic gastritis associated with *Clostridium perfringens* in broiler chickens. Avian Pathology 39: 7-10.

Domanska-Blicharz K and Bartczak R, 2019. Adenoviral gizzard erosions in commercial layer chickens. Pakistan Veterinary Journal 39: 138-141.

Ehling-Schulz M et al., 2006. Toxin gene profiling of enterotoxic and emetic *Bacillus cereus*. FEMS Microbiology Letters 260: 232–240.

El‐Din MIG et al., 2021. Chemical constituents and gastro‐protective potential of *Pachira glabra* leaves against ethanol‐induced gastric ulcer in experimental rat model. Infammopharmacology 29: 317-332.

Fahmi AA et al., 2019. Chemical composition and protective role of *Pulicaria undulata* (L.) C.A. Mey. subsp. *undulata* against gastric ulcer induced by ethanol in rats. Heliyon 5: e01359.

Fagerlund A et al., 2010. *Bacillus cereus* cytotoxins Hbl, Nhe and CytK are secreted via the Sec translocation pathway. BMC Microbiology 10: 304.

Feddern et al., 2019. A review on biogenic amines in food and feed: toxicological aspects, impact on health and control measure. Animal Production Science 59: 608–618.

Giergiel M et al., 2019. Ingestion of bedding material as a cause of acute copper sulfate poisoning in turkey poults. Poultry Science 98: 707–711.

Gjevre AG et al., 2013. Gizzard erosion and ulceration syndrome in chickens and turkeys: a review of causal or predisposing factors. Avian Pathology 42: 297-303.

Gomi A et al., 2013. Effect of Bifidobacterium bifidum BF-1 on gastric protection and mucin production in an acute gastric injury rat model. Journal of Dairy Science 96: 832–837.

Grafl B et al., 2012. Vertical transmission and clinical signs in broiler breeders and broilers experiencing adenoviral gizzard erosion. Avian Pathology 41: 599-604.

Grafl B et al., 2013. Quantity of virulent fowl adenovirus serotype 1 correlates with clinical signs, macroscopical and pathohistological lesions in gizzards following experimental induction of gizzard erosion in broilers. Veterinary Research 44:38.

Grafl B et al., 2018. Fowl aviadenovirus serotype 1 confirmed as the aetiological agent of gizzard erosions in replacement pullets and layer flocks in Great Britain by laboratory and in vivo studies. Avian Pathology 47: 63-72.

Grafl B et al., 2020. Successful reproduction of adenoviral gizzard erosion in 20-week-old SPF layer-type chickens and efficacious prophylaxis due to live vaccination with an apathogenic fowl adenovirus serotype 1 strain (CELO). Vaccine 38: 143-149.

Guo YX et al., 2018. Protocatechuic acid (PCA) induced a better antiviral effect by immune enhancement in SPF chickens. Microbial Pathogenesis 114: 233-238.

Haque MA et al., 2021a. Pathogenicity of feed-borne *Bacillus cereus* and its implication on food safety. Agrobiological Records 3: 1-16.

Haque MA et al., 2021b. Feed-borne *Bacillus cereus*: An emerging threat to food chain related hazard, safety and pathogenic potentiality. In: Abbas RZ, Khan A, editors. Veterinary Pathobiology and Public Health. Unique Scientific Publisher, Faisalabad, Pakistan; pp: 251-259.

Haque MA et al., 2022. *Bacillus* spp. contamination: A novel risk originated from animal Feed to human food chains in south-eastern Bangladesh. Frontiers in Microbiology 12: 783103.

Hoerr FJ, 1998. Pathogenesis of Enteric Diseases. Poultry Science 77: 1150–1155

Jabbar AA, 2022. Gastroprotective and immuno-supportive Role of *Alcea kurdica* against stress induced lesion in Japanese quails. Baghdad Science Journal 19: 716-724.

Kaldhusdal M et al., 2012. Non-soluble fibres and narasin reduce spontaneous gizzard erosion and ulceration in broiler chickens. Avian Pathology 41: 227-234.

Karki K et al., 2009. Clinical Laboratory Epidemiological Investigation of hemorrhagic proventriculitis and gizzard erosion in Nepal. Veterinary World 2: 54-56.

Kayode AAA et al., 2019. Medicinal plants used in the treatment of gastric ulcer in Southwestern and North central Nigeria. Research Journal of Medicinal Plants 13: 119-128.

Kichou F et al., 2020. Emerging and Reemerging Fowl Aviadenovirus Infections. In: Ennaji MM, editor, Emerging and Reemerging Viral pathogens. Academic press, pp: 781–803.

Kim YS et al., 2020a. Gastroprotective and healing effects of *Polygonum cuspidatum* root on experimentally induced gastric ulcers in rats. Nutrients 12: 1-15.

Kim YS et al., 2020b. Gastroprotective effects of Inulae Flos on HCl/Ethanol-induced gastric ulcers in rats. Molecules 25: 1-13.

Kim MR et al., 2021. *Brassica oleracea* prevents HCl/Ethanol-induced gastric damages in mice. Applied Sciences 11: 1-13.

Kiss I et al., 2021. Research Note: An overview on distribution of fowl adenoviruses. Poultry Science 100: 101052.

Kumar R et al., 2021. An outbreak of fowl aviadenovirus A–associated gizzard erosion and ulceration in captive Bobwhite quail (*Colinus virginianus*). Avian Diseases 65: 52–58.
Lam EKY et al., 2007. Probiotic *Lactobacillus rhamnosus* GG enhances gastric ulcer healing in rats. European Journal of Pharmacology 565: 171–179.
Li XH et al., 2020. Gastric ulceration and immune suppression in weaned piglets associated with feed-borne *Bacillus cereus* and *Aspergillus fumigatus.* Toxins 12: 703.
Lim TH et al., 2012. Outbreak of gizzard erosion associated with fowl adenovirus infection in Korea. Poultry Science 91 :1113–1117.
Lindgren Y et al., 2022. Gizzard erosions in broiler chickens in Sweden caused by fowl adenovirus serotype 1 (FAdV-1): investigation of outbreaks, including whole-genome sequencing of an isolate, Avian Pathology 51: 257-266.
Liu R et al., 2020. The gastroprotective effect of small molecule oligopeptides isolated from walnut (*Juglans regia* L.) against Ethanol-induced gastric mucosal injury in rats. Nutrients 12: 1-20.
Majed R et al., 2016. *Bacillus cereus* biofilms—same, only different. Frontiers in Microbiology 7: 1054.
Malinak CM et al., 2014. Tribasic copper chloride toxicosis in commercial broiler chicks. Avian Diseases 58: 642–649.
Manarolla G et al., 2009. Adenoviral gizzard erosions in Italian chicken flock. Veterinary Record 164: 754-756.
Mirzazadeh A et al., 2021. Reduced performance due to adenoviral gizzard erosion in 16-day-old commercial broiler chickens in Iran, confirmed experimentally. Frontiers in Veterinary Science 8: 635186.
Moula MM et al., 2020. Evaluation of broiler health status through flock health monitoring program in Bangladesh. Poultry Science Journal 8: 63-72.
Novoa-Garrido M et al., 2006. Association between gizzard lesions and increased caecal *Clostridium perfringens* counts in broiler chickens. Avian Pathology 35: 367-372.
Nkukwana TT et al., 2014. Effect of *Moringa oleifera* leaf meal on growth performance, apparent digestibility, digestive organ size and carcass in broiler chickens. Livestock Science 161: 139-146.
Ohh MH et al., 2016. Effects of dietary supplementation with astaxanthin on histamine induced lesions in the gizzard and proventriculus of broiler chicks. Asian-Australasian Journal of Animal Sciences 29: 872-878.
Ono M et al., 2001. Epizootic outbreaks of gizzard erosion associated with adenovirus infection in chickens. Avian Diseases 45: 268-275.
Ono M et al., 2003. Adenoviral gizzard erosion in commercial broiler chickens. Veterinary Pathology 40: 294-303.
Onyeka IP et al., 2020. Antiulcer effects of methanol extract of *Euphorbia hirta* and honey combination in rats. BioMed Research International 6827504: 1-8.
Pearlin BV et al., 2020. Role of acidifiers in livestock nutrition and health: A review. Journal of Animal Physiology and Animal Nutrition 104: 558-569.
Rozza AL et al., 2012. Morphologic and pharmacological investigations in the epicatechin gastroprotective effects. Evidence-Based Complementary and Alternative Medicine 708156: 1-8.
Sattar A et al., 2019. Evaluation of gastro-protective activity of *Myristica fragrans* on ethanol-induced ulcer in albino rats. Annals of the Brazilian Academy of Sciences 91: 1-8.
Schade B et al., 2013. Adenoviral gizzard erosion in broiler chickens in Germany. Avian Diseases 57: 159–163.
Smith TK et al., 2000. Feed-borne biogenic amines: natural toxicants or growth promotors? Proceedings of "the 5th International Symposium on Aquaculture Nutrition". Merida, Yucatan, Mexico; 19-22 Nov 2000, pp: 24-32.
Sun MC et al., 2018. Pretreatment with *Lactobacillus reuteri* F-9-35 attenuates ethanol-induced gastric injury in rats. Food and Nutrition Research 62: 1-8.
Takahashi K et al., 2001. Effect of dietary Stevia (*Stevia rebaudiana*) extract on gizzard erosion and ulceration induced by dietary histamine in broiler chick. Journal of Poultry Science 38: 181-184.
Tisljar M et al., 2002. Gizzerosine-induced histopathological lesions in broiler chicks. British Poultry 43: 86-93.
Tsilia V et al., 2016. *Bacillus cereus* NVH 0500/00 can adhere to mucin but cannot produce enterotoxins during gastrointestinal simulation. Applied and Environmental Microbiology 82: 289–296.
Uku UP et al., 2020. Phytochemical screening and antiulcer activity, of *Ficus thonningii* (Moraceae) aqueous fruits extract in Wistar rats. Asian Journal of Research in Medical and Pharmaceutical Sciences 9: 41-59.
Wang Y et al., 2021. Contamination with fumonisin B and deoxynivalenol is a threat to egg safety and contributes to gizzard ulcerations of newborn chickens. Frontiers in Microbiology 12: 676671.
Wang F et al., 2022. Protocatechuic acid: a novel detoxication agent of fumonisin B1 for poultry industry. Frontiers in Veterinary Sciences 9: 1-9.
Wu Y et al., 2021. *Lactobacillus plantarum* ZS62 alleviates alcohol-induced gastric injury in mice via an antioxidative mechanism. Drug Design Development and Therapy 15: 1667-1676.
Zhang Q et al., 2019. Contaminated feed-borne *Bacillus cereus* aggravates respiratory distress post avian virus H9N2 infection by inducing pneumonia. Scientific Reports 9: 7231.
Zhou D et al., 2020. Gastroprotective effect of gallic acid against ethanol-induced gastric ulcer in rats: Involvement of the Nrf2/HO-1 signaling and anti-apoptosis role. Biomedicine and Pharmacotherapy 126: 110075.
Zuo Z et al., 2020. Feed-borne *Bacillus cereus* exacerbates respiratory distress in chickens infected with *Chlamydia psittaci* by inducing haemorrhagic pneumonia. Avian Pathology 49: 251–260.