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Comparative Study of Oxidative Stress and Some Enzymatic Parameters in All serotypes of FMD Infected Calves in Thi-Qar Province

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Abstract

Foot-and-mouth disease is a contagious disease that impacts up to 70 species of cleft hoofed mammals. There are 7 different serotypes of FMDV, O, A, C, Asia1, SAT1, SAT2 and SAT3. Antioxidant mechanisms in mammalian bodies eliminate reactive oxygen species (ROS), that produces free radicals during stress factors such as viral diseases. Liver enzymes are highly affected by liver dysfunction that caused by viral infection. This study aimed to detect the effects of infection with FMD virus on antioxidant status and liver enzymes. This study applied on 80 calves (cow) from different regions, ages and sexes of Thi-Qar province during the period of December (2024) to March (2025). Blood samples were gained from 60 affected calves with (FMD virus) as well as other 20 samples from healthy calves -as control. Sera was classified after detecting the serotypes by Conventional PCR technique. Results reviled that SOD levels in groups A, O serotypes were significantly reduced when compared with those of mixed group (A&O), (MDA) levels were highly and significant rise in all afflicted categories compared to the healthy group. also a significant elevation in (ALT) and (AST) levels in groups of calves of serotype O. G.G.T levels were significantly increased in animals affected with serotype A as compared with others groups including control. In conclusion FMDV pathogenesis causes oxidative stress, with single serotypes (A/O) causing more severe antioxidant suppression and profound hepatocellular damage linked to serotype O infections.

Keywords: FMD, Conventional PCR, Serotypes, Antioxidant, ALT, AST

الملخص

مرض الحمى القلاعية هو مرض معد يصيب 70 نوعًا من الثدييات ذات الحوافر المشقوقة. يوجد 7 أنماط مصلية مختلفة من فيروس الحمى القلاعية وهي **O** و**A** و**C** و**Asia1** و**SAT1** و**SAT2** و**SAT3**. تعمل آليات مضادات الأكسدة في أجسام الثدييات على التخلص من أنواع الأكسجين التفاعلية (**ROS**)، التي تنتج الجذور الحرة أثناء عوامل الإجهاد مثل الأمراض الفيروسي وكذلك تتأثر إنزيمات الكبد بشدة بخلل وظائف الكبد الناجم عن العدوى الفيروسية. هدفت هذه الدراسة إلى الكشف عن آثار الإصابة بفيروس الحمى القلاعية على حالة مضادات الأكسدة وإنزيمات الكبد. طبقت هذه الدراسة على 80 عجلًا من مناطق وأعمار وأجناس مختلفة في محافظة ذي قار خلال الفترة من ديسمبر (2024) إلى مارس (2025). تم الحصول على عينات الدم من 60 عجلًا مصابًا بفيروس الحمى القلاعية بالإضافة إلى 20 عينة أخرى من عجول سليمة - كمجموعة ضابطة. تم تصنيف المصل بعد الكشف عن الأنماط المصلية بتقنية تفاعل البوليميراز المتسلسل. أظهرت النتائج أن مستويات **SOD** في المجموعات **A** و **O** المصلية قد انخفضت بشكل ملحوظ عند مقارنتها بمستويات المجموعة المختلطة (**A&O**)، وكانت مستويات (**MDA**) مرتفعة بشكل كبير وملحوظ في جميع المجموعات المصابة مقارنة بالمجموعات السليمة، كما كان هناك ارتفاع كبير في مستويات (**ALT**) و (**AST**) في مجموعات العجول من النمط المصلي. **O** كما زادت مستويات **GGT** بشكل ملحوظ في الحيوانات المصابة بالنمط المصلي **A** مقارنة بالمجموعات الأخرى بما في ذلك المجموعة الضابطة. نستنتج من هذا إن الاصابة بمرض الحمى القلاعية يسبب الاجهاد التأكسدي، حيث تسبب الأنماط المصلية الفردية (**A/O**) في تثبيط مضادات الأكسدة بشكل أكثر شدة وكذلك يسبب تلفا في الخلايا الكبدية بالأخص النمط المصلي **O**

الكلمات المفتاحية : الحمى القلاعية، انزيمات الكبد، مضادات اكسدة، الجذور الحرة، انواع مصلية

Introduction:

Foot-and-mouth disease (FMD) is a contagious disease that impacts up to 70 species of cleft hoofed mammals thorough cattle, goat, sheep, and pigs [1]. The viral agent of FMD belongs to the genus *Aphthovirus* and family *Picornaviridae*. The virus of FMD is a small, non-enveloped, positive-sense, single-stranded RNA virus, with

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genome of approximately 8500 bases ringed four structural proteins which form an icosahedral capsid. There are seven immunologically distinct serotypes of FMDV (A, C, O, Asia 1, and Southern African Territories 1, 2, and 3), with a wide spectrum of antigenically and epidemiologically different subtypes within each serotype. The major variety is seen a result of the high mutation rate, nearly-kinds dynamics, and recombination [2, 3, 4]. FMDV comes in seven distinct variations, or serotypes: A, O, C, SAT 1, 2, 3, and Asia 1.

All give rise to a similar disease and infection but one serotype dose not confer immunity against another [5]. Each serotype has different subtypes, resulting from the virus exhibiting a significant mutation rate [6]. Enzymatic and non-enzymatic antioxidant mechanisms eliminate reactive oxygen species (ROS), that develop during metabolic and physiological processes. The oxidant-antioxidant balance swings for them in the direction of oxidants under specific circumstances, and the rise in oxidants and reduced antioxidants cannot be stopped. The generation of reactive oxygen species, such as peroxides and free radicals, is a particularly harmful effect of oxidative stress [7]. Several antioxidant molecules present in blood, including superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) prevent and/or decrease the negative consequences of free radical reactions [8, 9, 10]. Malondialdehyde (MDA) along with other oxidant concentrations in plasma or serum could be identified individually in a lab [11, 12, 13]. The contribution of reactive oxygen species in the pathophysiology of viral illnesses has been the subject of an increasing number of research [14]. In addition, in order to include antioxidant medicines into their treatment regimen, physicians might need to evaluate oxidative stress. The knowledge about the ruminants' oxidative stress is still not well developed. It is very interested to be discovered about their role model in ruminants' health and production [15]. In recent years the invention of cellular damage causes by free radicals and body defenses it have become important issue especially in the clinical medicine as an integral agent in the estimation of metabolic condition of the animals [16]. Cells are shielded by antioxidants from the damaging effects of free radicals. According to [17], free radicals-molecules with an unshared electron-damage cells and may contribute to the onset of cancer and cardiovascular diseases. Specifically, with respect to unshared electrons, these dynamic electrons have a rapid interaction with oxygen and react to form reactive oxygen species (ROS). Environmental free radicals, as well as air pollution and UV radiation from the sun, ROS are naturally produced in the body during the food to energy transformation process. Additionally, ROS functions as a signaling molecule. In the last two decades, it has been shown that a variety of infections trigger the production of reactive oxygen species [18]. While the role of oxidants in the inactivation of viruses was observed over fifty years ago, their role during the infection phase has only been studied recently. The role of oxidants becomes more complicated in viral infections, as they not only regulate host metabolism and viral replication (which is a simpler scenario in microbial disease and self-damaging toxicity) [19]. The oxidant-antioxidant equilibrium that is defined to a certain condition, as described, is

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shifted in favor of oxidants and cannot be controlled. A particularly detrimental aspect of oxidative stress is the increase of reactive oxygen species, as well as the escalation of free radicals and peroxides [7]. Lipid peroxidation, which is a well-established mechanism of cellular damage, serves as a marker of oxidative stress in the tissues and cells [20]. The liver is an important metabolic organ and is abundant in enzymes, that play a crucial role in the metabolic processes and synthesis of proteins all over the body [21]. Particularly, application on degrading the toxic substances, secretion of bile, storage of glycogen, and drug metabolism [22]. Liver functions can be interrupted by liver diseases and/or drugs use [23, 24]. Liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamine transferase (GGT) and alkaline phosphatase (ALP), are highly affected by liver injury and dysfunction [25, 26]. AST is represented in both cytoplasm and mitochondria of hepatocytes, myocardium and skeletal muscles. ALT is a cytoplasmic enzyme present exclusively in the hepatocytes. GGT catalyzes transfer of glutamyl group from glutathione to amino acid. ALP is a family of zinc metallohydrolase enzymes present in liver, bone, intestinal epithelium, kidney, placenta and germ cells. High levels of ALT and AST are suggested to be in liver disease [27, 28] and mortality rate related to liver diseases, as well as ALT high levels are associated with diabetes mellitus [29]. Elevated levels of GGT in serum indicates to biliary injury. ALP is attached to biliary canaliculi, elevated ratio indicates cholesteric liver disease.

Material and Methods:

Samples collection:

Samples for this study were gained from 80 calves from different regions, ages and sexes of Thi-Qar province during the period extending from December (2024) to March (2025), 60 of these animals were (FMD infected) . Blood sample (10 ml) were collected into gel tube (non-anticoagulant), as well as other 20 samples from healthy calves -as control - then stored in a cooling box before processing in the laboratory. Blood was centrifuged at speed 3000-4000 rpm for 10-15 minutes, sera was sera was classified after detecting the serotypes by PCR technique. The serum collected in Eppendorf tubes (1.5ml) and stored at -20˚C until an enzyme-linked immunosorbent assay was produced and enzymatic assays. These methods were used according [30].

The PCR master mix reaction was prepared following the manufacturer's instructions provided by TransGen Biotech Int., China, 2025.

ELISA Methods:

1. Bovine Super Oxidase Dimutase (SOD) ELISA Kit: SunLong Biotech Co., LTD, www.sunlongbiotech.com
2. ELISA Bovine Catalase (CAT) Kit: SunLong Biotech Co., LTD, www.sunlongbiotech.com
3. ELISA Kit for Bovine Glutathione (GSH): SunLong Biotech Co., LTD, www.sunlongbiotech.com
3. Bovine Malondialchehyche (MDA) ELISA Kit: SunLong Biotech Co., LTD, www.sunlongbiotech.com

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Kinetic UV Method (IFCC):

1. Reagents ALT / GPT SL:

Quantitative determination of alanine amino transferase (ALT/GPT) in serum and plasma according to IFCC recommendations, produced by Giesse Diagnostics company with management system certified by DNV ISO 9001, ISO 13485. In presence of α-ketoglutarate, alanine is trasformed into pyruvate and glutamate by ALT/GPT in the sample. In presence of NADH and lactate dehydrogenase, pyruvate is coverted into lactate and NAD. NADH oxidation in time unite, measured at 340 nm, is proportional to ALT/GPT concentration in the sample.

2. **Reagents AST/GOT SL Kit:**

Quantitative determination of aspartate aminotransferase (AST) in serum and plasma in accordance with IFCC recommendations, produced by Giesse Diagnostics company with management system certified by DNV ISO 9001, ISO 13485.In the presence of α-ketoglutarate, AST/GOT in the sample transforms aspartate into oxalacetate and glutamate. Oxalacetate is then converted into malate and NAD in the presence of NADH and malate dehydrogenase. The consumption of NADH per unit of time, measured at 340 nm, is proportional to the concentration of AST/GOT in the sample.

3. **SL Kit for Alkaline Phosphatase Reagents**:

Quantitative determination of alkaline phosphatase (ALP) in serum and plasma using an optimized method according to DGKC recommendations, produced by Giesse Diagnostics company with management system certified by DNV ISO 9001, ISO 13485. The enzyme alkaline phosphatase hydrolyzes p-nitrophenylphosphate (4-NPP), releasing p-nitrophenol (4-NP). The rate of 4-NP formation is measured spectrophotometrically at 405 nm to quantify the enzyme activity in the sample.

GAMMA GT SL Kit:

Quantitative determination of glutamyltransferase (γ-GT) in serum, produced by Giesse Diagnostics company with management system certified by DNV ISO 9001, ISO 13485. The γ-GT in the presence of glycyl-glycine, splits the L-γ-glutamyl-3-carboxy-4-nitroanilide (carboxi-glupa) in L-γ-glutamyl-glycine and 5-amino-2-nitrobenzoate. The absorbance change in time unit measured at 450 nm is proportional to the enzyme activity in the sample.

Results and discussion:

Results of table (1) reviled significant decrease ($P \leq 0.05$) in levels of superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) in all affected groups as compared to healthy animals in control group, but SOD levels in groups A, O serotypes showed a significant decrease

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when compared with SOD levels of mixed group (A&O) , This indicates the animals were seriously affected with these virulent serotypes A and O, while levels of Malondialdehyde (MDA) were highly and significant increased ($P \leq 0.05$) in all affected groups as compared with the healthy one , this indicated those animals- in affected groups- were suffered from massive oxidative stress.

Calves infected with FMD virus, especially in cases of co-infection with (A&O) serotypes, show a marked reduction in the endogenous antioxidant parameters SOD, CAT, and GSH when compared to healthy calves. This reduction is an important factor in the pathogenesis of FMD and significantly affects tissue damage and the severity of the disease [31] and [32] have reported that calves infected with FMDV serotypes A and O showed significantly lower levels of SOD, CAT, and GSH compared to healthy calves. [31] pointed out that this depletion was due to increased oxidative damage (with markers like Malondialdehyde - MDA) and the clinical severity of the disease. Research on mixed infections (Serotype A&O) done by [33] argues that there is a much sharper decline in these defensive antioxidants than in single-serotype infections. [and others demonstrated that the greater the depletion of SOD, CAT, and GSH, the more severe the clinical signs and lesions (fever, vesicle formation, lameness). Decreased antioxidants with increased markers of stress indicate a worse outcome with infections. This points toward co-infection resulting in increased oxidative burden, whether added together or jointly acted upon. This could be because the depletion of SOD, CAT, or GSH is not a simple case of absence of production but rather the result of the host and virus confrontation the primary causes include massive reaction oxygen species (ROS) generation as well as direct consumption of antioxidants . Replication of FMDV, similar to other viral infections, within target tissues and subsequently in the cytoplasm and peroxisomes of host cells causes elevated levels of ROS as a result of reprogrammed cellular metabolism and energy production required for the production of tRNA and other constituents or structure elements of viral particles [31, 32]. Besides that, FMDV has the capability of causing the body to respond with potent inflammation that is out of balance. Responding Immunocytes such as neutrophils and macrophages recruited to infected areas particularly vesicles or other tissues respond to the infection by producing excessive superoxide anion and hydrogen peroxide), catalase (3, 4) hypochlorous acid at large amounts. Due to the burst of ROS, superoxide dismutase (which transforms superoxide into H_2O_2) is overwhelmed, and so is CAT that decomposes H_2O_2 as well as GSH which draws free radicals and enzymatically interacts together with glutathione peroxidase), [34, 33].

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Results of table (2) revealed a highly significant increase ($P \leq 0.05$) in (ALT) and (AST) levels in groups of calves that were diagnosed with serotype O of FMDV when compared with healthy animals in the control group and infected animals in other groups (serotypes A and mixed A&O). However, ALP levels in affected groups were not significantly difference from each other and those in control group. GGT were significantly increased in animals affected with serotype A as compared with others groups including control. Infection with serotype O leads to calves having 2-3 times more ALT and AST than controls or other infected groups. Focused liver damage caused enhanced destruction of liver cells. Mixed infections and serotype A show lower increases. Improved binding of serotype O to heparin sulfate proteoglycans (HSPGs) on hepatocytes that helps in replication and entry is noted to be binding of integrin-free pathways, thus increasing the viral load in the liver which disrupts the mitochondrial membranes of the hepatocytes causing release of AST (mitochondrial isoform) into the blood [33].

The difference in Hepatopathologies associated with O serotype shows the most damage, supporting FMDV O infection. Very significant differences ($p \leq 0.05$), also observed with ALT and AST show stronger effects for inflammatory stimuli suggest possibility for greater damage. Changes to ALT and AST by FMDV O infected calves suggest the existence of preferential presence within liver cells which may highlight a selective advantage to infection with that strain. This is consistent with findings by [35] that demonstrate serotype specific differences in fibrous tissue degenerative lesions and foetal tissue slicing. As evidence by the system infection's lack of significant increase in A and mixed A&O groups, suggested laparoscopic trends indicates that these types do not cause significant liver injury; or, any injury that does occur is subclinical during the level of these enzymes in serum. ALP is also connected to firing activity of osteosarcoma, and so can indicate pancreatitis. The lack of difference in ALP levels between any of the infected groups (O, A, A&O) and the healthy control group suggests the absence of significant cholestasis or major disease of the biliary system induced by any of the FMDV serotypes under study. This suggests that the hepatocellular damage induced by serotype O is likely centrilobular or midzonal and not periportal.

According to [36] discussion of viral hepatitis in livestock this pattern- higher transaminase without elevated ALP- is consistent with acute hepatocellular injury without obstruction. In 2022. GGT is a very sensitive indicator of biliary epithelial damage and cholestasis. Additionally, some medications and hepatic insults can cause it. When compared to controls the O serotype group and the mixed A and O

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group the particular increase in GGT in calves infected with serotype A suggests a distinct pattern of hepatic involvement. This suggests that cholestasis or biliary tract pathology is a more common characteristic of serotype A infection in this investigation. Although the exact causes of this serotype-specific cholestatic effect are unknown they may include variations in the livers viral replication sites the type of immune response triggered (e. g. A. focusing on bile duct epithelia) or causing particular metabolic alterations. [37] observed differences in tissue distribution and clinical manifestations among FMDV serotypes in 2021 which may help to explain the different enzyme patterns found in different organs. Although the lack of a discernible increase in GGT in the mixed infection group calls for more research it may indicate intricate viral interactions influencing pathology [38]. The idea that various FMDV are supported by these findings. Different serotypes can result in different patterns of organ damage especially in the liver. Serotype A is linked to cholestatic alterations whereas serotype O seems to be more closely linked to direct hepatocellular damage. Alongside virological and serological diagnostics monitoring liver enzyme profiles (ALT AST and GGT) may help determine the predominant serotype involved in an outbreak (particularly distinguishing O from A) or gauge the severity of hepatic complications in afflicted calves. Significant liver cell injury is indicated by the transaminase elevation in group O [39]. The distinct patterns of enzymes indicate that there may be various pathogenic mechanisms at work. Serotype O: Immune-mediated hepatocyte damage direct hepatocytelysis (e. g. G. either ischemic injury brought on by systemic inflammation or viremia or CTL activity [40]. Serotype A: Drug-induced changes brought on by treatment procedures intrahepatic cholestasis brought on by inflammation or metabolic changes or potential involvement of bile ductless (cholangiolitis). Mixed Infection Complexity: It's interesting that the mixed A and O group did not exhibit a pure A group for GGT. It may indicate a dominant strain that is less hepatitis in the mix interference between serotypes or a regulated immune response that results in distinct pathology. This demonstrates how complicated mixed infections are and how much more research is needed.

Conclusions:

1- FMDV pathogenesis is driven by oxidative injury, with single serotypes (A/O) causing more severe antioxidant suppression than mixed infections.
2- MDA elevation is a universal indicator of oxidative damage in FMDV-infected cattle, regardless of serotype.
3- The hepatic impact of FMDV serotypes in calves varies significantly according to this analysis. Profound hepatocellular damage linked to serotype O infection is demonstrated by elevated ALT and AST

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levels. Conversely cholestasis alterations which are indicated by elevated GGT are associated with serotype A infection. Because alkaline phosphatase levels were unchanged in every group there was no significant biliary obstruction. When assessing the hepatic complications and overall disease severity in affected calves it is crucial to take the infecting serotype into account. These serotype-specific enzyme profiles offer important insights into the differential pathogenesis of FMDV.

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Table (1): Antioxidant parameters in groups of calves affected with FMD-V of (A, O and (mix A & O)) serotypes compared with healthy calves. N=20 for each group.

Groups	SOD (pg/ml) Mean ± SD	CAT(ng/ml) Mean ± SD	GSH (ng/L) Mean ± SD	MDA (ng/ml) Mean ± SD
A	275.33 ± 10.69 c	0.58 ± 0.60 b	39.75 ± 23.19 b	131.16 ± 30.62 a
O	276.07 ± 12.11 c	0.91 ± 0.72 b	45.48 ± 27.12 b	136.44 ± 52.39 a
A & O	332.08 ± 19.14 b	0.68 ± 0.76 b	35.17 ± 21.10 b	121.55 ± 54.83 a
Control	981.46 ± 74.06 a	2.86 ± 1.61a	261.69 ± 127.57 a	48.71 ± 19.75 b
LSD	35.46	0.91	60.85	38.15

The significant differences at (P ≤ 0.05) indicated by different letters.

Table (2): Enzymatic parameters-as Liver Function Test- in groups of calves affected with FMDV of (A, O and mix A & O) serotypes compared with healthy calves. N=10

Groups	ALT (U/L) Mean ± SD	AST (U/L) Mean ± SD	ALP(U/L) Mean ± SD	GGT(U/L) Mean ± SD
A	24.1 ± 11.06 bc	67.1 ± 17.01b	304.11 ±82.07	257.4 ± 60.89 a
O	59.4 ± 20.72 a	233 ± 163.31 a	342.31 ±90.83	220.1 ± 59.58 ab
A & O	26.9 ± 5.04 b	101.5 ± 28.9 b	345.04±142.27	200 ± 78.41 b
Control	18 ± 1.63 c	51.5 ± 9.81 b	287.86 ± 52.33	70 ± 44.79 c
LSD	10.92	75.74	88.36	56.30

The significant differences at (P ≤ 0.05) indicated by different letters.