Journal of Animal Science and Veterinary Medicine
Volume 6(6), pages 188-194, December 2021
Article Number: 0FB3BD8B1
ISSN: 2536-7099
https://doi.org/10.31248/JASVM2020.216
https://integrityresjournals.org/journal/JASVM

Review Article

Acute phase proteins in veterinary medicine: A review

Mahdi Ali Abdullah

College of Veterinary Medicine, Duhok University, Kurdistan region, Iraq.

Email: mahdi.ali@uod.ac

Received 4th July, 2020; Accepted 30th October, 2021

ABSRTACT: The acute phase proteins (APPs) are a group of blood proteins that contribute to restoring homeostasis and limiting microbial growth in an antibody-independent manner in animals which are exposed to different pathological conditions like infection, inflammation, surgical trauma and stress. In the last two decades, many advances have been made in monitoring APPs in both farm and companion animals for clinical and experimental purposes. Also, the mechanism of the APPs response is receiving attention in veterinary science in connection with the innate immune systems of animals. This review describes the many of new results of research and role APPs in farm animal, with special reference to their functions, types, induction and regulatory expression, some of biological functions, and their current and future applications to veterinary diagnosis and animal production.

Keyword: Acute, animals, human, protein.

INTRODUCTION

Acute-phase proteins (APPs) are a class of proteins whose plasma concentrations are either increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation, injury, stress, bacterial, parasitic and viral infection, tumor, burns, surgery, immunological disorders and so many others pathological conditions (Gabay and Kushner, 1999; Kushner, 1982; Cray et al., 2009). This response is called the acute-phase reaction (APR) or acute-phase response. The terms of APPs and APR are often used synonymously, although some of APRs are (strictly speaking) polypeptides rather than proteins (Abbas et al., 2012).

The response of APPs is considered as important part of the innate immune system which play a role in mediating such of systemic effects as fever, leukocytosis, increased cortisol, and decreased of thyroxine (Davidson, 2013).

The APPs although, have been characterized as non-specific responders to pro-inflammatory signals, differences in APPs expression during disease across species have been reported, and evidence exists that circulating concentrations of APPs in blood and other biological fluids are a direct indication of diseases severity (Eckersall and Bell, 2010; Murata et al., 2004; Ceron et al., 2005). Additionally, more recent data based on the proteomic analyses of APPs during diseases suggests that modification of glycoproteins could be disease specific (Wilson et al., 2008).

A wide range of diseases affected different farm animals and early diagnosis of these diseases beside the proper way for treatment of disease is essential, therefore this review give a more knowledge about APPs with its measurements that are widely used as disease biomarkers and for prognostication in veterinary medicine and are increasingly used in varied areas of research.

ACUTE PHASE PROTEINS

Cytokines and the acute phase response

At the site of infection or location of tissue injury, pro-inflammatory cytokines and chemokines are released (Gruys et al., 2005). Cytokines and chemokines are protein and peptide mediators secreted by cells which play a key role in immune and inflammatory responses through activation and regulation of other cells and tissues. These inflammatory mediators initiate and modulate the APR, which are diffusing into the extracellular fluid and circulating in blood. Cytokines activate many of receptors on different target cells leading to a systemic APR which results in activation of the hypothalamic-pituitary-adrenal axis, reduction in growth hormone secretion, and a number of physical changes which are clinically characterized by pyrexia, anorexia and catabolism of muscle cells (Gruys et al., 2005)

Mechanism of synthesis of acute phase protein

The acute phase proteins are a large group of plasma proteins which originate mainly from the liver in response to pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) which are the major mediators of synthesis of APP in liver as showing in Figure 1 (Yoshioka et al., 2001; Heinrich et al., 1990; Uhlar and Whitehead, 1999). They are released very quickly into the circulation, where each performs a specific activity. During APR, the serum of APPs concentrations increases substantially unlike in healthy animals and humans, APPs are undetectable or in negligible quantities. However, some APPs collectively called “permanent” are continuously secreted and released into the bloodstream while the “induced” ones are present in plasma only during APR (Uhlar and Whitehead, 1999).

APPs can also be synthesized extrahepatically in some tissues such as testicular tissue, adipose tissue, lung, ovary, uterus, mammary glands, digestive tract (Uhlar and Whitehead, 1999; Ceciliani et al., 2012). The type and magnitude of APP expression varies between the species of animals and the plasma concentrations of major APPs in healthy animals are very low. During the acute phase of inflammation, their levels are greatly enhanced in the first few hours after exposure to the pathogenic factors (Petersen et al., 2004; Ceciliani et al., 2002). APPs kinetics depends on the animal species and extent of tissue damage. Serum APPs concentrations generally reach a peak within 24 to 48 hours. If a new stimulus does not appear and inflammation ceases, the feedback APPs regulation limits the response within 4 to 7 days after challenge. Also, some recent research found that the glucocorticosteroids have a double function in the induction and expression role of APPs which either group of glucocorticosteroid dependent on hepatic stimulation of hepatocytes by IL-6; or via the role of steroids down regulate cytokine production by monocytes and macrophages (Heinrich et al., 1990; Baybutt and Holsboer, 1990).

Classification of acute phase proteins

In general terms, APP can be classified according to important criteria, their quantitative variation as well as function.

According to protein concentration or depending on the concentrative level increase or decrease by at least 25% during APR (Eckersall and Bell, 2010; Murata et al., 2004; Ceron et al., 2005)

Negative acute phase proteins: Negative acute phase proteins are those proteins when the level in plasma concentration is decrease lesser than 25% due to response to inflammation. The reduction occurs very fast within 24 hours or may be decrease gradually over a period of days. The two important negative acute phase proteins are albumin and transferrin protein which has been described by Ingenbleek and Young (1994). The path way concentrations decrease is due to decreased production by the liver in response to inflammatory cytokines, and possibly increased loss or increased proteolysis (Eckersall and Bell, 2010; Murata et al., 2004; Ceron et al., 2005).

Positive acute phase proteins: Positive acute phase proteins are those proteins when the level in plasma concentration is increase more than 25% in response to inflammation usually during 1 to 2 days. However, a specific APPs may have both pro- and anti-inflammatory effects which are generally classified to three main groups major, moderate and minor acute phase proteins as showing in Table 1 (Eckersall and Bell, 2010; Gomez-Laguna et al., 2011; Tothova et al., 2011).

The function of most APPs has not been totally elucidated. Generally, positive APPs are responsible for opsonization and trapping of microorganisms with their products, activating complement system, scavenging free haemoglobin and its radicals, binding cellular remnants as nuclear fractions, neutralizing enzymes, as well as modulating the host immune response (Eckersall and Bell, 2010).

According to the magnitude of increase in the concentration of positive APPs (Eckersall and Bell, 2010; Murata et al., 2004; Tothova et al., 2011) as showing in Table 1

Major APPs: Those protein that increases between 100 to1000 fold during the stimuli and reaching to maximum level after two to three days then start to decreasing, while in normal healthy animals there is a low concentration in the serum of around <0.1 µg/dL. An example of a major APP is serum amyloid (SAA).

Moderate APPs: Those proteins are found in normal blood of healthy animals, but when the animal response to stimuli, it increases 5 to 10 times and reaching a maximum

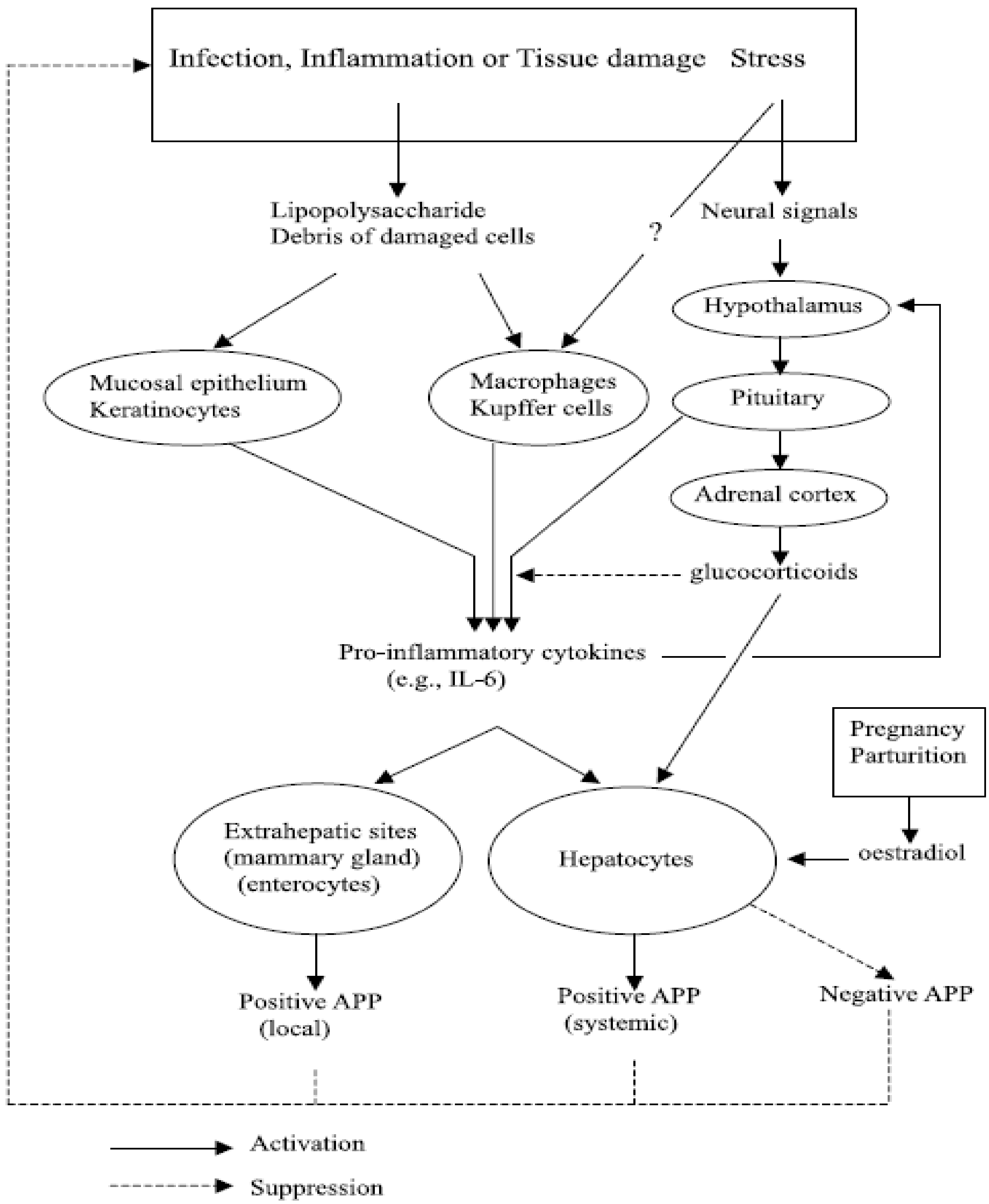

Figure 1. Induction and regulation network of acute phase protein synthesis in animals after different challenges (Murata et al., 2004).

around two to three days then start to decreasing less than major APPs. An example of a Moderate APP is haptoglobin (Hp)

Minor APPs: Those proteins that only increases between 50 to 100% above resting levels and at a gradual rate. An example of Minor APPs is fibrinogen (Fb). The rapidity and magnitude of the increase in each acute phase proteins are varies depending on the species of animals (Tothova et al., 2011).

Table 1. Expression of APPs in different species of animals according to their degree of importance.

Species	Major APPs	Moderate APPs	Minor APPs	Negative APPs
Dog	CRP, SAA	AGP,Hp, CP,Fb	-	Albumin, transferrin
Cat	AGp, SAA	Hp	-	Albumin, transferrin
Horse	SAA	Hp, Fb	-	Albumin
Cattle	Hp, SAA	AGP. MAP	Fb	Albumin
Sheep	Hp, SAA	AGP	Fb, Cp	Albumin
Goat	Hp, SAA	Fb, ASG	Cp	Albumin
Pigs	Hp, SAA	AGP, CRP	Fb	Albumin
Birds	Hp, SAA, OVT	AGP	MBL	Albumin

CRP: C-reactive protein; SAA: serum amyloid A; AGP: α1-acid glycoprotein; Hp: haptoglobin; Cp: ceruloplasmin; Fb: fibrinogen; ASG: acid soluble glycoprotein. Mannan binding lectin (MBL) ovotransferrin (OVT) (Francisco Veas, 2011).

Depending on their role during the response of inflammation (Tirziu, 2009, Khan and Khan, 2010)

- Mediators (C-reactive protein, fibrinogen).
- Modulators (complement proteins, inhibitors to coagulation cascade).
- Inhibitors (protease inhibitors – α1-antitrypsin, α2-macroglobulin).
- Scavengers and transporters (haptoglobin, serum amyloid A, ceruloplasmin).
- Immunomodulators (α1-acid glycoprotein).

Depending on their mechanism action of expression (Murata et al., 2004; Gruys et al., 2005)

- Type 1 dependent: Those proteins are induced by IL-1 and TNF-α.
- Type 2 dependent: Those proteins are induced by IL-6.

Useful of acute phase proteins in different domestic animal species

As mentioned before, the APPs are classified as positive, major, moderate, minor or negative depending on either the enhancement or the decrease in their serum concentration during the APR (Eckersall and Bell, 2010; Ceron et al., 2005). The synthesis and role of APPs may differ depending on the animal species. Some of APP may act as a positive APP in one species, it may not suffer any change in other species, such as C-reactive protein (CRP) in swine and in cattle (Ceciliani et al., 2012; O'Reilly and Eckersall, 2011) (Table 1).

While albumin participates as a negative APP in most of the animal species. On the other hand, haptoglobin (Hp) and fibrinogen (Fb) are considered as positive APPs, although the enhancement shown by the former may be up to ten times higher than the one observed by the latter. CRP is a really useful biomarker in human for monitoring the course of different clinical processes, and its measure is also of interest in swine and dog. Therefore, the serum concentration of CRP does not suffer big changes in the APR in bovine or in cat. Therefore, the selection of the appropriate APP for each species is of key importance (Veas, 2011).

General role of acute phase protein in the body

In general, the main function of APPs is to defend the host against pathological damages as a part of the innate immune response, assist in the restoration of homeostasis and in the regulation of different stages of inflammation (Tothova et al., 2011; Nazifi et al., 2011).

As showing Table 2, APPs are involved in many crucial metabolic and immune pathways and have roles that include scavenging extracellular haemoglobin, iron and free radicals and direct antibacterial and antiviral activity as opsonization and trapping of micro-organisms and their products, in activating complement, in binding cellular remnants like nuclear fractions, in neutralizing enzymes (Gruys et al., 2005). The response of APPs to various pathogenic challenges and other disruptions in homeostasis varies between species. APP profiles from both companion and farm animal species have been well documented, and in many veterinary species these clinical parameters are used diagnostically and for understanding the pathogenesis of important diseases (Eckersall and Bell, 2010; Nazifi et al., 2011).

However, chronic inflammation is considered as a series of individual inflammatory stimuli and is characterized by longer and slight increase in the serum concentration of APPs as compared to acute inflammation (Tothova et al., 2011; Jain et al., 2011).

APPs and uses as diagnostic tools

The determination of APPs levels in blood and milk samples from representative groups of animals is an

Table 2. Biological functions of some acute phase proteins with their biological function in some of animals species (Ceciliani et al., 2012; Tothova et al., 2011; O'Reilly and Eckersall, 2011).

Proteins	Abbreviation	Biological function	Classification
Haptoglobin	Hp	Bind free Haemoglobin	Positive
Serum amyloid	SAA	Binds cholesterol opspnin	Positive
Ceruloplasmin	Cp	Copper transport, iron metabolism	Positive
C-reactive protein	CRP	Complement activation, binding to memberance phosphorylcholine, opsonization	Positive
Fibrinogen	Fb	Blood clotting	Positive
Lipopolysaccharide	LPB	Bind to bacterial LSP, macrophages cell bacterial derived molecules	Positive
α1-acid glycoprotein	AGP	Bind drugs, inflammatory mediators and bacterial derived molecules	Positive
α1-antirypsin	ATT	Serine protase inhibitor	Positive
Transferrin	TF	Binds iron	Negative
Hemopexin	Hpx	Heme binding	Positive
Lactoferrin	LF	Binding and transferring Fe ions	Positive

Table3. Acute phase proteins associated with some of diseases in different species of farm animals.

Protein	Diseases	Species
Haptoglobin	Pneumonia, Inflammation, Sepsis	Swine
Serum Amyloid A	Pneumonia, Sepsis	Swine
C-reactive protein	Inflammation, Sepsis	Swine
α1-acid glycoprotein	Inflammation	Swine
Ceruloplasmin	Inflammation	Swine
Acid soluble glycoprotein	Inflammation	Swine
Haptoglobin	Infections bronchitis	Chickens
Serum Amyloid A	Infections bronchitis	Chickens
Lipopoly saccharides binding protein	Mastitis, Respiratory disease	Cattle
Serum Amyloid A	Mastitis, Respiratory disease, Amyloidosis	Bovine
Haptoglobin	Mastitis, Respiratory disease, Amyloidosis	Bovine
α1-acid glycoprotein	Mastitis, Respiratory disease	Bovine
Haptoglobin	Caseous lymphadenitis, Pulmonary damage	Sheep
Serum Amyloid A	Caseous lymphadenitis	Sheep
α1-acid glycoprotein	Caseous lymphadenitis	Sheep
Fibrinogen	Pulmonary damage	Sheep
Ceruloplasmin	Pulmonary damage	sheep
Haptoglobin	Inflammation	Goat
Serum Amyloid A	Inflammation	Goat
Fibrinogen	Inflammation	Goat
Acid soluble glycoprotein	Inflammation	Goat

attractive method that also enables determination of other biochemical parameters, providing a useful prognostic tool of animals health status and the degree of possible threats. A future diagnostic application of APPs is their use as part of pre-slaughter examination of slaughter animals. Such procedures should significantly improve the detection rate of animals suffering from subclinical inflammatory processes (Veas, 2011).

Serum samples are the most common sample used to measure the levels of APPs in both companion and farm animals. Recently, other specimens such as saliva or meat juice has been successfully used as samples for APPs measurements in dog (Parra et al., 2005) and pig (Gutiérrez et al., 2009).

There is a broad spectrum of possible applications of APPs based diagnostics for use with animals. It is necessary to develop and optimize rapid field tests that allow determination of APPs in a short time period, after collection of blood or milk samples from animals (Tóthová et al., 2013).

Modulation of some of acute phase proteins and related with some of disease in farm animals

APPs increase and down regulation of expression of APPs has been related with a number of farm animal diseases as show in Table 3 (Ceciliani et al., 2012; Petersen et al., 2004; Eckersall et al., 2007; Chan et al., 2010; Orro et al., 2011).

CONCLUSION

The APR and APPs generally can be used for assessment of animal health, including starvation and growth. A pro-inflammatory cytokines and blood proteins of hepatic origin are potential variables for monitoring the changes induced. APPs are more useful for monitoring health than the cytokines, because the latter are cleared from the circulation within a few hours, whereas APP levels after a single stimulus remain unchanged for 48 hours or longer. Determination of APPs can help in monitoring health of individual subjects especially when several acute phase variables are combined in an index.

The prospect of using APPs as biomarkers of inflammation and infection for veterinary applications has inspired a significant body of research, including the development of antibodies and other quantitative methods for analyzing APP expression during disease in food animal species. The interest application of APPs as potential veterinary biomarkers needs more studies about the proteomic strategies for the evaluation of APPs and measures of the host response in complex biological samples as well as accelerate further understanding of the innate immune mechanisms and pathophysiology of infection or inflammation in animals.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCE

Abbas, A. K., Lichtman, A. H., & Pillai, S. (2012). *Basic immunology: Functions and disorders of the immune system* (4th edition). Elsevier Health Sciences, Philadelphia, PA. p. 40.

Baybutt, H. N., & Holsboer, F. (1990). Inhibition of macrophage differentiation and function by cortisol. *Endocrinology*, 127(1), 476-480.

Ceciliani, F., Ceron, J. J., Eckersall, P. D., & Sauerwein, H. (2012). Acute phase proteins in ruminants. *Journal of proteomics*, 75(14), 4207-4231.

Ceciliani, F., Giordano, A., & Spagnolo, V. (2002). The systemic reaction during inflammation: the acute-phase proteins. *Protein and Peptide Letters*, 9(3), 211-223.

Cerón, J. J., Eckersall, P. D., & Martínez-Subiela, S. (2005). Acute phase proteins in dogs and cats: current knowledge and future perspectives. *Veterinary Clinical Pathology*, 34(2), 85-99.

Chan, J. P. W., Chang, C. C., Hsu, W. L., Liu, W. B., & Chen, T. H. (2010). Association of increased serum acute-phase protein concentrations with reproductive performance in dairy cows with postpartum metritis. *Veterinary Clinical Pathology*, 39(1), 72-78.

Cray, C., Zaias, J., & Altman, N. H. (2009). Acute phase response in animals: a review. *Comparative Medicine*, 59(6), 517-526.

Davidson, J. S. (2013). Inflammation and acute phase proteins in haemostasis. Acute phase proteins. Retrieved 15 October 2015 from http://www.intechopen.com/books/acute-phase-proteins/inflammation-and-acute-phase-proteins-in-haemostasis.

Eckersall, P. D., & Bell, R. (2010). Acute phase proteins: Biomarkers of infection and inflammation in veterinary medicine. *The Veterinary Journal*, 185(1), 23-27.

Eckersall, P. D., Lawson, F. P., Bence, L., Waterston, M. M., Lang, T. L., Donachie, W., & Fontaine, M. C. (2007). Acute phase protein response in an experimental model of ovine caseous lymphadenitis. *BMC Veterinary Research*, 3, Article number 35.

Gabay, C., & Kushner, I. (1999). Acute-phase proteins and other systemic responses to inflammation. *New England Journal of Medicine*, 340(6), 448-454.

Gómez-Laguna, J., Salguero, F. J., Pallarés, F. J., Rodríguez-Gómez, I. M., Barranco, I., & Carrasco, L. (2011). Acute phase proteins as biomarkers in animal health and welfare. In: Veas, F. (ed.). *Acute phase proteins as early non-specific biomarkers of human and veterinary diseases* (pp. 259-298). InTech.

Gruys, E., Toussaint, M. J. M., Niewold, T. A., & Koopmans, S. J. (2005). Acute phase reaction and acute phase proteins. *Journal of Zhejiang University Science B*, 6(11), 1045-1056.

Gutiérrez, A. M., Martínez-Subiela, S., Eckersall, P. D., & Cerón, J. J. (2009). C-reactive protein quantification in porcine saliva: a minimally invasive test for pig health monitoring. *The Veterinary Journal*, 181(3), 261-265.

Heinrich, P. C., Castell, J. V., & Andus, T. (1990). Interleukin-6 and the acute phase response. *Biochemical journal*, 265(3), 621-636.

Ingenbleek, Y., & Young, V. (1994). Transthyretin (prealbumin) in health and disease: nutritional implications. *Annual Review of Nutrition*, 14(1), 495-533.

Jain, S., Gautam, V., & Naseem, S. (2011). Acute-phase proteins: As diagnostic tool. *Journal of Pharmacy and Bioallied Sciences*, 3(1), 118-127.

Khan, F. A., & Khan, M. F. (2010). Inflammation and acute phase response. *International Journal of Applied Biology and Pharmaceutical Technology,* 1(2), 312-321.

Kushner, I. (1982). The phenomenon of the acute phase response. *Annals of the New York Academy of Sciences*, 389, 39-48.

Murata, H., Shimada, N., & Yoshioka, M. (2004). Current research on acute phase proteins in veterinary diagnosis: an overview. *The Veterinary Journal*, 168(1), 28-40.

Nazifi, S., Tabande, M. R., Hosseinian, S. A., Ansari-Lari, M., & Safari, H. (2011). Evaluation of sialic acid and acute-phase proteins (haptoglobin and serum amyloids A) in healthy and avian infection bronchitis virus-infected chicks. *Comparative Clinical Pathology*, 20(1), 69-73.

O'Reilly, E. L., & Eckersall, P. D. (2014). Acute phase proteins: a review of their function, behaviour and measurement in chickens. *World's Poultry Science Journal*, 70(1), 27-44.

Orro, T., Pohjanvirta, T., Rikula, U., Huovilainen, A., Alasuutari, S., Sihvonen, L., Pelkonen, S., & Soveri, T. (2011). Acute phase protein changes in calves during an outbreak of respiratory disease caused by bovine respiratory syncytial virus. *Comparative immunology, microbiology and infectious diseases*, 34(1), 23-29.

Parra, M. D., Tecles, F., Subiela, S. M., & Cerón, J. J. (2005). C-reactive protein measurement in canine saliva. *Journal of Veterinary Diagnostic Investigation*, 17(2), 139-144.

Petersen, H. H., Nielsen, J. P., & Heegaard, P. M. H. (2004). Application of acute phase protein measurements in veterinary clinical chemistry. *Veterinary Research*, 35(2), 163-187.

Tirziu, E. (2009). Acute-phase proteins in immune response. *Lucrări Ştiinţifice Medicină Veterinară*, 42(1), 329-339.

Tóthová, C., Nagy, O., Kovac, G., & Janciauskiene, S. (2013). The use of acute phase proteins as biomarkers of diseases in cattle and swine. *Acute Phase Proteins*. Pp. 103-136.

Tothova, C., Nagy, O., Seidel, H., & Kováč, G. (2011). Acute phase proteins as markers of diseases in farm animals. In: Veas, F. (ed.). *Acute phase proteins as early non-specific biomarkers of human and veterinary diseases* (pp. 231-258). InTech.

Uhlar, C. M., & Whitehead, A. S. (1999). Serum amyloid A, the major vertebrate acute-phase reactant. *European Journal of Biochemistry*, 265(2), 501-523.

Veas, F. (2011). Acute phase proteins as early non-specific biomarkers of human and veterinary diseases. *Janeza Trdine* 9, 51000 Rijeka, Croatia. Pp. 231- 259

Wilson, C. R., Regnier, F. E., Knapp, D. W., Raskin, R. E., Andrews, D. A., & Hooser, S. B. (2008). Glycoproteomic profiling of serum peptides in canine lymphoma and transitional cell carcinoma. *Veterinary and Comparative Oncology*, 6(3), 171-181.

Yoshioka, M., Watanabe, A., Shimada, N., Murata, H., Yokomizo, Y., & Nakajima, Y. (2002). Regulation of haptoglobin secretion by recombinant bovine cytokines in primary cultured bovine hepatocytes. *Domestic Animal Endocrinology*, 23(3), 425-433.