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THE ROLE OF ACUTE-PHASE PROTEINS AS BIOMARKERS FOR HEALTH AND DISEASE IN CAMELS: A COMPREHENSIVE REVIEW

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ABSTRACT

This review highlights the importance of acute phase proteins (APPs) as key biomarkers in both healthy and sick camels (*Camelus dromedarius*). The study of APPs in camels has gained significant interest in recent years due to their potential roles in health, disease diagnosis and immunological responses. This review provides an overview of their roles in maintaining physiological balance and their possible applications in veterinary diagnostics, examining how APPs are influenced by factors such as age, sex, pregnancy, lactation, postpartum changes and male reproductive aspects. It discusses camels' responses to various clinical conditions, including trypanosomosis, pneumonia, mastitis, urinary and genital tract infections, as well as transportation stress. The APPs act as early indicators of physiological disturbances and disease, making them valuable tools for monitoring animal health. The review also examines the significance of APPs in identifying subclinical infections and monitoring disease progression. Due to their sensitivity to physiological and pathological stimuli, APPs present a promising avenue for advancing camel medicine through early diagnosis, prognosis and treatment monitoring. This review aims to synthesise existing research on APPs in camels, focusing on their biological significance, response to various stressors and potential applications in clinical practice. It also emphasises the need for future research to establish reference ranges, understand species-specific APP responses and develop reliable assays for clinical application. Ultimately, this review highlights the potential of APPs to significantly improve health outcomes and enhance disease management in camels, instilling hope and optimism in their utilisation.

Key words: Acute-phase proteins, biomarkers, camel, diseases, health

The study of acute-phase proteins (APPs) in camels has attracted interest in recent years due to their potential roles in health and, importantly, disease diagnosis. These proteins, acting as biomarkers for various physiological and pathological conditions, are significant in veterinary medicine and animal health management. Various intrinsic and extrinsic stressors trigger acute-phase and inflammatory responses, thereby suppressing the physiological functions of animal tissues (Alotiby, 2024). The increasing awareness of animal welfare and global warming has sparked a growing interest in the relationships between acute-phase protein expression and different stressors, including climate change, malnutrition, injury and infection. Despite camels possessing unique physiological adaptations to maintain homeostasis and to thrive in arid and harsh environments (Ouajd and Kamel, 2009; Fesseha and Desta, 2020; Kandeel *et al,* 2022), all forms of stressors compromise immune function and consequently increase susceptibility to infectious diseases (Al Jassim and Veerasamy, 2015; Allam *et al,* 2017; Hafez and El-Rayes, 2023). Therefore, understanding these relationships is crucial for developing effective strategies to mitigate the impact of stressors on camel health.

The APPs, a group of proteins expressed during the acute phase reaction, hold significant potential as stress biomarkers and serve as a valuable tool for diagnosing inflammatory diseases in animals. Their role in this area has been thoroughly established, providing a strong foundation for their application (Tothova *et al,* 2014; Eckersall, 2019; Alves *et al,* 2020; Bozukluhan and Merhan, 2023). In human medicine, APPs have proven crucial in predicting the effectiveness of cancer therapy and acting as

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reliable markers of successful organ transplantation, highlighting their intertwined potential in cancer treatment and transplantation outcomes (Aoyama *et al,* 2024). Furthermore, Powanda and Moyer (2021) and Tharwat (2023) have proposed that selected APPs should be integrated into future and ongoing clinical studies, opening a promising pathway for understanding disease progression in both acute and chronic conditions in camels and other animal species. This emphasises their potential in veterinary medicine. This optimistic outlook for camel health management, driven by the potential of APPs, should inspire confidence within the veterinary community, encouraging a more proactive approach to health and animal welfare.

At the onset of an inflammatory process, which usually occurs following a physiological condition, acute protein reactant (APR) acts as a non-specific systemic response that rapidly resolves within 1−2 days to restore homeostasis (Eckersall and Bell, 2010; Lakota *et al,* 2011). This complex process involves the upregulation and downregulation of specific positive and negative acute-phase proteins or reactants (APPs or APRs). Haptoglobin (HP), serum amyloid A (SAA), fibrinogen (FB), ferritin (FR), ceruloplasmin (CP), C-reactive protein (CRP) and secretory non-pancreatic phospholipase 2-II (sPLA2-II) are recognised as positive APPs. Conversely, albumin, transferrin, antithrombin (AT), transthyretin (TTR), retinol-binding protein (RBP) and corticosteroid-binding globulin (CBG) are classified as negative APPs.

In hepatocytes, APPs synthesis is a spontaneous reaction to disrupted homeostasis, triggered by the acute phase response (Cray *et al,* 2023). Under normal physiological conditions, acute phase responses stabilise rapidly for a period of several days to weeks. However, the expression of APPs remains altered during stress, transportation, inflammation, infections and chronic diseases in animals (Espinosa *et al,* 2020; Mohamed *et al,* 2021; Razavi *et al,* 2023; Bozukluhan and Merhan, 2023). The classification of APPs primarily depends on changes in their concentration. For instance, a 10- to 100-fold increase is considered major, e.g., SAA and CRP. A 2−10−fold and less than 2−fold increase is classified as moderate and minor APPs α1-acid glycoprotein, FB, HP and CP, respectively (Khalil and Al-Humadi, 2020). Recently, numerous investigators have intensively studied and reviewed APPs variations during various infections and inflammatory states in animals (Alves *et al,* 2020; Bozukluhan and Merhan, 2023; Saco and Bassols, 2023; Smock, 2023; Tharwat, 2023).

The correlation between the strength of APPs, key stress biomarkers and the physiological adaptation of camels to hot environments is a fascinating area of study in camel medicine. Therefore, many researchers have used APPs measurement as a screening test to assess stress, prognosis, diagnosis and treatment of various camel diseases (EL-Bahr and EL-Deeb, 2016; Greunz *et al,* 2018; Tharwat and Al-Sobayil, 2018; Bakhet *et al,* 2021; El-Deeb *et al,* 2022). Therefore, this review aims to update basic knowledge on APPs in camels, suggesting their possible clinical application as a valuable prognostic and diagnostic tool in camel medicine.

Comparative studies indicate that studying APPs in camels can provide insights into the differences and similarities in immune responses across various species, thereby enriching our understanding of animal physiology and immunology (El-Deeb *et al,* 2019; Hussen and Schuberth, 2021). Recent studies on APPs in camels have focused on identifying specific proteins, understanding their roles in the immune response and evaluating their potential as diagnostic biomarkers (Tharwat, 2020; Bakhet *et al,* 2021; El-Deeb *et al,* 2022; Tharwat, 2023). These studies utilised various methods, including proteomic analysis, Enzyme-Linked Immunosorbent Assay (ELISA) and gene expression studies. Proteomic analysis is commonly employed to identify and quantify APPs in camel serum, whereas ELISA measures the concentration of specific APPs. Gene expression studies were conducted to comprehend the regulation of APPs at the molecular level.

Positive APPs

Positive APPs are primarily produced by the hepatocytes and released into the blood in response to cytokine stimulation (Alves *et al,* 2020). Pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumour necrosis factor-alpha and interleukin-1-beta, activate specific receptors on target cells, promoting metabolic changes that lead to local and systemic effects, including APPs (Yoshioka *et al,* 2002; Peterson *et al,* 2004; Tizard, 2018). For instance, IL-6 plays a critical role in the APR by stimulating the hepatocytes to generate positive APPs during inflammation, infection, or other stressors (Ceron *et al,* 2010; Gulhar *et al,* 2023). The APPs are not only essential for the innate immune response in camels but also in other animal species. They also serve as crucial biomarkers for various health conditions, animal welfare and food safety, making them invaluable tools for veterinarians

and researchers (Greunz *et al,* 2018; Tharwat, 2023). Several critical positive APPs, including HP, SAA, FB, FR, CP, CRP and spla2-II, have been identified in camels, with each playing a vital role in health, the body's immune response and diseases (Baghshani *et al,* 2010; El-Deeb *et al,* 2022).

Haptoglobin (HP), an α2-globulin, is a major APP in all animal species (Faye and Bengoumi, 2018; Tothova *et al,* 2014; Crays *et al,* 2023). It significantly enhances the stability of haemoglobin's peroxidase activity (Peterson *et al,* 2004). The HP's protective role against oxidative cascade reactions is associated with cell-free haemoglobin (Hb) and the propagation of oxidative reactions through pseudo-peroxidase activities of Hb, facilitated by binding to free Hb (Alayash *et al,* 2013). The Hb-HP complex, released from erythrocytes, prevents oxidative damage and preserves iron, as well-documented by Banerjee *et al* (2012). This complex, once formed, can be efficiently discharged by receptor-mediated endocytosis through the reticuloendothelial system, a process that reinforces the body's efficient defense mechanisms (Vlasova, 2018).

The primary role of HP, its bacteriostatic effect, is related to the Hb-HP complex properties, as it restricts the free iron accessible to bacteria. Peterson *et al* (2004) have comprehensively reviewed the functions of HP, including its immunomodulatory effects, stimulation of angiogenesis, regulation of fatty acid metabolism, induction of lipid synthesis in the liver and inhibition of neutrophil respiratory burst activity. As a versatile scavenger protein, HP is a fascinating area of study due to its diverse properties, such as antimicrobial, anti-inflammatory and antioxidant effects (Wan *et al,* 2021). The binding of HP to neutrophil integrins CD11b and CD18 produces anti-inflammatory effects. At the same time, its role as an antimicrobial and antioxidant agent is linked to its ability to remove free Hb from the blood, thereby reducing iron availability to pathogens. Notably, as a positive APP, HP levels increase during inflammation. This feature highlights its diagnostic value during intravascular haemolysis and inflammation (Gulhar *et al,* 2023). Elevated HP levels are associated with inflammation, infection and haemolytic anaemia (Cray *et al,* 2009).

According to Nazifi *et al* (2012), the reference values for serum HP in healthy dromedary camels aged between one and five years were 0.11–0.61 g/L, which were higher than those of cattle (0.022–0.047 g/L). Age and sex did not significantly affect serum HP concentration in dromedaries (Nazifi *et al,* 2006; Baghshani *et al,* 2010). Camels showed markedly high HP levels on day 21 postpartum, which contributed to a decrease in both the frequency and severity of illnesses (El-Sayed, 2025).

Numerous studies have highlighted the importance of HP as a clinically valuable parameter for evaluating the occurrence and severity of inflammatory diseases in camels. The HP levels were significantly higher in pneumonic camel calves than in healthy ones (El-Deeb, 2015). Bakhet *et al* (2021) reported substantial HP elevations in interstitial and fibrinous bronchopneumonia compared to control camels, suggesting that HP serves as a diagnostic parameter for pneumonia in camels. In response to parturition stress in dromedary camels, HP values demonstrated a significant increase relative to the values measured pre- and post-partum, indicating a normal physiological response to the release of cortisol-stress hormone (Tharwat and Al Sobayil, 2015). A notable rise in serum HP was also observed in racing camels, highlighting that non-inflammatory and psycho-physical stressors trigger the combined activation of both sympathoadrenal and the hypothalamic–pituitary–adrenal axes (Tharwat and Al-Sobayil 2018; Mohamed *et al,* 2021; El-Deeb and Abdelghani, 2022), suggesting that HP is not merely a biomarker, but a promising tool for assessing the health status of racing camels.

The HP is also considered a vital prognostic and diagnostic biomarker in camels suffering from various infections. Notable increases in HP levels have been documented in camels naturally infected with *Coxiella burnetii*, *Mycoplasma hemolamae*, *Toxoplasma gondii* and *Trypanosoma evansi* (Azma *et al,* 2015; El-Deeb and Elmoslemany, 2015; El-Bahr and El-Deeb, 2016; El-Deeb *et al,* 2019; Al Matwari *et al,* 2022). Camels with paratuberculosis showed significantly higher HP values compared to healthy controls (El-Deeb *et al,* 2014). Other researchers have suggested that HP may serve as a diagnostic and prognostic marker for respiratory and urinary tract infections, Q-fever and abortion in camels (El-Deeb, 2015; El-Deeb and Buczinski, 2015; Allam *et al,* 2017; El-Deeb *et al,* 2019; Bakhet *et al,* 2021; Hafez and El-Rayes, 2023).

Greunz *et al* (2018) showed that camels with chronic *Corynebacterium* lymph abscess had higher HP levels than healthy ones. The authors studied APPs in surgically castrated males treated with a gonadotropin-releasing hormone vaccine for one week. The HP showed a significant increase after vaccination and castration and remained elevated for seven days, with mild variations in the control group.

A study conducted by El-Deeb and Buczinski (2015) involving 74 camels with urinary tract infections revealed significantly elevated levels of HP in sick animals (2.45 g/L) compared to healthy ones (0.31 g/L). Furthermore, an investigation indicated a notable rise in HP values in pneumonic camel calves compared to their healthy counterparts (El-Deeb, 2015).

Fibrinogen (FB) is a precursor to fibrin, which is essential for blood clot formation, helps wound healing and provides a framework for tissue repair (Bayer, 2022). Elevated FB levels indicate inflammation and can be utilised to diagnose inflammatory diseases and conditions associated with tissue damage (Eckersall, 2000). The plasma FB concentration in camels is similar to that in humans, with values ranging from 150 to 400 mg/dL (Abdel Gader *et al,* 2013). Other researchers have provided a reference range for serum FB in apparently healthy dromedary camels of 3.10−3.27 g/l (Baghshani *et al,* 2010; El-Deeb and Buczinski, 2015). The same authors observed that road transport and urinary tract infections significantly raised FB levels in camels.

Numerous studies have demonstrated markedly higher levels of FB in camels suffering from interstitial and fibrinous broncho-pneumonia compared to healthy animals. These findings suggest that FB may serve as a diagnostic indicator of pneumonia in camels (Bakhet *et al,* 2021; Ahmed *et al,* 2021; Hafez and El-Rayes, 2023). In contrast, the concentration of FB was significantly higher in pneumonic camel calves (5.1±1.30 g/L) than in healthy ones (3.3 ± 0.30 g/L) (El-Deeb, 2015). The authors examined the clinical significance of FB as a diagnostic marker or therapeutic target for treating respiratory diseases in camels. Other researchers investigated the effect of walking and road transport on APP production in camels. They concluded that stress from road transport led to increased APP production, as shown by a significant rise in HP and FB (Mohamed *et al,* 2021). Significantly higher FB levels were observed in camels infected with *Mycoplasma hemolamae* than in healthy animals. Additionally, other researchers found that FB levels increased notably between days three and five, with higher levels observed post-castration in camels (Greunz *et al,* 2018). In female camels, El-Sayed (2025) noted significant increases in FB levels at parturition, whereas levels decreased significantly by the 21st postpartum.

Ferritin (FR), a cytosolic protein found in most tissues, is crucial in iron homeostasis. Its primary function is as an iron-carrier protein that regulates the body's iron levels. Small amounts of FR are secreted into the serum, making it an indirect biomarker of the total iron stored in the body. This property makes plasma FR a valuable diagnostic tool for iron-deficiency anaemia (Wang *et al,* 2010).

Ferritin is also a well-known acute-phase reactant, with levels that reflect both acute and chronic inflammation, as well as infectious diseases (Mahroum *et al,* 2021). Importantly, FR plays a key role during inflammation by sequestering iron, limiting its availability to pathogens and providing a protective function (Moreira *et al,* 2020). Furthermore, Gehrer *et al* (2023) highlighted the physiological role of FR in intracellular Fe dynamics. The review provided insights into the novel iron-dependent mechanisms that influence cell growth, differentiation and viability, as well as prognostic and diagnostic biomarkers for infectious and inflammatory disorders. Additionally, it explored how inflammatory mediators and cytokines affect the regulation and expression of FR. Recently, FR has been established as a critical biomarker for diagnosing viral and bacterial infections, inflammation and other infectious diseases (Chen *et al,* 2023).

Kotla *et al* (2022) provided a comprehensive review of the role of FR, emphasising its importance as a key storage protein in systemic, cellular and intracellular iron homeostasis. At the intracellular level, the FR plays a vital role in regulating iron homeostasis by sequestering excess iron and keeping it in a redox-inactive form, thereby making Fe available either during periods of deficiency or increased demand. In clinical medicine, both cellular and systemic levels of FR are critical indicators of iron status and essential biomarkers for inflammatory, immunological disorders and cancer.

Limited data are available on FR concentration in camels. Recently, Aldujaily *et al* (2025) showed that serum FR levels in healthy dromedary camels aged from one to seven years were 349.00±3.98 µg/L. The same authors noted that age did not significantly influence FR concentration. Ghali *et al* (2020) reported that serum FR concentration was significantly higher in adult male Iraqi camels (371.53±5.34 µg/L) compared to females (328.16±14.58 µg/L). In studies of Iraqi camels, FR values were significantly lower in animals with trypanosomosis and mastitis (Al-Rubaie *et al,* 2020; Darwish, 2023). The authors stutied that measuring serum FR could serve as a reliable marker for mastitis and *Trypanosoma evansi* infection. Furthermore, Aldujaily *et al* (2025) showed a strong link between iron deficiency and pica development in

camels, highlighting the correlation to low serum iron concentration, ferritin levels and persistent dietary iron insufficiency.

Ceruloplasmin (CP), a copper-binding protein with oxidase activity, commonly known as serum ferroxidase, accounts for 95% of blood copper transport; therefore, it contributes to iron metabolism and exhibits antioxidant properties (Fleming and Gitlin, 1990; Adamczyk-Sowa *et al,* 2016; Lopez *et al,* 2023). In the hepatocytes, CP is synthesised as a single polypeptide chain and secreted into the blood, where it binds 6 copper atoms per molecule. The CP participates in various biological processes, including copper transport, iron metabolism, tissue angiogenesis and antioxidant activity (Khalil and Al-Humadi, 2020). In protein electrophoresis, CP appears in the γ-globulins fraction, with 95% of plasma containing a copper-bound complex (Neşelioğlu *et al,* 2022). Essamadi *et al* (2002) isolated and purified CP from a 6-month-old young camel. They showed that the molecular weight of CP was approximately 130.000 Da using non-reducing SDS-electrophoresis, with slightly higher electrophoretic mobility than the human protein, indicating that the protein is more acidic and compact, with no differences between the adult and young camels.

Higher CP levels indicated inflammatory responses, infection and liver diseases (Lopez *et al,* 2023). Human studies have demonstrated that changes in copper homeostasis and CP are linked to Alzheimer's disease (Squitti *et al,* 2007). Additionally, CP has been recognised as a useful serum biomarker for chronic demyelinating and neurodegenerative processes, involved in oxidative stress mechanisms rather than an APP (Adamczyk-Sowa *et al,* 2016).

Faye *et al* (1995) previously reported a mean value of 41.4 ± 2.6 UO for CP in female camels over one year old. The authors studied that season, mineral supplementation and health status significantly influenced serum CP concentration. Nazifi *et al* (2000) found that age and sex did not significantly affect CP levels. El-Bahr and El-Deeb (2016), Allam *et al* (2017) and Hafez and El-Rayes (2023) found that camels with *Trypanosoma evansi* infection and respiratory diseases had significantly higher CP levels than healthy camels. During postpartum and in she-camels with endometritis, the CP values consistently exceeded those of healthy females (El-Deeb *et al,* 2022; El-Sayed, 2025).

Serum amyloid A (SAA) consists of a group of APPs predominantly produced in the liver. However, these may also be found in other body systems, including the stomach and intestines, during chronic infection (Den Hartigh *et al,* 2023). Typically, plasma levels of SAA remain low; however, these can increase sharply to 1,000 times their normal level in response to infection, inflammation and trauma (Zhou *et al,* 2016). Consequently, SAA serves as a valuable diagnostic and prognostic marker, as well as a therapeutic biomarker for monitoring infections, trauma, inflammatory responses and cancer (De Buck *et al,* 2016). The SAA attracts immune cells to the site of inflammation and promotes the activity of enzymes that break down the extracellular matrix; therefore, it is considered a highly sensitive marker of inflammation, with levels rising significantly during acute inflammatory responses. As a result, it is believed that SAA play various roles during the acute phase of these conditions. Recent research has also indicated that SAA is involved in immune regulation, particularly T-cell immunity (Chen *et al,* 2023).

Tharwat and Al-Sobayil (2018) investigated the impact of electroejaculation (EEJ) on the concentrations of SAA in camels. The authors found that SAA levels significantly increased in response to EEJ stress. This response activates the combined actions of the hypothalamic-pituitary axis, the sympathoadrenal system and the release of glucocorticoids, along with components of cellular immunity, ultimately enhancing hepatic synthesis and the release of APPs. The elevated levels of SAA, along with corresponding increases in cortisol, are likely a result of physical stress. In camels, Greunz *et al* (2018) indicated that SAA exhibited no change in surgically castrated males treated with a gonadotropin-releasing hormone vaccine for one week.

In female dromedary camels, significant increases in SAA were observed at parturition, compared to values pre- and post-partum, indicating the camel's immune response to parturition stress (Tharwat and Al Sobayil, 2015; El-Sayed, 2025). Significantly elevated levels of SAA have been observed in camels suffering from pneumonia and other respiratory diseases (Allam *et al,* 2017; Hafez and El-Rayes, 2023). The SAA levels were noticeably higher in dromedary camels with lameness due to punctured foot and traumatic injuries than in healthy camels. This suggests that SAA can be an effective diagnostic parameter for monitoring the response to lameness treatment (El-Deeb and Abdelghani, 2022). Chronic infections caused by *Toxoplasma gondii* and *Trypanosoma evansi* in camels have been associated with markedly increased SAA concentrations (Azma

et al, 2015; El-Bahr and El-Deeb, 2016). Additionally, Allam *et al* (2017) found that camels suffering from respiratory diseases had significantly elevated SAA levels compared to healthy camels. Moreover, a study on APPs in pneumonic camel calves revealed significantly higher SAA values relative to healthy counterparts (El-Deeb, 2015; Hafez and El-Rayes, 2023).

C-reactive protein (CRP) is an APP produced by the liver, with levels increasing in response to inflammation, mainly triggered by interleukin-6 (IL-6). It plays a key role in identifying and clearing foreign pathogens and damaged cells by activating the classical complement pathway and aiding phagocytic cells. While it has pro-inflammatory and anti-inflammatory effects, elevated CRP levels can indicate bacterial infections and systemic inflammation (Singh *et al,* 2025). Mouliou (2023) comprehensively reviewed the CRP role in clinical medicine as a recognised biomarker for identifying or excluding inflammation. The author noted that numerous scientific efforts have been aimed at uncovering its direct pleiotropic functions, such as its role as a vital immunochemical marker for various medical issues, including infections like sepsis, diseases, autoimmune disorders, malignancies and other health conditions, which have gained significant popularity.

In humans, CRP has been identified as a key marker of the presence, severity and treatment efficacy of infection (Powanda and Moyer, 2021). The authors noted that a high-sensitivity CRP test was more effective than the standard test and can be used to assess the risk of developing coronary artery diseases. In another study, high-sensitivity CRP has been established as an inflammatory biomarker associated with cardiovascular disease in patients (Osawa *et al,* 2024).

Few studies were conducted in camels to assess CRP as a negative APP. Bakhet *et al* (2021) reported highly significant elevations in CRP in interstitial pneumonia and fibrinous bronchopneumonia compared to healthy camels. The study results concluded that CRP is a diagnostic parameter for pneumonia in camels. Other studies have noted that camels with respiratory diseases have substantially increased serum CRP levels (Hafez and El-Rayes, 2023).

Negative APPs

Negative APPs are those whose plasma concentrations decrease in response to inflammation, infection, or other stressors. In camels, several proteins have been identified as negative APPs: albumin, transferrin, AT, TTR, RBP and CBG.

Albumin, the main negative APP across all mammalian species, is the most abundant plasma protein, constituting approximately 50−60% of total protein. Albumin plays a vital role in maintaining animal health, serving as a nutrient source and regulating osmotic pressure. Hypoalbuminemia, a condition characterised by low albumin levels, can result from protein loss due to kidney or gastrointestinal diseases and/or oedema caused by decreased synthesis linked to liver disease or malnutrition (Gounden *et al,* 2023).

In camels, albumin comprises 35−40 mg/ml of plasma proteins, with essential functions such as regulating blood osmotic pressure, maintaining blood pH and transporting fatty acids, hormones and drugs (Eckersall, 2008; Faye and Bengoumi, 2018). As dromedary camels are well-adapted to hot, dry climates, their plasma osmolality increases during water deprivation, making serum albumin crucial for blood pressure regulation (Malik *et al,* 2013). Furthermore, research examined serum protein and albumin patterns in growing, pregnant camels and during different lactation stages and found that albumin levels varied throughout the growth phase and lactation period (Elkhair, 2024; Adam and Elkhair, 2023). These fluctuations suggest that physiological states, such as growth and lactation and water deprivation can influence albumin concentrations, which may have implications for interpreting albumin levels during health and disease states.

Albumin is recognised as a negative APP in camels, suggesting that its serum levels decline during inflammatory responses. Hypoalbuminemia is part of the APR, during which hepatocytes concentrate on generating positive APPs (HP, SAA and FB) to combat infection or inflammation, leading to a reduction in albumin synthesis (Eckersall and Bell, 2010). Additionally, hypoalbuminemia may occur during inflammation when the liver prioritises the production of positive APPs (Gounden *et al,* 2023). Studying the biochemical aspects of camel albumin, identified as a positive APP, could enhance veterinarians' understanding of camel health, nutrition and disease management (Tharwat, 2023). Consequently, monitoring albumin levels in camels can be a useful diagnostic and prognostic parameter for evaluating the presence and severity of inflammatory conditions, aiding veterinarians in

assessing disease progression and the effectiveness of treatment strategies.

A study by El-Deeb and Elmoslemany (2015) found that urinary tract infections in camels exhibited significantly lower serum albumin levels compared to healthy controls. The authors explained that hypoalbuminemia was accompanied by elevated levels of positive APPs like HP, SAA and FB, indicating an active inflammatory response. Similarly, research on respiratory diseases in camels reported decreased serum albumin levels in affected animals (Greunz *et al,* 2018; Bakhet *et al,* 2021). The studies highlighted that, alongside the reduction in albumin, there were significant increases in pro-inflammatory cytokines and positive APPs, underscoring albumin's role as a negative APP during inflammation. Furthermore, Hafez and El-Rayes (2023) identified the most significant bacteria responsible for pneumonia in diseased camels, which exhibited notable increases in albumin levels, accompanied by substantial increases in APPs, including FB, CP, HP and SAA, compared to the control group.

Transferrin, an iron-binding protein, is an essential component of the body's iron transport system. Its levels decrease during inflammation, reducing iron availability to pathogens. With its strong affinity for f_e 3+ iron, it effectively binds almost all plasma iron, ensuring minimal free iron levels in the body. This process facilitates the delivery of f_e 3+ ions, a crucial function. The transferrin-iron complex, with its impressive turnover rate of approximately ten times per day, efficiently meets the demands of erythropoiesis. Transferrin's role in regulating iron release from the reticuloendothelial system and its absorption by the bone marrow is vital. The systemic iron homeostasis is heavily dependent on the regulation of its absorption, primarily in the proximal portion of the small intestine (Ogun and Adeyinka, 2022). This regulation is primarily facilitated by the binding of iron to transferrin, which transports it to various tissues and organs.

Studies on the role of transferrin in healthy and diseased camels showed that anaemic camels had markedly lower serum iron levels and reduced transferrin saturation percentage compared to healthy ones (Al-Dhalimy and Al-Hadithy, 2017). A study identified iron deficiency in camels, particularly among young males and those with low red blood cell counts and haemoglobin levels, which were associated with reduced transferrin levels (Al-Dhalimy *et al,* 2020). Additionally, camels infected with *Trypanosoma evansi* and those with mastitis demonstrated a significant decrease in total serum iron and ferritin levels and transferrin saturation (Al-Rubaie *et al,* 2020; Darwish, 2023). In contrast, the same authors found that infected male and female camels of different ages exhibited an increase in total iron-binding capacity and unsaturated iron-binding capacity, indicating profound systemic effects on iron metabolism. These findings underscore the diagnostic relevance of transferrin in monitoring camel health and managing disease-related anaemia, inspiring further research and exploration in the field of camel health for veterinarians, animal health researchers and veterinary science students.

Antithrombin (AT) is a serum protein produced by the liver, typically found at concentrations of 0.125 to 0.160 mg/ml. The anticoagulant properties of AT explain the role of heparin in treating and preventing thrombosis, as heparin binds to AT and induces a conformational change that significantly enhances AT's ability to inhibit reactions of the coagulation cascade. Beyond its role in blood coagulation, it also promotes the release of various compounds that help reduce inflammation (Rezaie and Giri, 2020). Regarding coagulation, AT is essential in preventing blood clotting by neutralising thrombin and other protease enzymes involved in the blood coagulation pathway. During acute inflammation, reduced AT levels may lower the risk of excessive clotting during infections. Therefore, AT is a pivotal regulator of coagulation and inflammation, with levels rising during acute inflammatory responses. In camels suffering from pneumonia, notable increases in APPs, such as HP and FR, have been observed, suggesting a corresponding rise in AT during such responses (Greunz *et al,* 2018; Ahmed *et al,* 2021).

In human medicine, optimising AT is a key treatment consideration, especially in high-risk scenarios such as pregnancy, postpartum period, surgery and trauma for individuals with AT deficiency (Rodgers and Mahajerin, 2023). Furthermore, the relationship between inflammation and haemostasis is vital; AT's role in maintaining coagulation balance is crucial, particularly in scenarios like disseminated intravascular coagulation, which is well-documented (Schlömmer *et al,* 2021).

Although, AT is a vital component of the APR, it is essential to emphasise that its levels undergo significant fluctuations in all inflammatory conditions. Notably, there is a lack of studies examining AT as a key APP in camels. Therefore, it is necessary to conduct further research to develop a comprehensive knowledge of its behaviour across different disease

states. Consequently, assessing AT alongside other camel APPs can provide valuable insights into the severity of inflammatory diseases and their impact on coagulation status, potentially transforming our understanding of these conditions.

Transthyretin (TTR), also known as prealbumin, is primarily produced in the liver. It serves as the primary transport protein for thyroxine, retinol-binding protein and vitamin A, showing varying affinities across mammalian species (Tóthová and Nagy, 2018). The TTR is crucial for regulating thyroid hormones, which are responsible for maintaining metabolic balance and thermoregulation in arid regions (Sabatino and Vassalle, 2025).

In humans, measuring TTR concentrations serves as a diagnostic tool for certain diseases; however, it is more commonly used as a nutritional biomarker to evaluate protein-calorie malnutrition, as well as a prognostic indicator in critically ill patients (Dellière *et al,* 2021). A study by Cotrina *et al* (2021) confirmed TTR's role in Alzheimer's disease as a neuroprotective agent through a drug discovery programme focusing on chaperone-like small-molecule compounds that enhance TTR/Amyloid-beta interactions. Furthermore, Ranasinghe *et al* (2022) thoroughly reviewed the function of TTR as a biomarker for disease prognosis, nutritional and refeeding status and protein-energy malnutrition. The same authors noted that TTR is also the only protein significantly linked to changes in lean body mass. Notably, recent research has highlighted TTR's roles in cell biology, particularly in supporting the health of neuronal, central and peripheral nervous systems, influencing and regulating cellular proliferation and fate, metabolism, angiogenesis and cancer (Magalhães *et al,* 2021). The authors explained that TTR's molecular mechanisms may go beyond its carrier functions, including receptor interactions and activation of intracellular signaling pathways.

In veterinary medicine, various studies have assessed TTR values in specific diseases such as protein-energy malnutrition in rats and neonatal calf diarrhoea (Henze *et al,* 2008; Tóthová and Nagy, 2018); however, its importance in animal health is rarely studied. An increase in TTR levels was observed in neonatal calves following colostrum intake; however, it gradually declines until the 3rd month of life, indicating adequate nutrition and liver synthesis (Tóthová *et al,* 2015). In contrast, TTR decreased in dogs with hypothyroidism and chronic renal failure (Piechotta *et al,* 2012; Raila *et al,* 2007). Therefore, further research is required to understand how various diseases affect TTR levels in animals.

Although direct studies on TTR in camels are limited, existing proteomic and serum protein electrophoresis research highlight its vital role in helping these animals physiologically adapt to harsh desert conditions. Furthermore, investigations into the functions of hormone-binding and regulatory proteins suggest that TTR may play a significant part in camel homeostasis by mediating thyroid hormone transport and stabilisation in a thermally stressful environment (Palha, 2002). Studies on serum protein electrophoretic profile of healthy dromedary camels fractionated serum proteins to albumin, α1 and 2, β1 and 2 and γ-globulins; however, TTR was not directly identified, it typically migrates in the prealbumin or alpha-globulin region, indicating its likely inclusion in the profile (Ahmadi-hamedani *et al,* 2014; Elkhair and Hartmann, 2014; Abdoslam *et al,* 2018; Adam and Elkhair, 2023). Furthermore, a comprehensive proteomic analysis of various camel organs demonstrated increased expression of proteins associated with metabolic regulation and cellular stress responses (Warda *et al,* 2013). Therefore, these studies reinforce the concept that camel proteins, including those involved in thyroid hormone transport, are uniquely adapted for stability and function under physiological stress; however, direct genetic characterisation of TTR in camels remains an area for future research, particularly in the molecular and functional expression of TTR in camels, which is warranted to fully elucidate its significance.

Retinol-binding protein (RBP) is the principal carrier protein of vitamin A in the bloodstream, responsible for transporting it from hepatic storage to peripheral tissues. In mammals, RBP usually circulates in a complex with TTR, stabilising the RBP-retinol complex and preventing renal loss, a phenomenon that has been well studied in both humans and various animal species (Steinhoff *et al,* 2022).

Steinhoff *et al* (2022) thoroughly examined the role of RBP in health and disease across human and mouse models, covering aspects such as thermoregulation, behavioural, neurological and cardiovascular functions, adipose tissue lipolysis, liver fat, embryonic development, retinoid homeostasis, insulin sensitivity, glucose tolerance and vision. The authors described how impaired retinal function impacts visual sharpness following birth. This condition typically stabilises within 4 to

5 months with adequate vitamin A intake; however, it does not normalise on a vitamin A-deficient diet. Nonetheless, the role of RBP in camels remains insufficiently studied. Due to its small molecular size, RBP is generally expected to migrate within the alpha-globulin region in electrophoretic patterns. However, the specific detection and quantification of RBP were not performed, emphasising the need for targeted analytical approaches, such as ELISA or mass spectrometry, to characterise RBP in camels.

Although, direct studies on RBP in camels are limited, the existing literature suggests a probable role for RBP in maintaining vitamin A balance, especially under diverse environmental and physiological conditions. Given the camel's unique adaptations to arid environments and the vital roles of vitamin A in immunity and reproduction, future research should focus on characterising RBP at a molecular level and investigating its physiological regulation. Understanding RBP's function in camels could offer more profound insights into their nutritional needs and the mechanisms that support their resilience. A notable study by Ghardan Mashhadi *et al* (2013) demonstrated that healthy camels had higher serum vitamin A levels, likely due to increased availability of green fodder, with remarkably stable levels across seasons. This stability in vitamin A levels, despite seasonal dietary changes, is a testament to the camel's remarkable resilience and adaptability. It also opens up an intriguing avenue for further research, particularly on the functions of RBP in camels, which may attract the interest of many researchers.

Furthermore, Abdelnour *et al* (2019) comprehensively reviewed the role of retinoic acid (RA), a physiologically active metabolite of vitamin A, as a key regulator of cell differentiation, development and *in vitro* embryonic growth in mammals. The review emphasised RA's role in enhancing oocyte nucleus maturation, cleavage and blastocyst formation, attributed to its anti-apoptotic and antioxidant properties against reactive oxygen species, which were achieved by modulating gene expression pathways. The review also suggested that adding up to 50 nM RA can significantly improve mammalian oocyte maturation media, offering a promising potential for the use of RA in assisted reproductive technology, inspiring further research and development in this field.

In camels, Saadeldin *et al* (2019) investigated All-trans RA and its effects on biological processes such as cell growth and fertility in dromedary camels, focusing on its influence on the *in vitro* maturation (IVM) of the cumulus-oocyte complex. Their results indicated that 20 μM RA supported polar body extrusion and oocyte meiosis, decreased the number of degenerated oocytes, reduced mRNA levels of apoptosis-related genes and transcripts associated with cytoskeleton pathways and increased Transforming Growth Factor beta (TGFβ) expression in cumulus cells compared to controls. The authors emphasised the role of RA in enhancing camel oocyte IVM, establishing a basis for further investigation in cumulus expansion mechanisms and meiotic pathways, in particular those linked to TGFβ in cell growth, differentiation and apoptosis. Although, the study did not directly investigate RBP, it underscores the crucial importance of retinol delivery mechanisms, which likely involve RBP, in reproductive function.

Corticosteroid-binding globulin (CBG), a high-affinity glycoprotein primarily synthesised by the liver and secreted into the blood to regulate the free hormone levels (Litwack, 2018). It modulates the bioavailability of these hormones and ensures their controlled release to target tissues. The potential impact of CBG levels on cortisol availability, particularly in the stress response during the acute phase, underscores the urgency of understanding this process (Cizza and Rother, 2012).

Henley and Lightman (2011) thoroughly reviewed CBG functions in humans, including its role as a transporter protein and as a temperature-sensitive protein that releases cortisol when the temperature rises. In neuroscience studies, CBG has been found in the hypothalamus and cerebrospinal fluid, suggesting a role in regulating glucocorticoid access to their receptors within the central nervous system (Henley and Lightman, 2011). Furthermore, CBG genetic variants were linked to hypotension and fatigue-pain syndrome, affecting cortisol's access to brain glucocorticoid receptors and revealing new mechanisms for regulating glucocorticoid access to the brain and tissues. Conversely, Meyer *et al* (2016) identified several mutations in the SERPINA6 gene that impact CBG expression or glucocorticoid affinity. These mutations were associated with typical clinical symptoms, including depression, headache, hypotension, fatigue, chronic pain, obesity and irregular hypothalamic-pituitary-adrenal axis activity.

In humans, CBG has been extensively studied; however, there are no specific direct investigations into the role and characteristics of CBG in camels. A recent study in dromedary camels linked increased cortisol levels and adrenocortical activity to the clinical observations, post-partum changes and

milk-serum antioxidant markers as indicators of stress (Khalfallah *et al,* 2024). This physiological shift suggests that CBG levels may also rise to buffer the cortisol surge and maintain hormonal balance. Furthermore, the study also identified notable interactions between cortisol and oxidative stress biomarkers, which may highlight the role of CBG in regulating stress responses during the critical physiological transition period.

Consequently, there is an urgent need to study camel CBG, given their unique adaptations to heat stress and dehydration. Accurately measuring CBG levels in camels is crucial for distinguishing between free and bound glucocorticoids, as it aligns with CBG binding, which significantly impacts circulating, free and active cortisol levels. Free cortisol levels are key indicators of physiological stress and metabolic adaptation to extreme conditions. The available physiological evidence and comparative endocrinology studies in humans and other animal species indicate that CBG plays a vital role in the regulation of glucocorticoid hormones and stress adaptation. Future research should concentrate on the molecular characterisation and regulatory mechanisms of camel CBG, which will deepen our understanding of camelid endocrine physiology and pave the way for potential practical applications in this field.

The clinical significance of APPs in camels

The data from this review offers a deep understanding of the behaviour of APPs in camels. This knowledge is both critical and directly applicable to managing their health. In clinical medicine studies, APPs are often utilised as practical tools and clinical biomarkers for detecting and monitoring disease progression. Their theoretical role, especially in comparative immunology research, is fascinating and engaging. The review discusses the assessment of APPs levels and uses practical methods to improve camel health management by identifying subclinical conditions that may not be visible through clinical examination alone. Notably, positive APPs are being studied and actively applied as early biomarkers for inflammation and infection in camel diseases, providing valuable information for timely diagnosis and treatment. The review also indicates that regular monitoring of positive APPs levels in camels is not just a suggestion; it is a practical approach that can help track disease progression and assess the effectiveness of treatments. This proactive approach significantly enhances understanding of immune responses across different species, contributing to the development of cross-species veterinary practices.

Moreover, this review is not merely a discussion; it is a comprehensive analysis that thoroughly addresses the behaviour of negative APPs in camels, emphasising their crucial role for various reasons, such as detecting nutritional status and metabolism, assessing liver function and identifying inflammatory and stress biomarkers, along with disease diagnosis and management. Understanding and applying this knowledge can significantly benefit the health and welfare of camels, offering hope for improved disease diagnosis and management. Since the liver produces many APPs, variations in their levels can provide insights into liver function and health. Albumin, transferrin and other negative APPs act as indicators of nutritional status and their levels can assist in evaluating camels' welfare, health and dietary requirements. A decrease in negative APPs can complement the rise in positive APPs, offering a more holistic view of the animal's inflammatory status.

Therefore, monitoring both camel's positive and negative APPs can improve the accuracy of disease diagnosis, facilitating better management and treatment of infectious and inflammatory diseases. Promising research into AT, TTR, RBP and CBG levels is shedding light on changes in stress hormone metabolism and stress biomarkers, a vital area of study for understanding how camels cope with stressors such as transportation, climate change and emerging diseases. This approach can help veterinarians and researchers develop more effective strategies to ensure the health and welfare of camels, particularly under stressful or disease conditions. Studying the acute phase response in camels can also provide valuable information for comparative immunology and help improve health management practices across different animal species. The application of advanced techniques, such as proteomics and genomics, can further elucidate the regulation and function of negative APPs, leading to improved diagnostic and therapeutic approaches and instilling hope for the future of camel health.

In conclusion, the APPs hold great potential as biomarkers for monitoring health and disease in camels. However, current knowledge remains limited and mainly derived from other animal species. Considering the camel's unique immunophysiological adaptations to arid environments, targeted research is urgently needed. Future studies should establish camel-specific baseline reference ranges and evaluate

the influence of age, sex, breed and reproductive status on APP levels. It is equally essential to characterise APP dynamics in major camel diseases such as trypanosomosis, respiratory infections, mastitis and parasitic infestations, with a focus on their utility for detecting early or subclinical cases. Additionally, assessing the diagnostic sensitivity, specificity and prognostic value of APPs in camels compared to conventional haematological, biochemical and immunological biomarkers will help clarify their role in monitoring treatment responses and welfare under environmental stress. Advancing these studies will significantly improve disease detection, prognosis, herd health management and evidence-based veterinary care, ultimately enhancing the productivity, welfare and resilience of camels in arid and semi-arid regions, where they play a critical socio-economic role.

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