Vol 17 No 2, p 173-180

ANTIOXIDANTS ROLE OF CAMEL MILK IN STREPTOZOTOCIN-DIABETIC RATS

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ABSTRACT

In the present study, investigation was done for the effect of camel milk on antioxidants status in streptozotocin–diabetic rats. Feeding of 250 ml of raw camel milk was given for normal and diabetic rats for 45 days resulted in significant reduction in plasma glucose and significant increase in plasma insulin levels and body weights. In addition, camel milk caused significant increase in the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, reduced glutathione, vitamin C and vitamin E in liver and kidney of diabetic rats with significant decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation in liver and kidney, suggesting its role in protection against lipid peroxidation induced membrane damage. The effects of camel milk were compared with glibenclamide. Results of the present study indicated that camel milk showed antioxidant effect in addition to its antidiabetic effect in type 2 diabetic rats.

Key words: Antioxidants, camel milk, glibenclamide, plasma glucose, plasma insulin, streptozotocin

Diabetes is the most significant chronic disease and cause of death in modern society (Stratmann *et al*, 2007). It is a complicated metabolic disorder characterised by high blood glucose level due to inability of the body cells to utilise glucose properly (Ugochukwu and Babady, 2002). Although several aspects of diabetes can be controlled by insulin treatment and other chemical therapies, numerous complications are common incidents of the disease. Hyperglycemia represents the main cause for these complications of diabetes because elevated glucose concentration directly injures cells and induces lipid peroxidation (Davi *et al*, 2005). Studies have shown that tissue antioxidant status may play an important role in the etiology of diabetes (Al-Azzawie and Saeed, 2006) and oxidative stress may be a common pathway linking diverse mechanisms for the complications in diabetes (Baynes, 1991). Oxidative stress may constitute a focal point for multiple therapeutic interventions, and for therapeutic synergy. Saudi Arabia, a country undergoing a rapid epidemiologic transition, is witnessing a steady increase in the prevalence of diabetes mellitus with the recent estimate of prevalence being as high as 23.7% among adult citizens (Al-Nozha *et al*, 2004). Management of diabetes without any side effects is still a challenge to the medical system.

Camel milk contains low cholesterol, low sugar, high minerals (sodium, potassium, iron, copper, zinc and magnesium), vitamin C (Knoess, 1979), low protein and large concentrations of insulin. Camel milk may be a therapeutic adjunctive option for diabetes mellitus in humans (Agrawal *et al*, 2005). Agrawal *et al* (2003) had reported that camel milk supplementation to type 1 diabetic patients proved effective in reducing glucose levels. Reduction in the occurrence of diabetes mellitus in population consuming camel milk was reported (Breitling, 2002). A study by Agrawal *et al* (2004) had shown the hypoglycemic activity of camel milk in STZ-induced diabetic rats. The hypoglycemic activity of camel milk in chemically pancreatectomised rats was also reported by Agrawal *et al* (2005). The antidiabetic and antihyperlipidemic potential of camel milk in streptozotocin-diabetic rats after 45 days of treatment, was previously reported and the optimum dose was fixed at 250 ml/day/experimental group (Khalid, 2010).

Till date, there was no biochemical investigation has been carried out on the effect of camel milk in tissue antioxidant status of experimental diabetic rats. The present investigation was carried out to study the effect of camel milk on tissue lipid peroxides and antioxidants in rats with STZ-diabetes.

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Materials and Methods

Male albino rats of Wistar strain with body weight ranging from 180 to 200 g were procured from Central Animal House, King Saud University, and they were maintained in an air conditioned room (25 ±1°C) with a 12 h light/12 h dark cycle. Feed and water were provided *ad libitum*. Procedures involving animals and their care were in accordance with the Policy of Research Centre, King Saud University.

The animals were rendered diabetes by a single intraperitoneal injection of streptozotocin (40 mg/kg bodyweight, Sigma-Aldrich, St. Louis, USA.) in freshly prepared citrate buffer (0.1 M, pH 4.5) after an overnight fast and were given 20% glucose solution for 24 h to prevent initial drug-induced hypoglycemic mortality. Streptozotocin injected animals exhibited massive glycosuria (determined by Benedict's qualitative test) and diabetes in streptozotocin rats was confirmed by measuring the fasting plasma glucose concentration, 96 h after injection with streptozotocin. The animals with plasma glucose above 240 mg/dl were considered to be diabetic and used for the experiment.

The animals were randomly divided into five groups of six animals each as given below. Rats of group II and IV were given 250 ml/day of raw camel milk daily through watering bottle instead of water, whereas animals in group I, III and V were given tap water, and rats of group V were given 600 µg/kg body weight of glibenclamide orally once in a day in the morning for 45 days.

Group I : Normal control

Group II : Normal control+raw camel milk (250 ml/day)

Group III : Diabetic control

Group IV : Diabetic rats+ raw camel milk (250 ml/day)

Group V : Diabetic rats+glibenclamide (600 µg/kg body weight) in water

After 45 days of treatment, the animals were fasted for 12 h, anaesthetised between 8:00 a.m. to 9:00 a.m. each morning using ketamine (24 mg/kg body weight, intramuscular injection), and sacrificed by decapitation. Blood was collected in a dry test tube and allowed to coagulate at ambient temperature for 30 min. Blood was collected in tubes with a mixture of potassium oxalate and sodium fluoride (1:3) for the estimation of plasma insulin, glucose, and ethylenediamine tetra acetic acid (EDTA) for the estimation of haemoglobin, glycated haemoglobin. Liver and kidney were immediately dissected out, washed in ice-cold saline to remove the blood. Tissues were sliced into pieces and homogenised in an appropriate buffer (pH 7.0) in cold condition to give 20% homogenate (w/v). The homogenates were centrifuged at 1000 rpm for 10 min at 0°C in cold centrifuge. The supernatants were separated and used for various biochemical estimations.

The estimation of thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxides (HP) was done by the methods of (Niehaus and Samuelson, 1968; Jiang *et al*, 1992). The levels of vitamin C, vitamin E and reduced glutathione (GSH) were estimated by the methods (Roe and Kuether, 1943; Baker *et al*, 1980; Ellman, 1959). The activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were measured by the methods of Kakkar *et al* (1978), Sinha (1972) and Rotruck *et al* (1973).

Data were analysed by one-way analysis of variance followed by Duncan's Multiple Range Test (DMRT) using SPSS version 11 (SPSS, Chicago, IL). The limit of statistical significance was set at $P<0.05$.

Results and Discussion

Table 1 showed the body weight changes, level of blood glucose and plasma insulin in normal and experimental groups. The diabetic control rats showed a significant decreases of body weight, increase in the level of plasma glucose and decrease in the level of plasma insulin. Oral administration of camel milk or glibenclamide to diabetic rats significantly reversed the above biochemical changes.

The present study investigated the effects of camel milk on oxidative stress of STZ-induced diabetic rats. Diabetics and experimental animal models exhibit high oxidative stress due to persistent and chronic hyperglycemia, which depletes the activity of antioxidative defense system resulting in elevated levels of oxygen free radicals (Hong *et al*, 2004; Ihara *et al*, 1999). The reactive oxygen species (ROS) and free radicals were found increased in both type of diabetes (Johansen *et al*, 2005). Moreover, the onset of diabetes has been confirmed closely associated with oxidative stress in both clinical and experimental diabetes mellitus (Rosen *et al*, 2001). Attacking of high levels of free radicals and simultaneously decreasing expression of antioxidant enzymes, which may enhance membranes susceptibility to lipid peroxidation and lead to pancreatic a-cell dysfunction as well as other cellular

organelles damage (Baynes, 1991; Lenzen *et al*, 1996; Maritim *et al*, 2003).

This is among the initial reports that analyses camel milk on body weight changes, plasma glucose, plasma insulin, lipid peroxidation and antioxidant enzymes levels in experimental diabetes for 45 days. Administration of camel milk improved the body weight in diabetic rats, which might be via glyceamic control. The positive effects in weight gain may be because of good nutritional value of camel milk. In the present study, streptozotocin-diabetic rats showed significantly decreased plasma glucose level and increased insulin levels on treatment with camel milk after 45 days. The hypoglycemic activity of camel milk may be because of high concentrations of insulin like protein in camel milk about contains 45-128 units/ litre (Singh, 2001) and it also contains high amount of zinc (Mohamed *et al*, 1995). Zinc is playing a major role for insulin secretory activity in pancreatic beta cells. Previous report shows the zinc supplementation attenuates insulin secretory activity in pancreatic islets of the ob/ob mouse (Begin-Heick *et al*, 1985) and also Richards-Williams *et al* (2008) reported that, extracellular ATP and zinc are co-secreted with insulin and activate multiple P2X purinergic receptor channels expressed by islet beta-cells to potentiate insulin secretion. Ming-Der Chen *et al* (1998) reported that, zinc supplementation alleviated the hyperglycaemia of ob/ob mice, which may be related to its effect on the enhancement of insulin activity. Present study shows that increased insulin levels may be due to the insulin like protein and high amount of zinc present in camel milk. The findings were in agreement with Agrawal *et al* (2004) who found an increase of body weight and decreased plasma glucose level in streptozotocin- diabetic rats after receiving 250 ml of camel milk daily for 22 days was found. Oral insulin has been known since many years but the critical draw back is its coagulum formation in acidic media in stomach, which neutralises its potency. One property of camel milk is that it does not form the coagulum in the stomach or the acidic media; thereby it prevents degradation of insulin in the stomach. Beg *et al* (1989) found that amino acid sequence of some of the camel milk protein is rich in half cystine, which has superficial similarity with insulin family of peptides.

Table 2 represents the concentration of TBARS and hydroperoxides in tissues of normal and experimental rats. There was a significant elevation in tissue TBARS and hydroperoxides during diabetes, when compared to the corresponding normal group. Administration of camel milk or glibenclamide significantly decreased the lipid peroxidation in diabetic rats.

Chronic hyperglycaemia is the primer of a series of cascade of reactions causing the over production of

Table 1. Effect of camel milk on body weight, plasma glucose and insulin in normal and STZ-diabetic rats.

Groups	Normal	Normal + Camel milk (250 ml/day)	Diabetic control	Diabetic + Camel milk (250 ml/day)	Diabetic + glibenclamide (600 µg/kg b.wt)
Body weight (g)	202.79 ± 8.40^a	203.93 ± 7.00^a	142.70 ± 9.92^b	171.04 ± 5.50^c	193.72 ± 7.57^a
Plasma glucose (mg/dL)	76.32 ± 07.59^a	75.45 ± 07.76^a	292.38 ± 19.20^b	141.57 ± 12.82^c	106.22 ± 8.68^d
Plasma insulin(mU/mL)	15.39 ± 1.31^a	15.29 ± 1.30^a	5.53 ± 0.41^b	9.97 ± 0.80^c	14.88 ± 1.26^a

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

Table 2. Effect of camel milk on lipid hydroperoxides and thiobarbituric acid reactive substances in the liver and kidney of normal and streptozotocin-diabetic rats.

Groups	Normal	Normal + Camel milk (250 ml/day)	Diabetic control	Diabetic + Camel milk (250 ml/day)	Diabetic + glibenclamide (600 µg/kg b.wt)
Lipid hydroperoxides					
Liver (mmol/100 g wet tissue)	79.70 ± 5.39^a	78.0 8 ± 7.03^a	125.91 ± 9.83^b	103.85 ± 9.03^c	91.69 ± 6.41^d
Kidney (mmol/100 g wet tissue)	61.69 ± 5.20^a	59.33 ± 5.37^a	159.32 ± 12.65^b	104.98 ± 9.60^c	84.71 ± 4.91^d
TBARS					
Liver (mmol/100 g wet tissue)	0.82 ± 0.07^a	0.80 ± 0.06^a	3.36 ± 0.30^b	1.93 ± 0.11^c	1.03 ± 0.09^d
Kidney (mmol/100 g wet tissue)	1.54 ± 0.10^a	1.49 ± 0.12^a	3.86 ± 0.28^b	2.41 ± 0.20^c	1.93 ± 0.10^d

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at p< 0.05 (DMRT).

free radicals (Wohaieb and Godin, 1987). Free radicals react with lipids and causes peroxidative changes that result in enhanced lipid peroxidation (Girotti, 1985). In present study, increased levels of lipid peroxidative products such as TBARS and hydroperoxides were observed in diabetic rats. Tremendous increase in lipid peroxidation observed in diabetic rats is attributed to chronic hyperglycemia which causes increased production of reactive oxygen species (ROS) due to the auto-oxidation of monosaccharides (Wolff and Dean, 1987), which cause tissue damage by reacting with polyunsaturated fatty acids (PUFA) in membranes (Das and Vasisht, 2000). The observed increase in these levels could be due to decrease in enzymatic and non-enzymatic defense system in streptozotocin- diabetic rats. Treatment with camel milk or glibenclamide prevented the increase of lipid peroxidation markers, which could be as a result of improved glycaemic control and zinc present in camel milk. Previous report agreement with the present result, high mineral content in camel milk (sodium, potassium, iron, zinc, copper and magnesium) as well as a high vitamin C intake may act as antioxidant, thereby removing free radicals, which may provide a stress free situation to the animals. The vitamin C levels in camel milk are three times that of cow milk and one-and-a-half time that of human milk (Beg *et al*, 1986). High concentrations of antioxidants may make

Table 3. Effect of camel milk on vitamin C, vitamin E and reduced glutothione in liver and kidney of normal and streptozotocin-diabetic rats.

Groups	Normal	Normal + Camel milk (250 ml/day)	Diabetic control	Diabetic + Camel milk (250 ml/day)	Diabetic + glibenclamide (600 µg/kg b.wt)
Vitamin C					
Liver (mg/mg protein)	0.87 ± 0.06^a	0.84 ± 0.05^a	0.50 ± 0.04^b	0.66 ± 0.05^c	0.77 ± 0.04^d
Kidney (mg/mg protein)	0.77 ± 0.04^a	0.72 ± 0.03^a	0.46 ± 0.03^b	0.56 ± 0.04^c	0.67 ± 0.05^d
Vitamin E					
Liver (mmol/100 g wet tissue)	5.47 ± 0.35^a	5.54 ± 0.42^a	3.53 ± 0.31^b	4.32 ± 0.39^c	4.89 ± 0.35^d
Kidney (mmol/100 g wet tissue)	3.42 ± 0.28^a	3.25 ± 0.31^a	1.34 ± 0.09^b	2.45 ± 0.20^c	2.96 ± 0.23^d
GSH					
Liver (mmol/100 g wet tissue)	14.85 ± 1.38^a	15.90 ± 1.36^a	09.54 ± 0.67^b	11.72 ± 0.98^c	12.78 ± 0.93^d
Kidney (mmol/100 g wet tissue)	12.99 ± 1.10^a	13.95 ± 0.96^a	07.07 ± 0.54^b	08.50 ± 0.71^c	9.89 ± 0.82^d

Values are means ± S.D for six rats.
Values not sharing a common superscript differ significantly at $p< 0.05$ (DMRT).

Table 4. Effect of camel milk on superoxide dismutase, catalase and glutathione peroxidase activities in the liver and kidney of normal and streptozotocin-diabetic rats.

Groups	Normal	Normal + Camel milk (250 ml/day)	Diabetic control	Diabetic + Camel milk (250 ml/day)	Diabetic + glibenclamide (600 µg/kg b.wt)
Superoxide dismutase					
Liver (U^*/mg protein)	10.07 ± 0.89^a	9.98 ± 0.63^a	5.09 ± 0.32^b	7.57 ± 0.58^c	8.53 ± 0.56^d
Kidney (U^*/mg protein)	15.95 ± 1.03^a	16.40 ± 0.87^a	08.66 ± 0.60^b	10.06 ± 0.85^c	12.31 ± 1.00^d
Catalase					
Liver(U^{**}/mg protein)	78.74 ± 5.83^a	80.99 ± 6.46^a	42.83 ± 3.72^b	56.54 ± 5.06^c	67.88 ± 6.10^d
Kidney (U^{**}/mg protein)	36.15 ± 3.20^a	38.63 ± 2.94^a	21.40 ± 1.86^b	25.94 ± 2.05^c	31.60 ± 2.76^d
GPx					
Liver ($U^@$/mg protein)	11.91 ± 1.02^a	11.81 ± 1.32^a	5.45 ± 0.29^b	6.21± 0.58^c	10.77 ± 0.58^d
Kidney ($U^@$/mg protein)	9.07 ± 0.76^a	9.13 ± 0.39^a	5.35 ± 0.39^b	6.81 ± 0.51^c	8.02 ± 0.50^a
GSH					
Liver ($U^\$$/mg protein)	7.39 ± 0.51^a	7.63 ± 0.43^a	3.74 ± 0.20^b	5.26 ± 0.40^c	6.68 ± 0.52^d
Kidney ($U^\$$/mg protein)	7.00 ± 0.38^a	7.12 ± 0.47^a	3.41 ± 0.14^b	5.02 ± 0.36^c	5.70 ± 0.32^d

Values are means ± S.D for six rats. Values not sharing a common superscript differ significantly at $p< 0.05$ (DMRT).
U* = Enzyme concentration required for 50% inhibition of NBT reduction/minute. U** = µmole of hydrogen peroxide consumed/minute, $U^@$ = µmol of GSH utilised/minute.$U^\$$ = µg of CDNB conjugate formed per minute.

the insulin receptors to respond better to available insulin. In this context, Faure *et al* (1995) reported that oral zinc treatment reduced lipid peroxidation in type I diabetic patients.

Zinc also plays an important role in the synthesis, storage, and secretion of insulin as well as conformational integrity of insulin in the hexameric form, the decreased zinc, which affects the ability of islet cells to produce and secrete insulin (Chausmer, 1998; Brandao-Neto *et al*, 2003). The participation of zinc as a component of the oxidant defense system is supported by the reported *in vitro* antioxidant action of zinc and the *in vivo* association of oxidative stress with zinc deficiency. Both in animal and in cell models zinc deficiency induces oxidative damage to cell components and alterations in antioxidants enzymes (Zago and Oteiza, 2001). Several complications of diabetes may be related to increased intracellular oxidants and free radicals associated with decreases in intracellular zinc and zinc-dependent antioxidant enzymes because zinc is widely described as an antioxidant (Chausmer, 1998; Brandao-Neto *et al*, 2003). Zinc is a possible protective agent against free radical injury (Zago and Oteiza, 2001).

For studying the effect of camel milk on free radical production, the activities of SOD, CAT, GPx, GST, GSH, vitamin C and vitamin E were measured (Tables 3 and 4). They presented significant increases in camel milk treatment when compared with diabetic control rats.

Reduced activities of SOD and CAT in erythrocytes and liver have been observed during diabetes. SOD is an important defense enzyme which catalyses the dismutation of superoxide radicals (McCord *et al*, 1976). CAT is a hemeprotein which catalyses the reduction of hydrogen peroxides and protects the tissues from highly reactive hydroxyl radicals (Chance *et al*, 1952). Therefore, reduction in the activity of these enzymes may result in a number of deleterious effects due to the accumulation of superoxide anion radicals and hydrogen peroxide. Administration of camel milk increased the activities of SOD and CAT in diabetic rats. In this context, Alissa *et al* (2004) reported an increase in SOD activity in zinc-treated rabbits.

Glutathione peroxidase plays a much greater role in detoxification of hydrogen peroxide than does catalase (Jain *et al*, 1991; Kakkar *et al*, 1997). GPx activity was decreased in the liver of diabetic rats and elevated after camel milk and glibenclamide treatments reflecting a response to an increase in the rate of hydrogen peroxide production. GSH functions as free radical scavenger and in the repair of free radical caused biological damage. GSH is required for the recycling of vitamin C and acts as a substrate for GPx and GST that are involved in preventing the deleterious effect of oxygen radicals. GSH is involved in the protection of normal cell structure and function by maintaining the redox homeostasis, quenching of free radicals and by participating in detoxification reactions. Indeed GSH depletion increases the sensitivity of cells to various aggressions and also has several metabolic effects, for example, a decrease in the rate of gluconeogenesis or an increase in glycogenolysis (Grodsky *et al*, 1982). Reduced level of GSH in the circulation during diabetes represents its increased utilisation due to oxidative stress. In present study, diabetic rats exhibited a decreased level of GSH, which might be due to increased utilisation for scavenging free radicals and increased consumption by GPx. Treatment with camel milk significantly increased level of GSH in diabetic rats. This confirmed that zinc reduced oxidative stress and prevented the antioxidant defense system. GSH-Px levels were increased by zinc treatment after 3 month in diabetic patients.

Vitamins C and E are interrelated by recycling process. Recycling of tocopheroxyl radicals to tocopherol is achieved with vitamin C, which is a powerful water-soluble antioxidant and present in the cytosolic compartment of the cell. Vitamin C serves as an electron donor for vitamin E radicals generated in the cell membrane during oxidative stress. Vitamin E neutralises the free radicals, preventing the chain reaction that contributes to oxidative damage (Sun *et al*, 1999). Both the vitamins C and E significantly decreased in the plasma, erythrocytes and the liver of diabetic rats. Low levels of plasma antioxidants have been implicated as a risk factor for the development of diabetes (Vatassery *et al*, 1983). Previous studies showed the reduced plasma concentration of vitamin C in diabetes (Jennings *et al*, 1987). It has been suggested that vitamin E deficiency may be one of the factors in the pathogenesis of abnormalities of diabetic microvascular flow (Karpen *et al*, 1982; Watanabe *et al*, 1984). Oxidative stress, increased polyol pathway, non-enzymic glycation of proteins and disturbed vitamin C metabolism may be important in the pathogenesis of diabetic microangiopathies (McLennan *et al*, 1991). The most important antioxidant in the cell membrane is a-tocopherol, it interrupts the chain reaction of lipid peroxidation by

reacting with lipid peroxyl radicals, thus protecting the cell structures against damage (Takenaka *et al*, 1991). The decreased level of a-tocopherol found in the diabetics as compared with control rats could be due to the increased oxidative stress, which accompanies the decrease in the level of antioxidants, and may be related to the causation of diabetes mellitus. In this context, Garg and Bansal (2000) reported the decreased level of plasma a-tocopherol in streptozotocin diabetic rats. Administration of camel milk or glibenclamide increased the vitamin C and E levels. Frei (1991) has previously shown the ability of vitamin C to preserve the levels of other antioxidants in human plasma. Also vitamin C regenerates vitamin E from its oxidised form. For all the parameters studied, camel milk showed significant effects in STZ-induced diabetic rats. Glibenclamide also showed a significant effect in all the parameters studied in diabetic rats. However, the effect exerted by camel milk was less effective than glibenclamide.

Conclusion

Camel milk exhibited antilipidperoxidative and antioxidant activities in streptozotocin- diabetic rats. Increase in activities of antioxidant enzymes, and reduction of lipid peroxidation was due to the high concentration of zinc, vitamin C and insulin like protein present in camel milk. So it was concluded that feeding of camel milk treatment could reduce the harmful effects of oxidative stress in diabetics.

Acknowledgement

Authors would like to express thank for support from the National Nutrition Policy Chair, King Saud University, Riyadh, Saudi Arabia.

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Bactrian camel (*Camelus bactrianus*) integrins avb3 and avb6 as FMDV receptors: Molecular cloning, sequence analysis and comparison with other species

Integrins are heterodimeric adhesion receptors that participate in a variety of cell–cell and cell–extracellular matrix protein interactions. Many integrins recognize RGD sequences displayed on extracellular matrix proteins and the exposed loops of viral capsid proteins. Four members of the áv integrin family of cellular receptors, avb3, avb6, avb1 and avb8, have been identified as receptors for foot-and-mouth disease virus (FMDV) in vitro, and integrins are believed to be the receptors used to target epithelial cells in the infected animals. To analyse the roles of the áv integrins from a susceptible species as viral receptors, we have cloned Bactrian camel av, b3 and b6 integrin cDNAs and compared them to those of other species. The coding sequences for Bactrian camel integrin av, b3 and b6 were found to be 3165, 2289 and 2367 nucleotides in length, encoding 1054, 762 and 788 amino acids, respectively. The Bactrian camel av, b3 and b6 subunits share many structural features with homologues of other species, including the ligand binding domain and cysteine-rich region. Phylogenetic trees and similarity analyses showed the close relationships of integrin genes from bactrian camels, pigs and cattle, which are each susceptible to FMDV infection, that were distinct from the orders Rodentia, Primates, Perissodactyla, Carnivora, Galliformes and Xenopus. We postulate that host tropism of FMDV may in part be related to the divergence in integrin subunits among different species.

Source: Du, J., Gao, S., Chang, H., Cong, G., Lin, T., Shao, J., Liu, Z., Liu, X., & Cai, X. (2009). Bactrian camel (*Camelus bactrianus*) integrins avb3 and avb6 as FMDV receptors: Molecular cloning, sequence analysis and comparison with other species. Veterinary Immunology and Immunopathology., 131(3-4),190(10)