REVIEW ARTICLE

MECHANISM OF CAMEL MILK ON DIABETES COMPLICATIONS AND CARDIOVASCULAR DISORDERS

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Abstract: Diabetes is a common metabolic disease that causes cardiovascular disease. Insulin and oral hypoglycemic drugs are the treatment for diabetes, but high percentage of patients cannot use allopathic drugs and rely on natural alternative healings. Camel milk with therapeutic properties, is a good source of vitamins C, minerals such as Mn, iron, Cu, Zn; and immunoglobulins compared to cow milk. Insulin of camel milk is a great substitute due to no coagulum formation in the stomach. Raw camel milk increases insulin secretion, reduces insulin resistance and affects signaling and glucose transport. It also decreases the complications due to diabetes like cardiovascular disorders, obesity, oxidative stress and promotes wound healing. There is high amount of unsaturated fatty acids in camel milk for heart health. Also, probiotic bacteria and hypocholesterolemia peptides reduce cholesterol absorption and hence better control of its blood level and cardiovascular issues. Therefore, camel milk is effective in preventing complications due to diabetes and cardiovascular disorders.

Keywords: Cardiovascular issues, camel milk, diabetes complications

Citation: Mohammadabadi T, Rehman AU, Jain R. Mechanism of Camel Milk on Diabetes Complications and Cardiovascular Disorders. Pak Heart J. 2022;55(04):311-317. DOI: https://doi.org/10.47144/phj.v55i4.2388

INTRODUCTION

Camel milk has many nutrients, which are crucial for holistic health. Calcium, magnesium, iron, copper, and zinc of camel milk are greater than cow milk.[1] The camel milk containing 3.17% protein; 3.47% fat; 4.28% lactose;112.93 mg/100 g calcium; 0.45 mg/100 g iron; 9.65 mg/100 g magnesium; 1.68 mg/100 g zinc and 5.38 mg/100 g vitamin C.[1]

Immunoglobulin G in camel milk is the most important and dominant immunoglobulin[2] and is ten times smaller than a human antibody. Therefore, these antibodies are easily captivated from the intestine and show antiviral, antibacterial, and immunological characteristics.[3-5]

Lactoferrin impedes adhesion of viruses to the target cells, hunks the connection between receptors (heparan sulfate) with viruses, binds viruses and prohibits localization into host cells.[6] Camel milk vitamin C (.040 to .050 mg/ml) is greater compared to cow milk (.010 mg/ml).[5]

Furthermore, camel milk contains high concentration of unsaturated fatty acids for health of the heart. This milk has little allergenicity because of low ß-casein and lack of ß-lactoglobulin protein.[7-8]

Milk from camels contains insulin-like protein and maybe controls diabetes, elevated cholesterol levels, liver, and renal disease, and wound inflammation.[1-8]

Diabetes mellitus is one of the most common metabolic disorders that linked with cardiovascular diseases, renal and hepatic failures. Three-quarters of the world's population cannot use allopathic medicines and therefore have to rely on medicines made from natural products.[9]

In 2020, approximately 19.1 million deaths were attributed to cardiovascular diseases (CVD) globally; and 244.1 million people were living with ischemic heart disease. Coronary heart disease and atherosclerosis is considered as the main causes of death in the western countries.[10] The atherogenic lipoproteins such as oxidized LDL, beta-VLDL, and lipoprotein (a) play a critical role in the proinflammatory reaction but HDL exerts anti-inflammatory functions.[11] Low fat dairy products can control atherosclerosis and blood cholesterol and triglyceride.[12]

Probiotics in the milk of camels may decrease cholesterol absorption through decomposing bile salts and restricting reabsorption. Some studies found that bioactive peptides obtained from camel milk proteins, lowered cholesterol absorption.[10]

Cardiovascular diseases in type 1 and 2 diabetes improved by immunoglobulins, lactoferrin and

antioxidants of camel milk. Ingesting camel milk for about 6 months reduced level of LDL and triglyceride in diabetic patients (type 1).[13]

It is a supplement that may be effective in many health issues. Thus, scientific studies and many review studies represent an adjunctive therapeutic option for diabetes complications and hence CVD.[13]

Thus, this review represents camel milk as an adjunctive therapeutic supplement for prevention of diabetes, its complications and CVDs based on scientific literature.

MECHANISM OF ANTI-DIABETIC EFFECTS

Insulin is the important agent for type 1 diabetes, which must be resistant to gut degradation and easily absorbed.[14] However, camel's milk may be used as adjunct supplement for diabetes. Chronic hyperglycemia causes long-term damage and adversely affects the function of various body organs. Camel's milk plays an important role in enhancing the kidney, liver and beta (β) cells function in type 1 diabetes and elevate the lipid metabolism.[14] Thus, camel milk controls long-term glycemic and decreases the insulin requirement in type 1 and type 2 diabetes.[9-15]. The consumption of camel milk improved fasting glucose level and glucose tolerance in diabetic induced rats.[16] Insulin-like protein and small-size immunoglobulins of camel milk regenerate β-cells and regulate blood glucose level.[15]

Camel milk is effective in diabetes by following mechanisms; its effect on insulin receptor activity, insulin synthesis and its secretion. Camel milk has also direct effects on transport of glucose in the tissues, and indirect impact on the ß-cells (Figure 1).[17] Insulin-like protein (52 U/liter) in camel milk is 3 folds greater than cow milk that transfer to the circulatory system and is linked to the lactation and the storage.[5]

The insulin in camel milk is rich in half cystine like human insulin peptides. It's shown that protein and peptide fractions of camel milk directly affects insulin receptors and cell signaling in insulin-sensitive tissues.[15]

Its bioactive proteins affect specific ways influencing insulin synthesis and secretion (Figure 1). Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), as well as endo protease dipeptidyl peptidase IV (DPP-IV) are vital in the insulin synthesis and secretion.[5]

Finally, the indirect effects of camel milk are antioxidant, anti-inflammatory, and anti-apoptotic properties which enhance the normal function of ß-cells in insulin secretion. The protective effects of small size immunoglobulins on ß-cells and its non-coagulation in the stomach explain its hypoglycemic properties.[17-18].

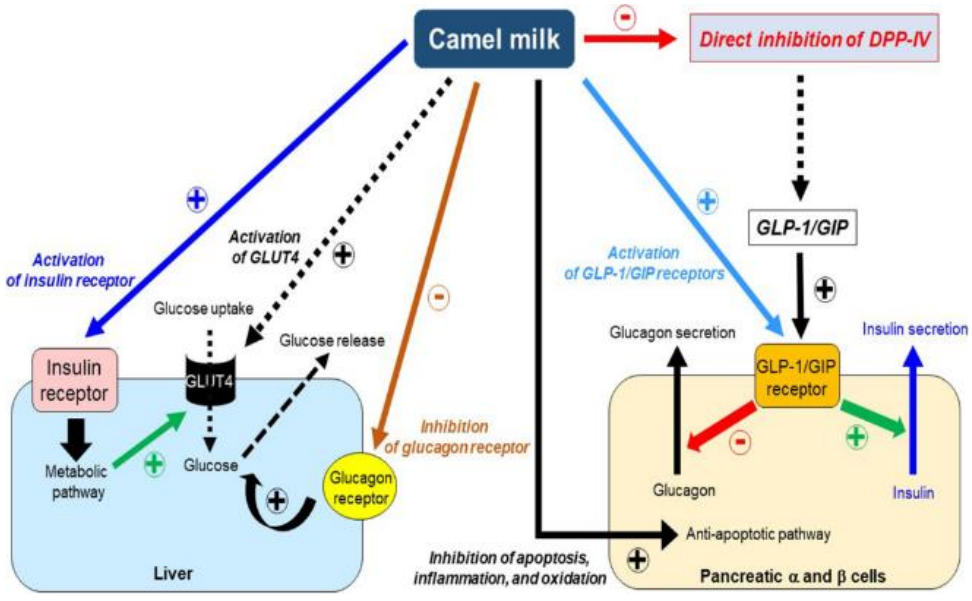

Figure 1: Mechanism of anti-diabetic effects of camel milk (Ayoub et al., 2018)[17]

GLUT4; Glucose transporter 4, GLP-1; Glucagon-like peptide-1, GIP; Gastric inhibitory polypeptide, DPP-IV; Endo protease dipeptidyl peptidase IV

The iron-binding glycoproteins of camel milk such as lactoferrin are effective in insulin resistance and signaling of insulin receptors that affect inflammation and obesity; and insulin receptors on fat cells. It is unclear if lactoferrin regulates function and signaling by binding the insulin receptors.[17-19] In fact, the known metabolic pathway through the P I3-kinase / Akt insulin activating axis regulates the expression and GLUT4 transportation to the cell membrane which is an essential agent in glucose uptake by insulin-sensitive tissues. Some bioactive peptides derived from whey proteins have beneficial effects on diabetes.[20]

However, proteins of camel milk may increase insulin by stimulation of glucose-mediated insulin secretion, inhibition of glucagon secretion and major enzymes; DPP-IV, which indirectly controls insulin secretion (Figure 1).[17] Current trials revealed whey proteins and peptides of camel milk inhibit *in vitro* DPP-IV activity in multiple amounts.[21-22-23]. Peptides produced from whey proteins of camel milk have inhibitory effects on DPP-IV that supports anti-diabetic properties of camel milk.[17]

It's proved that camel milk protein hydrolysates inhibit metabolic enzymes; dipeptidyl peptidase-IV and α amylase; regulate insulin secretion and carbohydrate digestion, and reduce blood glucose. [22-23]

The bioactive peptides, like other camel milk whey proteins, are a possible option for binding and stimulation of GIP and GLP-1 receptors in the pathway for insulin receptors. Most studies suggest the concept of immune-stimulating, anti-inflammatory, and antioxidant effects of camel's milk compounds, which restore immune cells and β cell's function.[17]

Other trials have also concluded the impact of whey proteins of camel milk on chemotaxis and B and T cells proliferation. These proteins were linked with reduction in pathological and histological changes in the pancreas and hence improving insulin secretion. The above effects along with positive impacts on GIP and GLP-1 receptors and the inhibitory impacts on DPP-I may explain the cellular and molecular reasons for its beneficial effects on managing diabetes mellitus.[24] In fact, peptides isolated from camel's milk ß-casein may have hypoglycemic action by applying negative allosteric regulation to reduce glucagon receptors or inhibit the release of glucose from the liver (Figure 1). In addition, the potential target selection of cells and regulation by bioactive compounds of camel milk may be possible by positive regulating of GLUT function and increasing glucose uptake.[15-19]

The minor size immunoglobulins of this milk may induce regulatory cells by interacting with host cell proteins, ultimately dipping the regulation of the immune system and preserving pancreatic ß-cells. Its milk was able to eliminate the toxic effects of chemicals and alloxan on the pancreas, liver, and kidneys by repairing effects on damaged cells and being a regenerative treatment for diabetes. Notably, the hypoglycemic effects of its milk will be lower when diabetic cases have previously been given with cow's milk.[14] The effectiveness of milk of camel in treating alloxan-induced diabetes may help to manage diabetes in humans.[15] Decrease in blood glucose following milk consumption regulates cellular sugar without internal and oral insulin. Removal of free radicals protects ß-cells. The high concentration of antioxidants effectively reduces body fat in individuals with type 1 diabetic patients, as insulin receptors become more sensitive to the available insulin.[17] It does not react to acid, and the quality and quantity of tiny micelles of milk fat form insulin-like molecules-conjugated components resilient to pepsin enzyme digestion and enable the absorption of intact molecules.[17]

CAMEL MILK AND DIABETES COMPLICATIONS

Diabetes is connected with cardiovascular diseases and renal and liver failures.[14] There are acute severe problems due to high blood sugar, like diabetic ketoacidosis and non-ketotic hyperosmolar coma. Chronic hyperglycemia causes chronic damage and dysfunction of various organs; eyes, renal, nervous system, heart, and blood vessels. However, control of sugar metabolism improved through exercise, diet and antidiabetic drugs that reduce the risk factors.[17] Researchers reported that long-lasting high blood glucose in diabetes increases angiotensin II, which induces thrombosis, oxidative stress, inflammation, insulin resistance and endothelial damage, and causes retinal disorders, peripheral nerve damage, secondary kidney damage disease, cardiovascular disease, and delayed wound healing.[25] Type 1 diabetes cases are prone to ketoacidosis, a lethal medical emergency if not treated properly.[26] Insulin deficiency stimulates triglycerides formation from lipids in fat cells and leads to fatty liver disease and hyperlipidemia.[25-26] Camel milk improves inflammation, wounds, hypercholesterolemia, oxidative stress, kidney failures, obesity and liver problems as main complications due to diabetes.[27-28] The reducing oxidative activity by whey proteins of milk of camel enhances immune cell proliferation and wound

healing caused due to diabetes by enhancing glutathione and the cellular antioxidant defense system.[15-28]

HEPATIC AND RENAL FAILURE

Decreased liver enzyme and liver diseases are common in diabetic cases. The researchers observed a significant improvement in liver enzyme function in diabetic rats fed camel milk compared to buffalo and cow milk.[13] Nephropathy due to diabetes is one of the common complications of diabetes; microalbuminuria occurs when urine albumin levels are between 30- 300 mg within 24 hours. The milk of camel is vital in controlling microalbuminuria in type 1 diabetic patients. The story of microalbuminuria in patients with type 1 diabetes treated with camel's milk starts to decrease after 24 hours. After adding milk of camel to the diet for six months, there was a high reduction in microalbuminuria.[29] The reduction of glucose by camel milk enhanced liver and kidney activity and cardiovascular issues in diabetic subjects (type 1 and 2).[24]

Camel milk reduced oxidative stress, hepatic steatosis, inflammatory cell infiltration, recovered liver functions enzymes (Aspartate amino transferase, Alanine amino transferase) to 50 to 90%, and normalized triglyceride and cholesterol. Also, administration of camel milk increased hepatic protein synthesis and reduced urea/uric acid and creatinine, and diabetes-associated liver and renal damage were improved.[8]

Regarding to the studies, consumption of camel milk was effective in maintaining normal renal and hepatic function in streptozotocin-induced diabetic rats.[30]

DIABETIC WOUNDS

Late wound healing occurs in diabetic patients, one of the most severe complications associated with diabetes. Taking whey proteins improved wound healing in people with diabetes through increasing the immune response of injured cells and reducing of diabetes complications.[28] Recent studies suggest that it has therapeutic effects on diseases caused by oxidative stress due to increasing antioxidant activity.[8] This result is associated with increased cell epithelial synthesis, granule tissue formation, extracellular matrix regeneration and angiogenesis. Treatment with its milk increased hydroxyproline and total collagen levels in diabetic rats.[17] Some of the effects of whey proteins or their peptide fragments have been attributed to the antioxidant function of whey proteins in the camel milk which increase the immune cells proliferation and accelerate the wound healing in diabetic cases. This indicates oxidative processes and a weakening of inflammatory by restoring of IL-10 as anti-inflammatory cytokines and lowering of other cytokines; IL-6 and TNF-α.[28] Interestingly, lactoferrin is also a good choice, which has led to the regulation of the release of IL-6, IL-1, and TNF-α *in vitro* experiments. Whey improves wound healing by enhancing the cellular antioxidant defense system and GSH production.[17-28] In another study, there was a correlation between the camel milk and b-defensins expression and consequently wound healing. Studies show that consuming camel milk in chronic diabetic wounds affects regulating immunity. Targets for camel milk proteins may be crucial cell surface receptors; chemokines and toll-like receptors.[28]

OXIDATIVE STRESS

Hyperglycemia may increase ROS production through the non-enzymatic reaction of sugars with proteins, glucose autoxidation, and changes in the activity of the polyol pathway and subsequent effects on the whole body.[21] In addition, oxidative stress in diabetic subjects reduces vitamin C, glutathione and vitamin E as non-enzymatic antioxidants. It may cause complications of diabetes due to destroying metabolic reactions.[17] The effects of camel milk possibly related to chelating effects on toxins and may be activity against free radicals.[13] Vitamins C, E and B2, and minerals (magnesium, zinc, potassium, copper and sodium) are high that prevent tissue damage by toxic substances.[17] Because camels specifically graze on natural plants, some phytochemicals that get into camel's milk may be more beneficial to diabetic cases treated with this milk.[13] The consumption of camel milk reduced oxidative stress in comparison to cow's milk.[8] Administration of camel whey protein in streptozotocin-induced type 1 diabetic mouse have antidiabetic effects by decreasing the free radicals and improving antioxidant.[15]

Using camel milk in induced type 1 diabetic rats enhanced antioxidative enzymes (catalase, glutathione peroxidase and super oxide dismutase) in pancreas and completely normalized oxidative damage in pancreas.[24]

CARDIOVASCULAR DISEASES

Hyperlipidemia and hypercholesterolemia happen with diabetes and increase the risk of cardiovascular disease.[15] The high degree of oxidative stress may lead to development of vascular complications caused by diabetes mellitus. Thus, diabetes is associated with cardiovascular diseasess.[9]

Probiotic and bioactive peptides obtained from proteolytic activity in camel milk have hypocholesterolemic property. The interaction between its milk's bioactive peptides decreases cholesterol.[13] Cholesterol-lowering peptides also prevent cholesterol absorption by electrostatic and hydrophobic reactions or through decreasing cholesterol solubility.[13] These friendly bacteria deconjugate bile salts and inhibit cholesterol reabsorption, thus reducing cholesterol absorption in the intestine.[8] Also, probiotics make short-chain fatty acids in the gut from fermentation of carbohydrates that affect cholesterol synthesis and transferring from plasma to the liver.[31]

The decrease in blood cholesterol may be result of formation of cholesterol-apoprotein complex by connection between cholesterol with arginine and tyrosine, which depends on the amount of arginine in the protein.[32] The high amount of L-carnitine in milk positively affects the lipid level by reducing the absorption of outside cholesterol.[33] Thus, entering a larger chain of fatty acids into the mitochondria for catabolism in β-oxidation decreases and indirectly increases blood lipid.[33-34]

Using milk of camel for 1.5 months noticeably reduced triacylglycerol, LDL, VLDL, cholesterol, and FFA in plasma, heart, liver, and kidney and improved HDL.[35] After consuming this milk for 180 days in type 1 diabetes, triacylglycerol's and LDL reduced.[36] The intake of camel milk for five weeks lowered cholesterol to 4.35 mmol/l.[13] Non-cream fermented camel milk in male Wistar rats significantly decreased triacylglycerol, total cholesterol, HDL, VLDL, LDL and atherogenic index LDL /HDL ratio.[12]

Fermented camel milk may be improve oxidative stress and reduce triacylglycerol, HDL and LDL. Lowering oxidative stress might cause to reduce LDL and the occurrence of cardiovascular diseases and atherosclerosis can be prevented.[10]

Researchers[37] concluded that LAB strains isolated from raw camel's milk; *Lactococcus lactis and Lactobacillus plantarum* may be considerably effective on lowering of cholesterol. It is proved that camel milk fermented with *Bif. longum* BB536 considerably reduces the risk of dyslipidemia by reducing triglycerides, VLDL, and LDL and increasing HDL.[8]

Probiotic bacteria convert cholesterol to coprostanol by intestinal bacteria, and cause to increased fecal excretion and reduction in cholesterol. Also, these bacteria regulate lipogenic enzymes activity and bile acid receptor, and Apolipoprotein A-V and decrease triglyceride concentration.[8]

According to a study, 1% decrease in serum cholesterol leads to a two to three percent reduction in the risk of cardiovascular diseases. Current researches have proven that non-hydrolyzed casein does not influence cholesterol; However, casein hydrolysates obtained by trypsin or bacteria decreased cholesterol by 24-87 percentage.[32] Lactic acid bacteria; *L.delbrouki, L. bulgaricus, L. helveticus, Lactococcus lactis and Saccharomyces cerevisiae* produce ACE inhibitors from the milk fermentation. Fermented camel milk had greater ACE inhibitors than cow milk. The reason may be because of more proline and differences in the casein structure.[38]

CAMEL MILK AND BLOOD LIPIDS

Camel milk has anti-inflammatory effects, immune modulatory function on pancreatic β cells, and antioxidants components which regulate blood pressure and lipids and decrease the occurrence of cardiovascular disorders.[7]

Half a liter of raw milk of camel in type 1 diabetic patients for three months reduced required insulin doses; 41 to 30 u/d, blood sugar; 115 to 100, and LDL 92 to 72 mg/dl. Still, cholesterol and TG content did not change.[38] LDL, TG, required insulin dose, and albuminuria was reduced in type 1 diabetes patients who consumed ½ liter milk of camel daily for six months.[36] Destroying of beta cells prevented insulin secretion, increased glucose, LDL and triglycerides of blood.[19] The atherogenic index reduced in diabetic rats fed camel milk, leading to lower LDL/HDL ratio and an increasing of HDL. High concentration of vitamin C also plays a key effect on oxidation of peroxides and reducing LDL in diabetic cases.[35] Plasma HDL was enhanced noticeably in diabetic rats after 45 days.[36]

Using skim fermented camel milk in Wistar rats significantly decreased triacylglycerol, total cholesterol and atherogenic index LDL /HDL ratio.[13]

Other researchers found that cholesterol, triglyceride, HDL and LDL+ VLDL amount decreased in mice fed on diet rich in cholesterol and fermented camel milk for 42 days by 52%, 35.3%, 61, and 53%, respectively.[32]

Diabetes is linked with significant changes in lipoprotein profile and triglyceride (TG) that cause reducing the risk of heart and vascular complications; Therefore, reducing heart disease risk happens by decreasing cholesterol through medication and foods. Elevated LDL in diabetic subjects can lead to LDL

receptors defects. HDL is protected by reversing transported cholesterol, neutralizing the atherogenic effects of oxidized LDL and inhibiting LDL oxidation.[35]

After three months consuming camel milk, cholesterol and triglyceride level decreased by (9%) as well as LDL (7%) in diabetic patients (type 1) who received insulin injections. Reductions of TG (3-fold) and LDL and cholesterol (2-fold) were declared in diabetic subjects fed camel's milk. Also, a noticeably decrease in TG, cholesterol (45%), and LDL (30%) was concluded in the diabetic cases fed insulin and milk of camel compared with the control treatment. High upsurge of HDL in cases who given insulin and milk of camel observed; 41-49 mg/dl in cases fed insulin and milk.[29]

Triglyceride and cholesterol levels in diabetic patients (type 1) reduced by 37% and 25%, respectively, after 16 weeks using camel milk without any effect on HDL, LDL and VLDL.[36]

Levels of total cholesterol, triglyceride, and LDL declined in diabetic rats fed with camel milk protein and camel milk protein hydrolysates.[15]

Table 1: The effect of camel milk on blood parameters (mg/dl) of diabetic patients (Adapted from Agarwal et al., 2009)[36]

	Before using camel milk	After using camel milk
HBA1 (%)	9.54±0.44	8.65±0.38
Insulin dose (u/d)	41.61±3.08	28.32±2.66
Mean plasma glucose	128.7±1.17	125.46±1.24
Microalbuminuria	119.48±1.68	22.52±2.68
Total cholesterol	77.22±0.03	76.32±0.04
HDL	26.82±0.02	26.28±0.03
LDL	65.18±0.14	45.54±0.1
VLDL	6.84±0.02	6.3±0.02
Triglyceride	92.7±0.18	31.5±0.17
Peptide C (nm/l)	0.18±0.14	0.24±0.17
Insulin (pm/l)	127.08±2.86	130.63±3.86

CONCLUSION

In most studies, the beneficiary impacts of raw camel milk on diabetes proved; improving risk factors like cardiovascular challenges, hepatic and renal failures due to diabetes. Consuming camel milk for 180 days lowers triacylglycerol and LDL in diabetes (type 1), and 1% decrease in cholesterol diminishes the cardiac diseases risks about 2% to 3%. More trials are required to prove the efficacy of processed camel milk like making powder on diabetes complications and CVDs. The number of evidence shows that the milk of camel is safe without any side effects and effective for diabetic persons for long-term hypoglycemic effects.

AUTHORS' CONTRIBUTION

TM, AUR, and RJ: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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