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Review Article

The Role of Camel Milk in Treatment of Type 2 Diabetes: A Review

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ABSTRACT

Diabetes mellitus is one of the most common metabolic diseases worldwide. In patients with type 2 diabetes, insulin sensitivity and glucose homeostasis are impaired and leading to hyperglycemia. Several studies have reported that camel milk with various mechanisms can improve hyperglycemia and its subsequent complications in type 2 diabetic patients. The present study uses the information in Google Scholar and PubMed databases from 2002 to 2016 to review the role of camel milk in treatment of type 2 diabetes. The key words "type 2 diabetes", "insulin resistance", "oxidative stress", "hyperglycemia", "insulin", and "camel milk" were used to collect information. Camel milk was shown to be effective in improving glucose homeostasis by insulin-like proteins. Also, it has RQ-8 peptide that can act as an antioxidant and reduce the damage caused by oxidative stress in the development of diabetes. This kind of milk is effective in improving insulin sensitivity due to its unique combination of fatty acids. It can be concluded that camel milk can be used as a natural product which can be useful to delay or slow down the progression of type 2 diabetes.

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Introduction

Diabetes is a common metabolic disorder that is increasing worldwide. Type 2 diabetes or non-insulin-dependent diabetes is a multi-factorial disorder, which results in impaired glucose homeostasis in the body. Due to the vital and the constant need of the body tissues, including the brain to glucose, the body always maintains glucose levels in a definite and stable range. When consuming carbohydrates, fast insulin secretion prevents the endogenous glucose production and glucose uptake in peripheral tissues is accelerated and through this, the level of glucose is regulated in the body (1).

In patients with non-insulin dependent diabetes, by changes in insulin sensitivity at the cellular level, the body glucose homeostasis would be impaired and causes acute and chronic hyperglycemia, which ultimately leads to vascular changes (2). The prevalence of Type 2 diabetes has an increasing trend and according to the latest figures released by the International Diabetes Mellitus Association, the number of people with diabetes in 2013 was 382 million, and is estimated to be 592 million in 2035. According to the latest figures from the International Diabetes Federation (FIDA) in 2013, more than

4.3 million people had diabetes in Iran, and the prevalence of this disease in the adult population aged 20 to 79 was estimated to be 8.43% (3).

The camel's milk in comparison to the cow's milk contains five times more potassium and vitamin C (4), four times sodium, three times more calcium and magnesium, and more unsaturated fatty acids, folic acid, and chlorine (5). It also contains ten times more lactoferrin protein (6). This milk also has antibacterial and antiviral properties, antibodies, anticancer compounds, and bioactive peptides that can combat diseases like cancer, Alzheimer's, gastric ulcer, tuberculosis, HIV, and hepatitis C (7). The fat and lactose of the camel's milk is less than that of the cow's milk, and it contains insulin-like material; so it is a good option for people with diabetes (8). The general compounds of the camel milk were shown in Table 1 (9, 10). These unique features of camel milk have made the product an ideal choice for exploring as a natural product to improve the metabolic status of people with diabetes (11).

Table 1: The general compounds of the camel milk.*

The compound name	Available in quantity
Water (%)	84-90
Density (%)	0.96-1.1
Ash (%)	0.35-0.95
The solid, non-fat material of the milk **(%)	7.01-14.3
Lactose (%)	2.9-5.8
Fat (%)	1.1-5.5
Protein (%)	2.5-5.5
PH coagulation	6.48-6.7

*The milk combinations of different types of camels varies depending on the climate conditions. **SNF: Solids not fat.

Materials and Methods

The present study, as a review article, was done by searching "type 2 diabetes "," insulin resistances", "oxidative stress", "hyperglycemia", "insulin", and "camel milk" as keywords in PubMed and Google scholar database between 2002 to 2016.Both review articles and research articles were used, while 94 were Persian and English articles, and out of which; 19 papers were selected and their results were included.

Results

Insulin-Like Compounds in Camel Milk and Diabetes

One of the roles of camel milk is its hypoglycemic activity, which is probably due to its high protein density similar to the insulin found in the camel milk. Figure 1 shows the chemical structure of small protein molecules similar to the insulin found in camel milk (12).

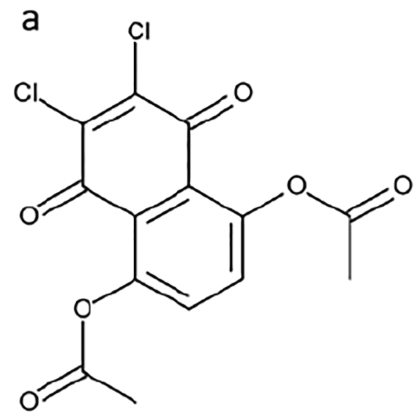

Figure 1: The small molecule insulin-like protein found in camel milk.

The camel milk has 45-128 units/liter of protein similar to insulin. Insulin in the acidic stomach was shown to become clabber, thus its function will be neutralized. One of the characteristics of the camel's milk is lack of clabber creation in the acidic environment and stomach; so it prevents the insulin reduction. In Figure 2, some of the confirmed functions of the insulin-like protein in the camel's milk were shown (13).

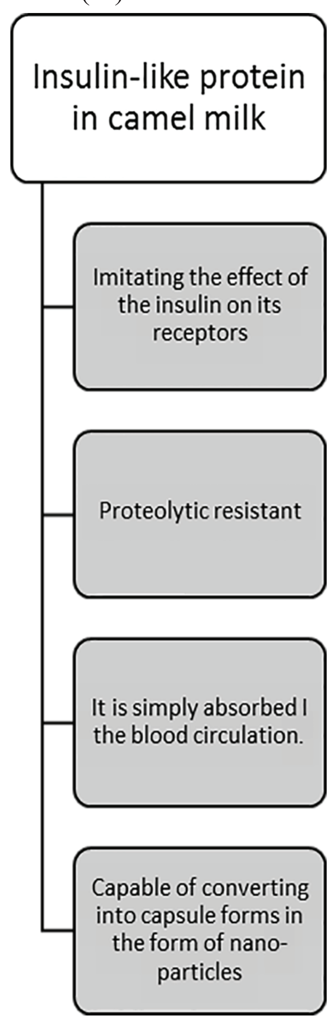

Figure 2: The confirmed functions of insulin-like proteins in the camel's milk.

Oxidative Stress, Diabetes and Camel Milk

It seems that glycation, and oxidative stress, are two important key processes in the development of diabetic complications and many other illnesses. Regarding the presence of relatively high levels of glycosylated proteins even in some non-diabetic complications, it has been suggested that oxidative stress is involved in the production of glycosylated proteins by increasing the production of reactive species or reducing the levels of antioxidants in the body (14).Oxidative stress is caused by the imbalance between the production of free radicals and metabolic reactions. In cells, oxidant compounds or reactive oxygen species (ROS) should be eliminated by protective mechanisms (15).

Antioxidant defense systems under normal conditions can neutralize reactive, active species by an enzymatic method (such as cytosolic and mitochondrial superoxide dismutase, glutathione reductase, glutathione peroxidase, and catalase) and non-enzymatic antioxidants (such as anti-oxidant vitamins A, C and E coenzymes and cofactors). Therefore, the endogenous defense system protects the body against reactive radicals. Under oxidative stress conditions, high reactivity molecules such as reactive oxygen species, radical hydroxyl, radical proxyl, superoxide anion, and reactive nitrogen species such as nitrite peroxide are increased (16).

Chronic oxidative stress, caused by a persistent increase in blood glucose, especially after eating and producing ROS, results in a progressive decline in the function of pancreatic beta cells, and ultimately in type 2 diabetes. Oxidative stress plays an important role in the progression and complications of diabetes (17).The results of animal and human studies show that oxidative damage by free radicals leads to the progression of microangiopathy and macroangiopathy. Extracellular fluids contain several antioxidants that interact with oxidative processes. Antioxidants such as ascorbic acid, beta-carotene and alpha-carotene maintain LDL cholesterol against oxidative damage (18). In diabetic patients, low concentrations of antioxidants have been reported. Therefore, the use of antioxidants in diabetic patients is recommended (19).

Prevention of Coronary Artery Disease and Camel Milk

It seems that there is a strong relationship between increased insulin levels and coronary artery disease and increased blood insulin levels play a crucial role in the progression and the intensification of atherosclerotic lesions. Decrease in plasma insulin concentration and an improvement in insulin action may have beneficial effects on coronary artery disease (20), and studies have shown that long-term antioxidants can lower plasma insulin concentrations and improve lipid profiles. (20, 21).

All of this information led researchers to assume the antioxidant theory for the prevention of the coronary artery disease in people with diabetes. Several studies on food antioxidants showed that changes in the level of LDL cholesterol in the plasma were an important factor in prevention of cardiovascular disease. Also, changes in LDL cholesterol concentrations are mainly due to changes in the level of free oxygen radicals in the plasma (20).

By the study of vitamin E effects on atherosclerosis, Pritchard has shown that taking vitamin E is an effective factor in delaying the oxidation of LDL cholesterol and preventing proliferation of smooth muscle cells and preventing platelet accumulation and adhesion in diabetic patients (22). Reductions in plasma insulin concentrations have been reported in previous studies in type 2 diabetic patients (21). The beneficial effects of antioxidants on the plasma insulin concentration have been reduced due to reduced changes in the ratio of oxidized glutathione to reduced glutathione, which improves the activity of beta cells of the islets of Langerhans, and decreases insulin secretion (21).

Therefore, it can be assumed that antioxidants, which increased the reduced glutathione, improved the physical condition of the plasma membrane as well as the membrane activity as insulin-mediated glucose transport. The study of Pauluso in 1993 and 1995 also showed a significant decrease in blood glucose concentration (20, 21). Now that, in humans, oxidative stress plays a role in the onset and progression of diabetes and most of these people have a poor diet because in terms of natural antioxidants present in the food. Hence, it is necessary to reduce the synthesize antioxidants and natural ones that can prevent oxidative stress and their harmful effects (23). The use of synthetic antioxidants is more effective in preventing the harmful effects of free radicals, but it has some side effects. Another approach is the use of natural antioxidant peptides that have fewer side effects (24).

Biological Effects of Peptides in Camel Milk

Bioactive peptides are peptides derived from food, which beyond their nutritional value have physiological and quasi-hormonal effects in the body. These peptides are found in milk, eggs, meat and fish, as well as in plants. The bioactive peptides are inactive in their parent protein sequences (bioactive peptides are inactive specific protein fragments with the precursor protein sequence), and can be released by enzymatic hydrolysis through gastrointestinal digestion or during food processing (like fermented milk). Bioactive peptides usually contain from 2 to 20 amino acids (25, 26).

Following digestion, bioactive peptides can enter the bloodstream through the intestines and apply their systematic effect, or produce local effects in the gastrointestinal tract. The structure and composition of amino acids and the sequence of these peptides may have diverse roles, including pseudo-opioid, mineral binding, immune modulation, antimicrobial, antioxidant, anticoagulant, cholesterol-lowering, and blood pressure-lowering. Many of the known bioactive peptides are multi-functional and can have more than one bio-effect and are even used as active food ingredients or nutrients. However, camel milk proteins can act as the main source of some bioactive peptides (27-29).

Research results have shown that purified peptide camel milk, called RQ-8, has a RGLHPVPQ sequence with a molecular weight of 903.1 413 Dalton. In the RQ-8 peptide sequence, there are two non-polar amino acids, including leucine and glycine, which share the anti-oxidant properties of the peptide. It is very important to have high hydrophobicity for antioxidants and to achieve hydrophobic targets (30). Possibly, the presence of hydrophobic amino acids in the purified peptide sequence may contribute to inhibiting lipid peroxidation by increasing the solubility of the peptides in the lipid and thus facilitating interaction with free radical species. Amino acid residues including histidine, proline, valine, glycine and leucine, which are present in the peptide sequence, are likely to contribute to radical absorption activity. Aromatic amino acids can be effective as a proton or electron donator to the radicals of electron-deficient centers. Hence, they are effective in absorbing radicals (31).

The histidine or histidine-containing peptides in the sequence of RQ-8 have the ability to trap radical lipids due to the imidazole ring. Aromatic amino acids such as tryptophan show antioxidant activity, because they can easily donate proton to free radicals. Several amino acids like leucine, arginine, proline, valine and histidine are generally considered to be antioxidants. As already mentioned, the RQ-8 peptide contains the above mentioned amino acids, which suggests that it may have potent antioxidant activity (30).

Generally, the peptide has inhibited the oxidation of linoleic acid, and acts as a radical absorber for 1, 1-diphenyl-2-picyril hydrazil (DPPH) (IC50=0.046 mg/ml) and 2.2-Azino-bis (3-ethyl) Benzothiazolin-6-sulfonic acid (ABTS) (IC50=0.085 mg/ml), superoxide (O2Å) (IC50=0.156 mg/ml), and hydroxyl (OHÃ-) (IC50=0.021 mg/ml) (32).These results indicated that the RQ-8 peptide isolated from the camel milk casein protein has antioxidant activity. Accordingly, it has been suggested that the use of this peptide may be a promising antioxidant in preventing or delaying the development of chronic diseases, such as diabetes.

Dietary Fat, Hormonal System, Diabetes and Camel Milk

The quality and quantity of lipids in the dietary regimen play an important role in the co-morbidity and insulin sensitivity in animals and humans (33). Some studies have shown that high-fat diets can cause hyperglycemia and insulin resistance. Fatty acids with varying degrees of saturation can lead to fat-induced insulin resistance. It seems that the combination of fatty acids or type of fat may be able to affect insulin function independently and change the sensitivity to insulin (34). It has been reported that approximately 40 to 75% of the intake of energy from fat is usually saturated fatty acids (SFA) that decrease cellular glucose uptake by insulin (35).

It has been reported in several studies that mono-unsaturated fatty acids (MUFA) can make the insulin function normal and prevent insulin resistance from high fat diets in rats and improve glucose responses and obesity indices in mice (35, 36). In addition, recently, a MUFA diet has been associated with direct in vivo secretion of insulin, and in a rat study, a MUFA regimen has been involved in improving insulin secretion and glucose tolerance (36). In general, the findings of this study showed that animals receiving noticeable amounts of MUFA significantly had lower overweight and dietary and calorie intakes, and these changes were associated with an increase in the concentration of des acyl ghrelin and a decrease in plasma insulin concentrations. Therefore, higher levels of des acyl ghrelin may play an important role in controlling appetite and weight and improving insulin resistance

Table 2: The composition of camel milk fatty acids.

The name of the fatty acid	Existing amount (%)
Butyric acid	2.1
Caproic acid	0.9
Caprylic acid	0.6
Capric acid	1.4
Lauric acid	4.6
Myristic acid	7.3
Palmitic acid	29.3
Stearic acid	11.1
Oleic acid	38.9
Linoleic acid	3.8
Cholesterol*	31.3-37.1

*In mg per 100 grams milk

in growing rats (37, 38).

The fatty acid composition of the camel's milk shown in Table 2 (9, 39, 40), it is noteworthy that camel milk has a significant amount of Oleic acid, which is a MUFA, and could possibly have a role in reducing insulin resistance in patients with diabetes. The other specific factor is that the camel milk fat has low short chain fatty acids with a number of 4 to 12 carbons (9). It has been shown that diet with short chain fatty acids with 4 to 12 carbons can significantly increase triglyceride, cholesterol, and free fatty acids in the plasma and create a state of insulin resistance throughout the body (41).

The induction of insulin resistance is accompanied by a significant increase in the production of apoB and very low density lipoprotein (VLDL), which in turn exacerbates insulin resistance. High concentration of fatty acids produced by VLDL triglyceride hydrolysis leads to the induction of liver enzymes such as peroxisome proliferator-activated receptors (PPAR) and FAS, which results in the superiority of the formation of lipoproteins against their oxidative degradation (42, 43). Put the camel milk as part of a diet due to having a lower percentage of short chain fatty acids with 4 to 12 carbons (6 to 8 times less than cow's milk) can have a role in preventing the above mentioned mechanism for preventing the creation or avoiding the worsening of insulin resistance(9). Another ingredient in camel milk, which can play a role in the metabolism of lipoproteins and insulin resistance, is the CLA. Numerous studies reported the effects of its various isomers on the reduction of body mass, as well as the reduction of blood lipids and insulin resistance (10, 44).

Conclusion

According to the available information, camel's milk has many nutrients that are very useful for human health. This unique nutritional compound, due to having small protein molecules that can pass through the digestive tract healthily, easily absorbed into the bloodstream and shows insulin-like activity which can stimulates the insulin receptors on the cell surface and induces its blood glucose effects without any anti-genetic effects. On the other hand, camel milk is rich in peptide RQ-8, which can be effective in preventing or delaying diabetes with antioxidant activity. The fatty acid profile of camel milk also reduces insulin resistance by altering the lipoprotein metabolism and free fatty acid content of the blood. It also improves insulin sensitivity by altering the balance of the digestive hormones. It seems that continuous use of camel milk as a natural product can be useful in preventing or slowing the trend of type 2 diabetes, as it covers most aspects of the pathogenicity of the disease.

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Conflict of Interest

None declared.

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