Abstract
In the last decade, there has been an emergent interest, supported by various experimental and epidemiological studies, for health benefits of camel milk, in preventing various pathologic conditions, ranging from cancer to diabetes. However, the precise mechanisms by which camel milk induce these health benefits remain to be investigated. Various reports have shown that consumption of camel milk by diabetes patients on a daily basis reduces blood sugar and glycosylated hemoglobin (HbA1C) levels and also reduces insulin requirements. Despite that these findings provide scientific evidences of anti-diabetic activities of camel milk, research is yet to be initiated with assurance for patients of diabetes and other metabolic disorders. This review summarizes the medicinal values of bioactive constituents of camel milk and reviews camel milk findings from the most significant preclinical studies in diabetes.

Keywords: Camel milk, diabetes mellitus, blood glucose, HbA1C, insulin resistance.

DOI: https://doi.org/10.47391/JPMA.367

Introduction
Diabetes mellitus has now been considered as a major public health issue globally. International Diabetes Federation (IDF) has recently pointed out the shocking figures on the global concern on diabetes in atlas 2017 (8th edition), which are as follows: every individual out of eleven adults has diabetes, one in two diabetic individual is undiagnosed, one in six births is diabetic in pregnancy, more than a million children and adolescents have type 1 diabetes, three quarters of diabetic adults have been living in low and middle income countries, two-thirds of diabetic adults are of working age and most importantly this atlas has also pointed out that 12% of global health expenditure is spent on this typical disorder. The Kingdom of Saudi Arabia has the highest prevalence of metabolic disorders including diabetes in the Middle East and North Africa. Diabetes Mellitus affects the quality of life, increases complications like (retinopathy, renal impairment, cardiovascular disease) and this could lead to increase in mortality rate. Diabetes Mellitus is not caused by a single factor; it is affected by multiple factors (genetic, social, environmental), which could be managed by a combination of healthy diet, physical activity, and medication, however, it requires life long management and cannot be eliminated. Till now, no medication is considered as curable for diabetes, therefore, some people try complementary and alternative medicine for the purpose.

Despite of the availability of insulin therapy, oral medication, and diet plans, diabetes and its associated secondary complications remain a challenge to treat. Although insulin is the prime therapy, but patients with diabetes are always looking for an alternative. Therefore, numerous attempts were accomplished in past two to three decades to develop a novel approach for the management of diabetes other than insulin, but none of them were found to be comparable to insulin therapy. In the last decade, camel milk and its bioactive constituents have gained considerable attention among scientist and clinicians for their potential health benefits. According to A Systematic Review published in 2017 on Beneficial Effects of camel milk on Diabetes Mellitus which showed that camel milk has potential to reduce blood sugar, decrease HbA1C, decrease insulin requirements and improve lipid profile in both diabetes type 1 and type 2. However, the mechanisms involved in its anti-diabetic actions are still to be investigated. In this review, up-to-date information was gathered on implication of camel milk as a therapeutic agent for management of diabetes mellitus.

Bioactive composition and medicinal values of camel milk
In deserts, camel dairy husbandry is a substitute to cow dairy husbandry. Cow dairy farming requires water and electricity in bulk, whereas camel farming is well adapted in deserts as camels are able to eat salty desert plants and easily survive in warm climatic conditions. Day-by-day demand of camel milk is on the rise and now camel milk is also available in local markets of Saudi Arabia, United Arab Emirates (UAE), Somalia, Mauritania, Kenya, Mali, Ethiopia, Niger, Sudan, Chad and also in United States. The milk from cows, buffaloes, goats and sheep has been intensively studied and numerous publications are currently available on PUBMED and other citation sites; however, milk from camels was not studied well as compared to others such as...
from cow, which is widely consumed by humans.14 Camel milk contains a α-hydroxyl acids which plays an important role in cosmetic and skin disease as (acne, dermatitis. Eczema). Also, camel milk is known to have a beneficial effect on autoimmune disease and can reduce autism in children.15 Camel milk constituents, such as lactoferrin, immunoglobulins, lysozyme and vitamin C have been studied by various investigators to show their medicinal properties in patients with various diseases.16-18 Investigators also studied camel milk constituent beta-casein and beta-lactoglobulin and found that camel milk contains very low amount of these milk constituents .These findings have been well correlated with low allergic effects of camel milk. Moreover, the high quantity of unsaturated fatty acids have shown its drinking health benefits for humans.19

From the therapeutic point of view, camel milk has mainly two active constituents, which are lactoferrin and immunoglobulins.17 The camel lactoferrin is an abundant camel milk constituent, which has been extensively studied for its therapeutic values.10,20 Investigators from different parts of the world have reported that it has potent anti-inflammatory, antibacterial, anti-fungal, anti-viral properties.10-12 It inhibits growth of staphylococcus aureus, Escherichia coli, klebsiella pneumonia, clostridium, helicobacter pylori, etc. Not only these, it also inhibits growth of candida albicans. Moreover, studies have also shown that it has anti-human immunodeficiency viral property, it also has anti-HBC, anti-CMV, anti-herpes simplex virus-1 effects.10

In spite of these health benefits of camel milk, use of camel milk has only been restricted to some parts of Asia, Africa and Australia. In 2013 European society has given license to the United Arab Emirates (UAE) based company to supply camel milk and products, which is now being exported to various regions of Europe mainly, Netherlands, Denmark and England. Moreover, another company Al Nassma is now manufacturing camel milk chocolate which is now very famous in London markets.10 These attractive properties of camel milk and products are possibly due to its unique nutritional properties compared to the broadly consumed milk from other species. In brief, the medicinal values of camel milk are illustrated in Table 1 with 7 studies regarding the importance of camel milk against arthritis, cancer, hepatitis C, autism, viral infection, allergy, immunotherapy.

**Table-1:** Medicinal values of camel milk.

<table>
<thead>
<tr>
<th>Main finding</th>
<th>Author Year</th>
<th>Year</th>
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<tbody>
<tr>
<td>Cartilage protective and anti-arthritic</td>
<td>Rasheed N, Alghasham A, Rasheed Z.18</td>
<td>2016</td>
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<tr>
<td>Immune therapy for patients</td>
<td>Abdel Gader AG, Alhaider AA10</td>
<td>2016</td>
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<td>with autoimmune diseases</td>
<td></td>
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<tr>
<td>Camel milk has anti-cancer</td>
<td>-Abdel Gader AG, Alhaider AA,10</td>
<td>2016</td>
</tr>
<tr>
<td>Properties but still research is in</td>
<td>-Rasheed Z.16</td>
<td>2017</td>
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<tr>
<td>the pre-clinical phase.</td>
<td></td>
<td></td>
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<tr>
<td>Camel milk protein lactoferrin showed</td>
<td>-Abdel Gader AG,Alhaider AA,10</td>
<td>2016</td>
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<tr>
<td>anti-viral activity</td>
<td>-Rasheed Z16</td>
<td>2017</td>
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<tr>
<td>Lactoferrin from camel milk</td>
<td>Redwan el-RM, Tabll A.24</td>
<td>2007</td>
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<tr>
<td>inhibited hepatitis C virus</td>
<td></td>
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<tr>
<td>Therapeutic benefits of camel milk</td>
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<td>against allergies</td>
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<tr>
<td>Camel milk supplementation</td>
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<tr>
<td>has also shown significant therapeutic</td>
<td>Shabo Y, Barzel R, Margoulis M, Yagil R.25</td>
<td>2005</td>
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<tr>
<td>improvement for paediatric patients with</td>
<td></td>
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<tr>
<td>autism</td>
<td>-Abdel Gader AG,Alhaider AA,10</td>
<td>2016</td>
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<td></td>
<td>-Rasheed Z16</td>
<td>2017</td>
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</table>

**Anti-inflammatory effects**

Camel lactoferrin also has immune system modulatory functions. It regulates maturation and activation of neutrophils, macrophages and lymphocytes, thereby possibly performing antioxidant and anti-inflammatory effects. Reports have also shown that lactoferrin is the main component of camel milk, through which camel milk shows anti-cancer effects, however mechanisms behind are still not known.10 Recently, lactoferrin from camel milk was found to be cartilage protective and anti-arthritic.18 It inhibits the inflammatory activity against IL-1β-induced activation of human OA chondrocytes via blocking of nuclear kappa B signaling events. Furthermore, it also inhibits IL-1β-induced cyclooxygenase-2 expression and prostaglandin E2 production in osteoarthritis human chondrocytes. These findings are of importance to understand the chondroprotective mechanisms and clinical applications of camel lactoferrin.18

Moreover, based on these heavy chain antibodies, immune therapy for patients with autoimmune diseases such as multiple sclerosis and Alzheimer’s disease is on the rise.10

**Anti-cancer effects**

The camel immunoglobulin is another protein of camel milk, famous for its medicinal values.20 Most of the immunoglobulin from camel blood has the unique property of containing only two heavy chains, whereas light chains are absent.21 Due to their short size, most of these immunoglobulins in the lactating camel pass on to the milk. Single antigen-binding domains of heavy-chain immunoglobulins have been reported to have values for the development of biosensor and also diagnosis of cancer.22 Not only these, it has also been reported that camel milk has anti-cancer properties10,23 Anticancer activity of camel milk and its active constituents have well been described by number of investigators,9,10 but still research is in the pre-clinical phase.
Anti-infective effects
Nonetheless, for viral infection, efficacy of camel milk was well investigated and found to be more effective as compared to milk from other species. Anti-viral activity of camel milk was first reported in chronic active hepatitis patients. It was observed, that camel’s milk is more effective than milk from other species in improvement of clinical and biochemical status of patients with liver disorders. These anti-viral activities of camel milk can be through lactoferrin, which has shown anti-viral activity. Lactoferrin from camel milk inhibits hepatitis C virus (HCV) genotype 4. This was observed when peripheral blood leukocytes from hepatitis C patients were treated with this camel protein. To observe the anti-viral activity of camel lactoferrin, it was investigated if direct interaction between camel lactoferrin and HCV caused inhibition of virus entry into the cells. In this respect, camel lactoferrin proved to be a more potent anti-viral agent compared to lactoferrin from other species. Studies have also proven that camel milk supplementation to patients with drug resistant tuberculosis have shown improvement in their respective investigative tests and clinical symptoms.

Anti-allergic effects
Furthermore, there are numerous small-scale studies that showed therapeutic benefits of camel milk against allergies. As Shabo et al., have reported that a group of children with severe milk allergies failed to respond to all modern therapies and have completely recovered after daily administration of camel milk. These findings have been fully supported by El Agamy et al., showing that camel milk has unique immune-modulatory properties, which plays an important role to fight against viral and bacterial infections. Many investigations have also claimed that camel milk supplementation have shown significant therapeutic improvement for paediatric patients with autism.

Table 2: Anti-diabetes effects of camel milk.

<table>
<thead>
<tr>
<th>Main finding</th>
<th>Author Year</th>
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<tr>
<td>Consumption of camel milk by type 1 diabetic patients will reduce the requirement of insulin by 30%</td>
<td>Mullaicharam AR, Alhaider AA, 2014</td>
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<tr>
<td>At the end of 3 months camel milk therapy in persons with type 1 diabetes, the insulin requirement was reduced significantly</td>
<td>Al-Basmy AA, El-Sayed MK, Al-Shoeibi ZY, Abd El-Ghany AA, 2017</td>
</tr>
<tr>
<td>At the end of 4 weeks of camel milk therapy for young diabetic type 1 patients, significant reduction of blood glucose levels was observed</td>
<td>Mohamad RH, Zekry ZK, Al-Mehdar HA, 2009</td>
</tr>
<tr>
<td>Camel milk in combination with insulin was found to be more effective for the treatment of type 1 diabetes as compared with camel milk alone or insulin treatment alone</td>
<td>El-Sayed MK, Al-Shoeibi ZY, Abd El-Ghany AA, 2011</td>
</tr>
<tr>
<td>Administration of 500 ml of camel milk for 5 weeks to diabetic dogs showed significant reduction of blood glucose levels</td>
<td>Abdel Gader AG, Alhaider AA, 2016</td>
</tr>
<tr>
<td>Administration of camel milk to diabetic rats for 4 weeks significantly reduced blood glucose levels</td>
<td>Abdel Gader AG, Alhaider AA, 2016</td>
</tr>
<tr>
<td>500 ml/day consumption of camel milk for at least 3 months, could improve the health status of diabetes patients by maintaining of levels of blood glucose, HbA1C and decreasing insulin resistance</td>
<td>Mirmiran P, Ejtahed H, Angoorani P, Eslami F, Azizi F, 2017</td>
</tr>
</tbody>
</table>

Anti-diabetes effects
As shown in Table 2, there are multiple studies on animals about the benefit of camel milk in diabetes mellitus type 1 and type 2. In a systematic review about the camel milk benefits for diabetes mellitus has concluded that consumption of camel milk on a daily basis among the humans decreases the level of fasting blood sugar from 115.66 to 100 mg/dL, p = 0.002, HbA1c (from 9.54% to 9.08%, p = 0.002), with reduction in the dose of insulin by 37%. This is may be related to the excessive amount of insulin like proteins and insulin that can raise the activity of insulin receptors. Investigators from different parts of the world have reported that 3 months therapy of camel milk to type 1 diabetes patients significantly reduced blood glucose levels. Moreover, they also investigated that at the end of 3 months camel milk therapy, insulin requirement for these diabetic patients was also reduced significantly. Agrawal et al., have demonstrated that drinking of camel milk on a daily basis people with type 1 diabetes for one year, could be an adjunct to insulin therapy. Moreover, Mohamad et al., have also demonstrated that treatment of young type 1 diabetes patients with camel milk for 4 weeks showed significant reduction of blood glucose levels. Furthermore, El-Sayed et al., have demonstrated that camel milk in combination with insulin was found to be more effective for the treatment of type 1 diabetes as compared with camel milk alone or insulin treatment alone. In spite of these important implications of camel milk for people with type 1 diabetes, the mechanisms behind have not been fully investigated. In 2015, Shori has shown in her excellent review that camel milk has an insulin-like protein.
that probably performs anti-diabetic action in type 1 diabetes patients. It is important to point out that mucosal surfaces are the most common pathways for delivering drugs to the human body. However, oral administration of insulin has usually failed to pass through mucosal barriers, as it has been degraded by digestive enzymes before going to the bloodstream. Insulin-like protein of camel milk has a unique property of encapsulation in nanoparticles such as lipid vesicles that protect it in the stomach from digestive enzymes to reach the target. Because of these lipid encapsulation, camel milk has not been coagulated in an acidic environment of the stomach and most importantly, it has a better buffering ability than milk from other species such as cows, buffalo etc. It is also reported that amino acid sequence of camel milk proteins rich in cysteine residue, have a similar feature of insulin family of peptides. Furthermore, camel milk contains higher amount of polyunsaturated fatty acids, higher vitamin B3 and larger lipid micelles as compared to milk from other species.

Administration of camel milk to diabetic experimental animals has also proved to maintain hyperglycaemia. In 2010, Sboui et al., conducted two studies on diabetic dogs, demonstrating that administration of 500 ml of camel milk for 5 weeks to diabetic dogs showed significant reduction of blood glucose levels. Investigators have shown that administration of camel milk to diabetic rats for 4 weeks significantly reduced blood glucose levels. Studies have also illustrated that raw camel milk form was more effective than pasteurized camel milk for controlling hyperglycaemia in diabetic rats. Most importantly, treatment of diabetic rabbits with camel milk was better than biosynthetic insulin for reduction of glucose level. Recently, Mirmiran et al., have reviewed almost all top articles demonstrating the potential of camel milk on type 2 diabetes patients. They have also shown anti-diabetes potential of camel milk in type 2 diabetes patients. Camel milk consumption increased insulin level, which could contribute to maintain hyperglycaemia. It is noteworthy that investigators have made this statement of anti-diabetic activity of camel milk on just 20 type 2 diabetes patients. More recently, Mirmiran et al., have summarized the beneficial effects of camel milk consumption on type 2 diabetes patients in their excellent review. They have co-related potential of camel milk with different disease markers, which have been altered in type 2 diabetes patients, such as altered oxidative damage and abnormal regulation of inflammatory reactions. Camel milk contains high level of anti-oxidative agents such as zinc, selenium and many other trace elements and also it is well reported that camel milk reduces lipid peroxidation and inflammation under different pathological conditions via its anti-oxidant and anti-inflammatory abilities. Based on these evidences, it is suggested that camel milk has potential to reduce blood glucose levels, HbA1C and insulin requirements for both type 1 and type 2 diabetes.

Conclusions and future implications

Thus far, the last available literature strongly encourages the use of camel milk in clinical settings for diabetes patients but considerable amount of information about camel milk and its molecular anti-diabetic activity is still missing and till date it remains to be investigated. An extensive evaluation of the potential risks or benefits of using camel milk alone or together with anti-diabetic drugs may open a new area of research wherein camel milk or its bioavailable active constituents could be developed to enhance its clinical appeal for controlling diabetes. With the availability of safety profile of camel milk in humans, the window of opportunity is even wider to test camel milk for its potential therapeutic efficacy as an anti-diabetic entity in human diabetes. In conclusion, for researchers and
physicians in the research area of testing natural products, camel milk might represent much safer for humans, as the positive outcomes of studies described here might have potential for its rapid clinical development and application.

**Disclaimer:** None.

**Disclosure statement:** None.

**Funding Sources:** None.

**References**