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ANTIDIABETIC, ANTICOLITIS AND ANTICANCER ACTIVITY IN CAMEL MILK: A SYSTEMATIC ANALYSIS

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ABSTRACT

Camel milk is a nutrient-dense diet with anti-inflammatory, immune-regulating, gut microbiota-maintaining effects, a protein-rich vehicle with a wide range of therapeutic applications in gastrointestinal affections such as colitis, diabetes and cancer. In addition, the global awareness of camel milk and its products is now increasing with expected large camel products economic growth. Camel milk exosomes and camel albumen complexes with oleic acid showed promising anticancer actions. Camel milk ameliorates oxidative stress by increasing the expression of antioxidant genes as well as reducing angiogenesis and tumour growth factors in cancer. Camel milk is equipped with noticeable antidiabetic power comprising 52 insulin U/L, rich in β–cells nourishment and enhancing mediators and proteins. Camel milk boosts the expression of carnitine palmitoyltransferase type I, insulin receptor substrate type 2 and fatty acid synthases, which aids in insulin production and regulation and helps diabetic patients improve and normalise blood glucose, lipid profile, total glycerides and high-density lipoprotein levels. Camel milk has a unique quality as a powerful antimicrobial system made up of H_2O_2, lysozymes, immunoglobulins, antioxidants and low-weight molecular antibodies. Camel milk showed more nutritional and medicinal properties than other ruminant milks, hence numerous western countries are becoming more interested in raising camels for milk and byproducts.

Key words: Anticancer, bioactive components, camel milk, colitis, diabetes

Camel milk is high in insulin, lactoferrin, minerals and protein such as iron, vitamins, sodium, magnesium, iodine and potassium (Mabood *et al,* 2017). Autism, jaundice, hepatitis, anaemia, asthma, lactase deficiency and breast cancer are just a few of the conditions for which camel milk has shown to be helpful (Rahim *et al,* 2020). Camels' milk may be stored for extended periods without refrigeration (Mullaicharam, 2014). Combination of camel milk and urine were effective in treating breast and prostate cancers (Gupta *et al,* 2021). Camel milk dramatically inhibited cell growth, viability and migration. The rise of microtubule-associated protein1 light chain 3 (LC3-II) protein, together with a decrease in the expression of autophagy proteins, suggested autophagy induction. Confocal microscopy revealed (GFP)-LC3 puncta, which showed autophagosome production in response to camel milk therapy (Krishnankutty *et al,* 2018). The capacity of alpha-lactalbumin (α-LA), a tiny milk calcium-binding globular protein, to form complexes with oleic acid has been shown to have significant anticancer effect, especially breast cancer (Uversky *et al,* 2017).

β-Lactoglobulin is naturally missing in camel milk, making it similar to human milk and avoiding the major allergic protein in cows' milk. Whey protein/casein and β-casein/αs-casein ratios are greater in camel milk than in bovine milk. One of the key reasons for human milk's simple digestion in babies has been attributed to its high whey protein content and β-CN dominance. Camel milk also includes significant levels of proteins such as lactotransferrin, peptidoglycan recognition protein and whey acidic protein, which have beneficial functions in the immunological system. Camel milk's distinct physiochemical qualities make it a potential alternative to bovine milk for daily dairy consumption and newborn formula basis. Camel milk has piqued the curiosity of both academics and industry throughout the world in recent years. Although the amount of protective proteins in camel milk has been thought to contribute to its health and therapeutic advantages, little is known about how these bioactive proteins operate. This research investigates the applications of camel milk as a therapeutic tool with a focus on its anticolitis, antidiabetic and anticancer properties.

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Materials and Methods

The PRISMA checklist and guidelines were used to implement the analysis (Page *et al,* 2021).

Search strategy

The search engines Google Scholar, PubMed and Web of Science were used to retrieve the data. The range was between January 2013 and January 2021. The search approach comprises combination of several keywords e.g. Camel milk, composition, therapeutic, biological functions and benefits. The keywords that were used are shown below in Table 1.

Table 1. The keywords that were used in searching databases.

Search context	keywords
Camel milk	Composition of camel milk, Nutritional Value of camel milk, Benefits of camel milk, biological functions of camel milk, camel milk and its products.
Diseases	Therapeutic effects of camel milk, Camel milk and diabetes, camel milk and colitis and camel milk as anticancer.

Inclusion criteria

To collect high-quality research, journals having an impact factor were chosen. The papers focused on camel milk, its composition and its medical benefits of camel milk were included. The publications considered in the study were about diseases such as cancer, diabetes and colitis, as well as the influence of camel milk on reducing the effects of diseases on the human body.

Exclusion criteria

The papers omitted from the analysis did not fulfill the study's inclusion criteria. This study disregarded articles that give hetero-analysis on the selected issues and also excluded studies that were not in English or not accessible. Studies that were not primarily focused on the qualities of camel milk were also omitted. Finally, studies that did not address any intervention or outcomes of interest were excluded.

Results and Discussion

Identification and data input

About 988 papers were obtained from databases and 254 relevant articles were retrieved from various websites, organisations and pre-existing citations in the databases. The papers that did not fall under eligibility criteria were eliminated from the study (n= 176). Abstracts and titles were examined to sort the relevant themes and complete articles were retrieved and evaluated based on eligibility criteria if the abstract and title offered adequate information. After retrieving the articles, filtration based on the accessibility, language and overall merit, a total of 22 articles were selected which are shown in Fig 1 and Table 2.

The included studies

After extensive filtration and deliberation, 22 articles were selected as the best fit for evaluating camel milk. The studies were published between 2013 and 2021. The studies evaluated throughout the investigation were conducted in various territories. Every study and review included in the analysis discovered a connection between camel milk and its composition, as well as camel milk and therapeutic benefits.

The therapeutic effect of camel milk

Camel products and byproducts are gaining popularity across the world as a source of essential nourishment and a way to improve human health. When compared to other milk products, camel milk has more therapeutic, immune-restorative and nutrient-rich potential, making it a superior animal of the twenty-first century. Camel milk protein's bioactive peptides are one of the most essential features in maintaining human health since they assist to prevent many microbial infections and increase the immune system's normal function. Bioactive peptides are formed during the digestion of camel milk protein and serve as hypoglycemic and anti-obesity agents (Mudgil *et al,* 2018). Even though it is accessible in pasteurised and fresh raw milk at room temperature, bovine milk has a shorter shelf life than camel milk (Khalifa and Zakaria, 2019). Camel milk has a unique quality as a powerful antimicrobial system (Muhialdin and Algboory, 2018). This dynamic antimicrobial system is made up of H_2O_2, lysozymes, Immunoglobulins, antioxidants and low-weight molecular antibodies and it has a long shelf life. Camel milk, like bovine milk, is substantially supplemented with vital nutritional components; yet, in allergic reaction sensitive babies, camel milk is better since it includes β-casein and lactalbumin whey protein in comparable proportions to human milk (Ali *et al,* 2019; Solanki *et al,* 2017). Camel milk has an elevated concentration of mesophiles (Lactobacilli and Leuconostoc), as well as some bacteria such as *E. coli* and salmonella and their accumulation might be attributable to harsh scorching circumstances in drought-stricken areas. Although these organisms have both positive and negative effects on human health, their primary benefit is to improve intestinal digestibility (Issa and Tahergorabi, 2019).

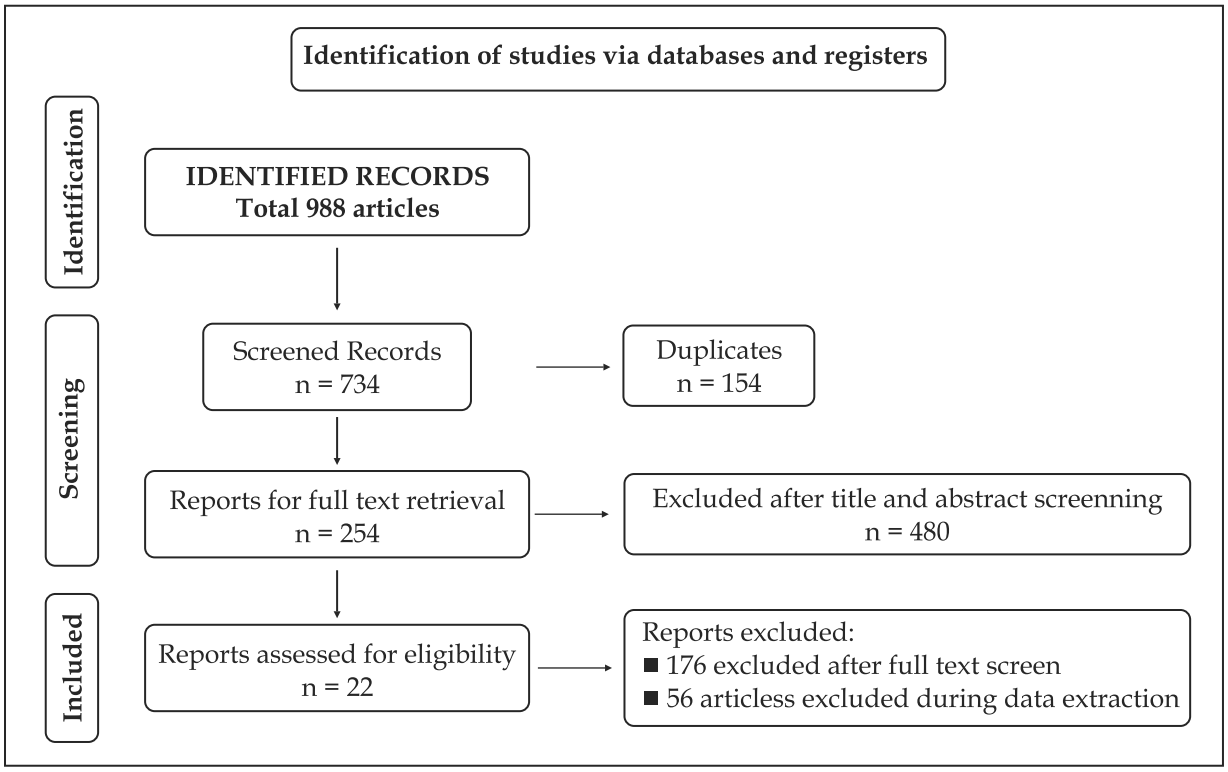

Fig 1. The PRISMA flow chart of article selection, screening and output.

Table 2. The selected studies on camel milk after search, identification and filtration.

Variables	Topic	References
Effectiveness of camel milk on diabetes	— The short-term therapeutic efficacy of camel milk vs. buffalo milk in alloxan-induced diabetic rabbits — A comparison of the hypoglycemic and antithrombotic (anticoagulant) effects of whole bovine and came milk in rats with streptozotocin-induced diabetes mellitus — Characterisation and identification of novel anti-diabetic and anti-obesity peptides derived from camel milk protein hydrolysates — A review of camel milk's role in the treatment of type 2 diabetes	• (Deeba *et al*, 2020) • (Khan *et al*, 2013) • (Korish *et al*, 2020) • (Mudgil *et al*, 2018) • (Shahriari *et al*, 2018)
Effectiveness of camel milk on cancer	— Camel milk reduces inflammatory angiogenesis in mice by downregulating proangiogenic and proinflammatory cytokines — *In vitro* and *in vivo* therapeutic effect of camel milk and its exosomes on Mcf7 cells — The use of human, bovine and camel milk albumins in oleic acid-based anticancer complexes — Research on camel milk's antimicrobial and antioxidant properties, as well as its role as an anti-cancer and anti-hepatitis agent. — The antigenotoxic and anticytotoxic effects of camel milk in cisplatin-treated mice	• (Alhaider *et al*, 2014) • (Badawy *et al*, 2018) • (El-Fakharany *et al*, 2018)
Effectiveness of camel milk on colitis	— Camel's milk ameliorates TNBS-induced colitis in rats via downregulation of inflammatory cytokines and oxidative stress.	• (Arab *et al*, 2014) • (He *et al*, 2022)
Nutritional property and Consumer acceptance of camel milk	— The effects of some milk heat treatments on the compositional, rheological and organoleptic qualities of camel milk labneh. — Composition of camel milk: a health blessing.	• (Desouky *et al*, 2013) • (Ali *et al*, 2019) • (Fufa and Haile, 2020)
	— A review of camel milk production and composition and its beneficial uses. — A review paper on the quality and therapeutic aspects of camel milk. — A review of camel milk and its associated health claims. — A review of the role of camel milk and milk products in domestic diet and therapeutic advancement.	• (Sakandar *et al*, 2018)

Fermentation of camel milk is beneficial for improving digestibility, ensuring milk preservation and keeping microbes at bay (Solanki and Hati, 2018). When compared to camel milk, bovine milk contains fewer bioactive peptides (ACE-inhibitory peptides and anti-oxidative peptides) generated by lactic acid bacteria (Moslehishad *et al,* 2013). Gariss (fermented camel milk) is a kind of camel milk that has been fermented (Sulieman *et al,* 2006).

Camel milk has a great reputation in the cosmetics industry because it contains a lot of alpha-hydroxyl acid and liposomes, which help to reduce wrinkles and dryness in the skin, giving it an anti-aging effect (Choi *et al,* 2014; Mohan *et al,* 2020).

Colitis treatment by camel milk

The antioxidant and anti-inflammatory characteristics of camel milk were thought to be beneficial in lowering signs of colon affection. Camel milk was administered to adult mice with and without drug-induced colitis using 2,4,6-trinitrobenzene sulfonic acid (Arab *et al,* 2014). Camel milk (10 ml/kg b.i.d. via oral gavage) successfully reduced the degree of colon injury, as demonstrated by improvements in macroscopic damage, colon weight/length ratio, histological changes, leukocyte influx and myeloperoxidase activity. The administration of camel milk reduced the levels of TNF- and IL-10 cytokines in the colon. The attenuation of camel milk to colon damage was also connected with suppression of oxidative stress by a decrease of lipid peroxides and nitric oxide, as well as enhancing antioxidant defenses via colon glutathione restoration and overall antioxidant capacity. Caspase-3 activity, an apoptotic marker, was also suppressed. As a result, camel milk may be an intriguing supplementary method to colitis treatment. Bacillus amyloliquefaciens-enriched camel milk was able to alleviate chemicals-induced colitis in mouse models (Khalifa *et al,* 2022). The colitis disease index was lowered and body weight and colon length were improved. Furthermore, therapy reduced Myeloperoxidase and pro-inflammatory cytokines. Furthermore, the inflammatory process mRNA and protein markers nuclear factor kappa B, phosphatase and tensin homolog, proliferating cell nuclear antigen, cyclooxygenase-2 and occludin were down-regulated.

The preventive impact of camel milk in mice with colitis caused by dextran sodium sulfate was assessed (He *et al,* 2022). Camel milk can prevent body weight loss, lower the disease activity index and minimise colon tissue damage. Furthermore, camel milk has been shown to lowers inflammatory factor overexpression and limits apoptosis of intestinal epithelial cells. Furthermore, camel milk effectively regulated intestinal microbiota in mice with colitis by increasing the diversity of the gut microbiota, increasing the abundance of beneficial bacteria and decreasing the number of harmful bacteria (Fig 2).

Camel milk and cancer

The exosomes from camel milk showed a higher apoptosis rate, inhibition of oxidative stress, lower inflammation rate and improved immune response. Overall, delivery of camel milk-derived exosomes had a greater anticancer impact but a lower immunological response than camel milk therapy. Furthermore, local injection of exosomes resulted in greater results than oral treatment. These data imply that camel milk and its exosomes have an anticancer impact on the tumour microenvironment, perhaps by inducing apoptosis and inhibiting oxidative stress, inflammation, angiogenesis and metastasis. As a result, camel milk and its exosomes have the potential to be used as an anticancer agent in cancer treatment (Badawy *et al,* 2018). Compared to the complexes of oleic acid with human and bovine albumins, the complex of camel albumin with oleic acid demonstrated the most powerful anti-tumour effects (El-Fakharany *et al,* 2018). Various diseases, including cancer and hepatitis, have been linked to oxidative stress. Camel milk may decrease oxidative stress by increasing antiproliferative effects and regulating antioxidant genes during cancer and hepatitis (Khan *et al,* 2021).

Camel milk has been shown to have a regulatory effect on parameters of the primary components of inflammatory angiogenesis, providing insight into the possible therapeutic advantage underpinning the anti-cancer properties of camel milk. Camel milk treatment reduced wet weight, vascularisation, collagen deposition, macrophage recruitment and levels of vascular endothelial growth factor, interleukin and transforming growth factor (Alhaider *et al,* 2014).

The antioxidant, anticancer, antihypertensive and anti-angiotensin-converting enzyme activities of fermented camel milk with fermented bovine milk in a lab setting were compared (Ayyash *et al,* 2018). Fermented camel and bovine milks were made using the probiotic strain of *Lactococcus lactis* KX881782 (Lc. K782) found in camel milk and the control strain of *Lactobacillus acidophilus* DSM9126 (La.DSM) found in bovine milk. Water-soluble extract (WSE) proteolytic

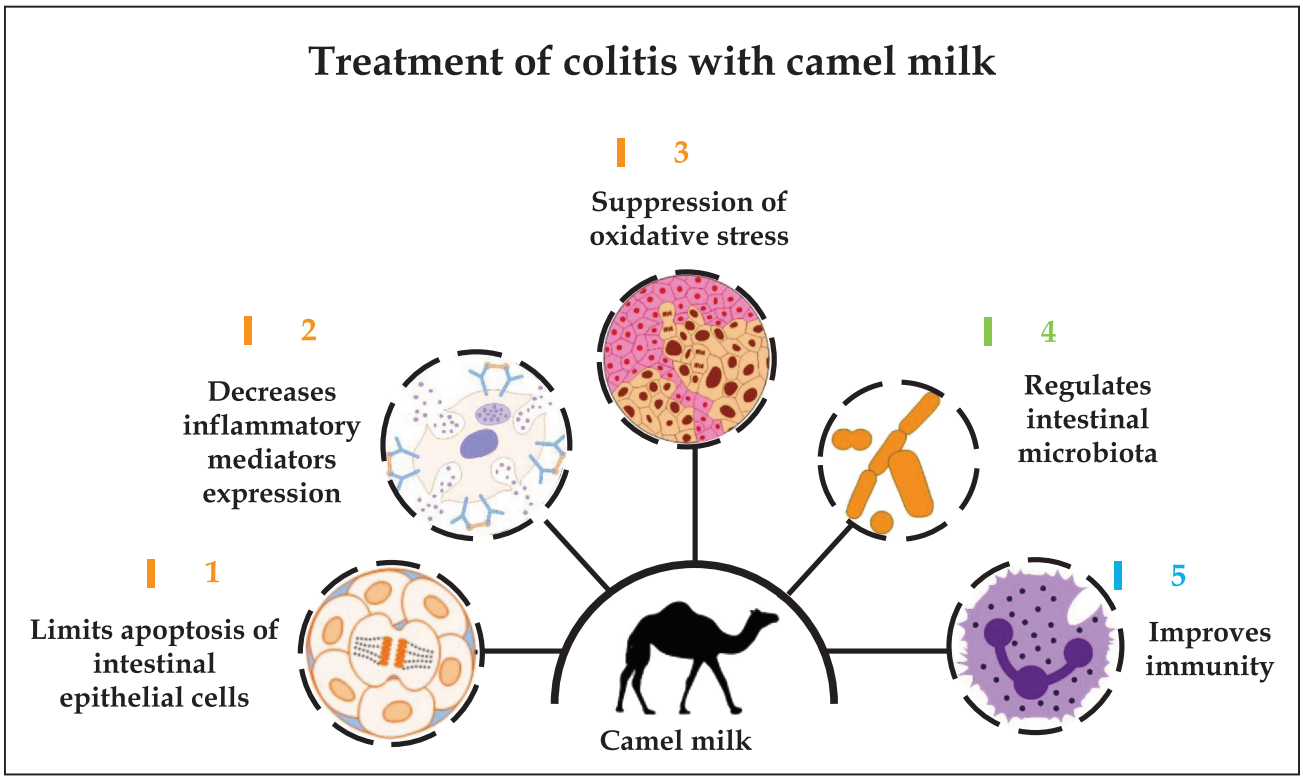

Fig 2. Outline of the mechanism of action of camel milk in treatment of colitis.

activities in all fermented camel milk were higher than those in fermented bovine milk. The maximum antioxidant activity was found in fermented camel milk. When fermented camel milk extracts were used to treat cancer cells, the proliferation of Caco-2, MCF-7 and HELA cells was significantly reduced (Ayyash *et al,* 2018).

Camel milk and diabetes

The anti-diabetic activities of camel milk and bovine milk were studied in streptozotocin-induced diabetic rats by oral feeding for 8 weeks. Camel milk is more successful in improving body weight, lowering blood glucose levels and lowering glucose tolerance (Korish *et al,* 2020). Camel milk protein contains bioactive peptides that the inhibit enzymes responsible for causing diabetes and obesity as well. Camel milk contains RQ-8 peptide and acts as an antioxidant property, which lowers the oxidative stress that is associated with type-II diabetes (Shahriari *et al,* 2018). In a trial to investigate the potential anti-diabetic benefits of camel milk in diabetic rats induced by streptozotocin, for 30 days, the rats were fed fresh camel milk which considerably lowered blood glucose, urea, uric acid and creatinine levels while increasing albumin, albumin/globulin ratio and restoring all liver function marker enzymes and lipid profile to near control levels (Khan *et al,* 2013).

In a study on the therapeutic applications of camel milk in the management of type 1 diabetes, there were significant reductions in HbA1c (7.8 1.38 - 6 0.96; p 0.001), MBI (17 4.4 - 19.7 2.97; p 0.001) and required insulin dose (32 12 - 17.88 12.40; p 0.005) as compared to baseline values (Agrawal *et al,* 2005). The synthetic peptides produced and discovered from camel milk whey hydrolysates and lactoferrin isolated from milk may be suitable candidates for testing *in vivo* for their hypothesised effects on insulin-dependent responses, either alone or in conjunction with insulin (Anwar *et al,* 2021).

Camel milk boosts the expression of carnitine palmitoyl transferase type I, insulin receptor substrate type 2 and fatty acid synthases, which aids in insulin production and regulation and helps diabetic patients improve and normalise blood glucose, lipid profile, total glycerides and high-density lipoprotein levels. As a consequence, frequent use of camel milk can help to reduce the risk of diabetic complications (Aqib *et al,* 2019).

Short-term therapeutic efficacy of camel milk vs buffalo milk in alloxan-induced diabetic rabbits showed improved hematological (RBC, MCV, Hb, MCH) and serological markers (AST, ALT, creatinine, BUN, TPs and TOS) with camel milk treatment. Camel milk with glibenclamide significantly lowered

blood glucose levels compared to buffalo milk, while kidney function improved significantly. Camel milk and glibenclamide helped to return the liver and kidney pathological exam to near normal values (Deeba *et al,* 2020).

Camels milk may be utilised for a variety of beneficial domains, including medicine and sustenance. Camel dairy and meat production on a large scale has gained popularity as the general public becomes more aware of the benefits of camels and their products. Camel milk production and animal health improve when camels are maintained in a semi-intensive setting rather than on the conventional camel rearing method (Abdel Fattah and Roushdy, 2016). Camel milk's nutritive and therapeutic values are proved to be better than other ruminant species, hence several western nations are increasingly interested in rearing camels for milk and its byproducts. Furthermore, these countries have made significant contributions to the development of milk-based products, as well as consumer education and awareness of these products.

Camel milk consumption has been linked to lower fasting blood glucose levels and better lipid profiles (Mohammadabadi, 2019). Raw camel milk contains three times more insulin and/or insulin-like proteins (52 units of insulin per liter) than cow milk. These proteins interact directly with insulin-sensitive tissues and insulin receptors, potentiating insulin action and signaling (Abdulrahman *et al,* 2016). Camel milk proteins and bioactive peptides act directly or indirectly on particular cellular pathways and influence insulin generation and release by pancreatic β–cells. Camel milk is rich in lactoferrin. Lactoferrin reduces hyperglycemia through increasing insulin sensitivity, anti-inflammatory responses and activating insulin receptors. It is possible to prevent diabetes-related liver and kidney diseases, as well as enhance wound healing, by drinking camel milk. The action of camel-milk insulin was eliminated by pepsin, indicating that it is vulnerable to digestion by digestive enzymes (Abou-Soliman *et al,* 2020). Pepsin entirely abolishes the action of camel-milk insulin hence it was construed that camel's milk's anti-diabetic activity is not due to insulin or insulin-like protein alone. It has been hypothesised that insulin in camel milk is resistant to proteolysis. Camel milk lipid vesicles have also been proposed to help in the absorption of camel milk insulin into circulation by encapsulating and preserving the insulin from stomach digestion (Malik *et al,* 2012). Furthermore, insulin-like proteins in camel milk may be able to imitate insulin's interaction with its receptor. Bioactive peptides are presumably generated following the digestion of camel milk proteins, which are tiny and quickly absorbed into the bloodstream. The existence of small chemical compounds with anti-diabetic potential in camel milk is currently under investigation.

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Data availability statement

All data are within the manuscript

Funding statement

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